Serum uric acid levels in non-alcoholic steatosis patients: a meta-analysis

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**Background and Objectives:** Experimental and observational studies suggest a role for increased uric acid in non-alcoholic fatty liver disease (NAFLD). This study aimed to systematically review the association between serum uric acid (SUA) levels and NAFLD. **Method and Study Design:** We used PubMed, and the EMBASE database to identify all applicable studies through November 2015. We used the weighted mean difference (WMD) to demonstrate the differences between the control and NAFLD groups in continuous data. We calculated the odds ratios (ORs) for dichotomous data using the Mantel-Haenszel method. A total of 16 observational studies were identified and used for the analysis of continuous data, and 4 studies were analyzed for dichotomous data. **Results:** The WMD was 52.3 (95% CI: 39.0, 65.5, \(p<0.00001\)). The pooled OR in observational studies was 2.08 (95% CI: 1.93-2.24, \(p<0.00001\)). The results were heterogeneous for the comparison of continuous data and homogeneous for the comparison of dichotomous data. The SUA cutoff value for the occurrence of NAFLD was 308, with a sensitivity of 94.12% [71.3-99.9] and specificity of 70.6% [44.0-89.7]. **Conclusion:** We observed a positive association between increased SUA levels and the diagnosis of NAFLD in all analyses. Our results suggest that SUA is upregulated in patients with NAFLD and might be related to the pathogenesis of NAFLD.

**Key Words:** serum uric acid, non-alcoholic fatty liver disease, fatty liver, SUA, NAFLD

**INTRODUCTION**
Non-alcoholic fatty liver disease (NAFLD) is one of the most important global public health problems of the twenty-first century; it affects approximately 20–30% of the general population, and its prevalence is increasing worldwide.\(^1\) NAFLD comprises a histological spectrum of liver disease from nonalcoholic fatty liver or simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis.\(^1\) Although the majority (70–90%) of patients with NAFLD follow a benign, non-progressive clinical course,\(^2,3\) a significant minority have NASH and are at greater risk for progression to cirrhosis and hepatocellular carcinoma.\(^4,5\) Hence, distinguishing NASH from NAFLD has important prognostic and management implications.

At present, liver biopsy remains the criterion standard for diagnosing NAFLD\(^6\) because it allows other causes of liver damage to be excluded and the severity of the fatty infiltration into the hepatocyte, lobular inflammation, hepatocyte ballooning and fibrosis to be estimated.\(^7\) However, liver biopsy is poorly suited as a diagnostic test for such a prevalent condition due to its invasiveness, sampling variability and cost. The noninvasive tests available for distinguishing NAFLD include an assessment of clinical signs and symptoms, routine laboratory and radiological imaging tests, and combinations of clinical and blood test results.\(^3,9\) Unfortunately, these tests are of limited use.\(^8,10\) A number of investigators have attempted to identify potential noninvasive markers for NASH diagnosis, such as biochemical markers (the Nash Test),\(^11\) ferritin\(^12\) and serum fragment of cytokera...
components of metabolic syndrome (MetS), or indexes of liver and kidney function. Hwang et al suggested that increased SUA concentrations, even within the normal range, are independently associated with the presence of NAFLD. A better understanding of the SUA levels in NAFLD patients will provide a more accurate interpretation of the SUA-NAFLD relationship and has potential implications for NAFLD treatment in the population. Therefore, we performed a meta-analysis to explore the potential diagnostic value of SUA.

METHOD

Data sources
We identified studies that were published in the English language by searching the PubMed and EMBASE databases. Studies that were eligible for this analysis were updated on November 2015 with the following keywords: “nonalcoholic fatty liver disease”, “NAFLD” or “nonalcoholic steatohapatitis” plus “uric acid” or “clinical chemistry” (Supplementary table 1). All eligible studies were retrieved, and their bibliographies were reviewed for other relevant publications. Additional papers and book chapters were identified by a manual search of the references from the original manuscripts and reviews. The scientific analysis was approved by the ethics committee of Anhui Medical University.

Study selection
To be included, a study had to fulfill the following criteria: (1) patients with a distinct NAFLD diagnosis by ultrasonography or liver biopsy and (2) participant population of any sex or ethnicity with NAFLD.

The following studies were excluded: (1) those with overlapping articles or duplicate data; (2) articles about animal experiments; (3) studies with pregnant individuals; (4) studies with NAFLD patients with other competing causes of steatosis, such as excessive alcohol, viral hepatitis, autoimmune hepatitis, and hemochromatosis; and (5) conference report, letters, and case reports.

All reports were independently conducted by two investigators. The results were compared, and any questions or discrepancies were resolved through iteration and consensus.

Data extraction and quality assessment
Data extraction was independently conducted by two researchers (Huang F and Yao L). The following data were extracted: year of publication, name of the first author, country, participant characteristics (age, gender, ethnicity and body mass index), method of diagnosing NAFLD, SUA measurement methods, and serum SUA levels. Discrepancies were resolved by discussion and consensus.

The present study followed the quality standard of reports for observational studies in epidemiology guidelines (PRISMA) for observational studies. Selection criteria were established before the search to avoid selection bias. The search results were double-checked by a third investigator (Liu A).

Statistical analysis
For studies that reported means and standard deviations of SUA levels, we analyzed the levels in NAFLD patients and in a non-NAFLD control group for each study using weighted mean differences (WMDs) and 95% confidence intervals (CIs). For studies that reported dichotomous and categorical data, we separated the cohorts into hyperuricemia and un-hyperuricemia (cut-off value: men = 7 mg/dL or 420 μmol/L; women = 6 mg/dL or 360 μmol/L). We used τ² to analyze the heterogeneity. If the studies were found to be heterogeneous, a random-effects model rather than fixed-effects model was used to analyze the pooled estimates. Subgroup analysis was performed to investigate the factors that affected the pooled estimates and the source of heterogeneity. Sensitivity analysis was conducted to assess the influence of a single study on the analysis. We used Harbord’s regression test for funnel-plot asymmetry and Egger’s test to assess the publication bias. Receiver operating characteristics (ROC) curves were generated to determine the cut-off values for the optimal sensitivity and specificity of the relationship between SUA levels and the occurrence of NAFLD. Meta-analysis was performed using Review Manager Version 5 (Cochrane Collaboration and Update Software) and Stata Version 13 for all analyses. Subgroup analysis was performed to evaluate the factors that might impact the pooled effects and to identify the source of any heterogeneity.

RESULTS

Literature search
In the present analysis, a total of 2,461 candidate articles were identified regarding the SUA levels and the diagnosis of NAFLD. In these articles, 1,210 were from PubMed and 1,251 were from EMBASE. After the duplicates were removed, 1,680 articles remained, of which 1,642 were excluded because they did not fit our selection criteria. After the full texts of the remaining 38 studies were reviewed, a total of 22 publications were identified, including 16 articles that used continuous data and 6 that used dichotomous data. A flow diagram showing the methodology used to select relevant studies is presented in Supplementary figure 1.

Study characteristics
Of the 17 independent cohort studies that used continuous data, 35,936 participants and 12,374 NAFLD cases were identified. Four studies were conducted in Western countries, and 13 were conducted in Asian countries. Nine studies were conducted in general population settings, seven were conducted in inpatients settings, one was conducted with postmenopausal women, and one was conducted with obese women. The selected studies were published from 2001 to 2015, and the number of participants per study ranged from 95 to 9,019. The mean SUA levels for the NAFLD subjects ranged from 279 to 449 μmol/L. The mean ages of the subjects were similar among the studies except for the study by Xu et al, which focused on elderly patients. NAFLD was diagnosed by ultrasound in 15 studies by liver biopsy in 1 study, and by CT in 1 study (Table 1). All studies showed significantly higher SUA levels in NAFLD subjects compared with the controls. The SUA levels were typically presented in μmol/L, but those that were measured in mg/dL were converted to μmol/L by
Table 1. Observational Studies involved in the meta-analysis

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Region</th>
<th>Diagnostic method</th>
<th>NAFLD (N)/Total (N)</th>
<th>NAFLD, males (%)</th>
<th>NAFLD age</th>
<th>Assay method</th>
<th>SUA in NAFLD patients (μmol/L)</th>
<th>SUA in controls (μmol/L)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cai, 2014</td>
<td>China</td>
<td>Ultrasonography</td>
<td>934/2191</td>
<td>72.4</td>
<td>46.0±10.0</td>
<td>Automated Analyzer</td>
<td>320±88</td>
<td>254±80</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cao, 2013</td>
<td>China</td>
<td>Liver biopsy</td>
<td>44/95</td>
<td>22.7</td>
<td>45.5±12.59</td>
<td>NR</td>
<td>330.4±113.63</td>
<td>295.8±78.47</td>
<td>0.035</td>
</tr>
<tr>
<td>Chang, 2014</td>
<td>Taiwan</td>
<td>Magnetic resonance spectroscopy.</td>
<td>210/420</td>
<td>62.8</td>
<td>44.1±12.7</td>
<td>Automated Analyzer</td>
<td>392.63±83.28</td>
<td>326.97±71.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fenkci, 2007</td>
<td>Turkey</td>
<td>NR</td>
<td>84/105</td>
<td>NR</td>
<td>44.9±11.5</td>
<td>Enzymatic method</td>
<td>313.71±98.84</td>
<td>279.64±65.44</td>
<td>NR</td>
</tr>
<tr>
<td>Hu, 2012</td>
<td>China</td>
<td>Ultrasonography</td>
<td>2730/7152</td>
<td>61.2</td>
<td>48.42±12.94</td>
<td>Automated Analyzer</td>
<td>365.44±82.38</td>
<td>308.09±77.00</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hwang, 2011</td>
<td>Korea</td>
<td>Ultrasonography</td>
<td>2124/9019</td>
<td>75.9</td>
<td>44.0±13.0</td>
<td>Automated Analyzer</td>
<td>331.46±88.78</td>
<td>272.27±100.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kucucukazman, 2014</td>
<td>Turkey</td>
<td>Ultrasonography</td>
<td>154/211</td>
<td>42.8</td>
<td>46.3±10.7</td>
<td>NR</td>
<td>325.55±76.95</td>
<td>284.11±76.95</td>
<td>0.001</td>
</tr>
<tr>
<td>Li, 2009</td>
<td>China</td>
<td>Ultrasonography</td>
<td>1051/8925</td>
<td>66.3</td>
<td>56.8±8.84</td>
<td>Automated Analyzer</td>
<td>370.3±86.6</td>
<td>321.1±82.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lin, 2015</td>
<td>China</td>
<td>Ultrasonography</td>
<td>1424/4305</td>
<td>31.7</td>
<td>62.7±9.0</td>
<td>Automated Analyzer</td>
<td>301.9±77.4</td>
<td>327.2±76.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liu, 2014</td>
<td>China</td>
<td>Ultrasonography</td>
<td>121/528</td>
<td>0</td>
<td>54±7.4</td>
<td>Automated Analyzer</td>
<td>279.96±44.98</td>
<td>255.70±51.49</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lonardo, 2001</td>
<td>Italy</td>
<td>Ultrasonography</td>
<td>60/120</td>
<td>55.0</td>
<td>51.7±1.44</td>
<td>ELISA kit</td>
<td>316.66±10.06</td>
<td>238.53±10.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Omagari, 2002</td>
<td>Japan</td>
<td>Ultrasonography</td>
<td>141/1264</td>
<td>65.2</td>
<td>48±19.25</td>
<td>NR</td>
<td>337.38±333.21</td>
<td>272.27±346.37</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Seung, 2003</td>
<td>Korea</td>
<td>Ultrasonography</td>
<td>120/360</td>
<td>100</td>
<td>42.8±0.88</td>
<td>Automated Analyzer</td>
<td>371.71±6.21</td>
<td>344.49±0.402</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tarantinoa, 2011</td>
<td>Italy</td>
<td>Ultrasonography</td>
<td>85/105</td>
<td>38.5</td>
<td>33.45±13.63</td>
<td>NR</td>
<td>310.15±84.6</td>
<td>207.17±23.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tian, 2014</td>
<td>China</td>
<td>Ultrasonography</td>
<td>2286/5638</td>
<td>66.1</td>
<td>NR</td>
<td>Automated Analyzer</td>
<td>449.86±83.37</td>
<td>354.87±63.28</td>
<td>NR</td>
</tr>
<tr>
<td>Xu, 2011</td>
<td>China</td>
<td>Ultrasonography</td>
<td>227/878</td>
<td>61.2</td>
<td>71.2±3.8</td>
<td>Automated Analyzer</td>
<td>372.60±88.5</td>
<td>336.40±82.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Zhang, 2014</td>
<td>China</td>
<td>Ultrasonography</td>
<td>215/844</td>
<td>59.5</td>
<td>50.36±6.50</td>
<td>Radioimmunoassay</td>
<td>328.6±84.5</td>
<td>301.6±90.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

NR: not reported.
Studies with data on SUA levels in NAFLD and controls, alphabetically ordered. SUA levels are reported in μmol/L. Levels that were measured in mg/dL were converted to μmol/L by mal by 59.48.
Table 2. Studies involved in the meta-analysis with dichotomous data

<table>
<thead>
<tr>
<th>First Author, year</th>
<th>Region</th>
<th>Reagent sources</th>
<th>Assay method</th>
<th>Cut-off</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anajas, 2013</td>
<td>Brazil</td>
<td>serum</td>
<td>Automated analyzer</td>
<td>330 μmol/L. Men: 420 μmol/L, Women: 360 μmol/L</td>
<td>6</td>
<td>10</td>
<td>31</td>
<td>82</td>
</tr>
<tr>
<td>Xu, 2010</td>
<td>China</td>
<td>serum</td>
<td>Automated analyzer</td>
<td>Men: 420 μmol/L, Women: 360 μmol/L</td>
<td>145</td>
<td>671</td>
<td>726</td>
<td>5870</td>
</tr>
<tr>
<td>Ryu, 2010</td>
<td>Korea</td>
<td>serum</td>
<td>Automated analyzer</td>
<td>420 μmol/L</td>
<td>305</td>
<td>365</td>
<td>1412</td>
<td>3559</td>
</tr>
<tr>
<td>Lee, 2009</td>
<td>Korea</td>
<td>serum</td>
<td>Automated analyzer</td>
<td>Men: 420 μmol/L, Women: 360 μmol/L</td>
<td>954</td>
<td>999</td>
<td>2656</td>
<td>6123</td>
</tr>
</tbody>
</table>

Subgroup, sensitivity, and bias analysis

Subgroup analysis was performed to investigate the source of heterogeneity and the factors that affected the pooled estimates. The effects of SUA on the NAFLD in the subgroup meta-analyses are presented in Table 3. The observed effect was significant among studies between subgroups by subject characteristics, such as age and BMI. The difference was not significant between subgroups by study location (p=0.27), and gender (p=0.25). To detect the stability of this meta-analysis for observational studies, single studies were excluded. The exclusion of any individual studies did not markedly change the overall effect (Supplementary figure 2). Visual inspection of Begg’s funnel plot showed asymmetry (Figure 2) for the analysis of the continuous data. The exclusion of a single study did not alter the combined results. There might have been publication bias in Begg’s funnel plot of the dichotomous data due to the limited number of publications.

Using the ROC curves, SUA levels higher than 308 μmol/L had optimal sensitivity and specificity for determining NAFLD (94.1% [71.3-99.9] and 70.6% [44.0-89.7], respectively). The accuracy was 0.834 at the cut-off value (Figure 3).

Table 3. Subgroup analysis of the observational studies

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cohorts</th>
<th>WMD (95% CI)</th>
<th>I² (%)</th>
<th>p ¹ (subgroup difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>11</td>
<td>32.3 (31.3, 33.3)</td>
<td>98</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>≥50</td>
<td>5</td>
<td>59.3 (31.3, 87.3)</td>
<td>99</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2</td>
<td>26.5 (14.3, 38.7)</td>
<td>85</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Women</td>
<td>3</td>
<td>35.1 (26.7, 43.5)</td>
<td>83</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Study location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>12</td>
<td>49.7 (33.9, 65.5)</td>
<td>99</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>5</td>
<td>65.6 (42.4, 88.7)</td>
<td>86</td>
<td>0.0002</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>6</td>
<td>31.3 (30.3, 32.3)</td>
<td>99</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>≥25</td>
<td>8</td>
<td>74.4 (71.3, 77.4)</td>
<td>85</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Measurement method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Automated analyzer</td>
<td>10</td>
<td>35.9 (34.9, 36.9)</td>
<td>92.5</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Radioimmunoassay</td>
<td>1</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Enzymatic method</td>
<td>2</td>
<td>77.2 (73.6, 80.8)</td>
<td>92</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>71.7 (57.5, 85.9)</td>
<td>89</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

WMD: weighted mean difference. Stratiﬁed and meta-regression analyses of the effects of the study characteristics. p ¹-value tested for heterogeneity of subgroups; p ²-value for the heterogeneity between subgroups in the meta-regression analysis.

Meta-analyses

The first 17 articles provided data on continuous SUA levels, and a significant positive relationship was observed between SUA levels and the diagnosis of NAFLD (Figure 1A). We tested the heterogeneity of the 17 observational studies, and the τ² statistic was 698 (p=0.00001). Therefore, the pooled estimates were assessed using a random-effects model rather than fixed-effects model. The WMD was 52.3, and the 95% CI ranged from 39.0 to 65.5 (p<0.00001) (Figure 1A).

In the dichotomous data, the τ² was 34% (p=0.21) using a fixed-effects model for the meta-analysis. The odds ratio (OR) was 2.10, and the 95% CI was between 1.95 and 2.27 (p<0.00001) (Figure 1B). All observations suggested that serum SUA levels were positively associated with the risk of NAFLD.
Figure 1. Forest plot of the meta-analysis. (A) Forest plot of the observational studies. IV, Random: Inverse variance heterogeneity random-effects model. Horizontal lines = 95% CI. The size of the data marker corresponds to the weight of that study. The diamond represents the summary estimate. The result favors experimental groups. (B) Forest plot of the dichotomous data. M-H, fixed: Mantel-Haenszel heterogeneity fixed-effects model. Horizontal lines = 95% CI. The size of the data marker corresponds to the weight of that study. The diamond represents the summary estimate. The result favors experimental groups.

Figure 2. Funnel plots of continuous data (A) and dichotomous data (B). MD: mean difference; OR: odds ratio.
Recent experimental evidence has suggested that uric acid may have a causative role in the pathogenesis of NAFLD, which can lead to liver cirrhosis or even hepatoma. Therefore, it is important to investigate the relationship between SUA and NAFLD. Uric acid is responsible for clearing free radicals from the body and acts as an antioxidant in the cardiovascular system. SUA levels and NAFLD are associated in that most patients with NAFLD also have insulin resistance, which increases the synthesis of uric acid. Moreover, uric acid excretion is also lower in insulin-resistant patients. Choi Y et al demonstrated that uric acid promoted hepatic fat synthesis by activating SREBP-1c under endoplasmic reticulum stress and that severe hepatic steatosis could be induced by injecting uric acid into ob/ob mice. Moreover, the impaired oxidation process might be related to the pathogenesis of uric acid in the development of NAFLD. The association between SUA level and NAFLD suggested that SUA could play an important role in developing NAFLD that might have revealed the impaired oxidative function of the liver in NAFLD as well as a compensatory mechanism against that increased oxidative stress.

To our knowledge, this is the first meta-analysis to investigate the association of SUA levels with NAFLD. Although the relationship between SUA levels and metabolic syndrome has been widely discussed. The information regarding NAFLD has been rather limited in the different analyses. Our search method had no language or date restrictions, and by including EMBASE, we also incorporated grey literature that has been accepted for scientific meetings, which added strength to our study. However, this meta-analysis does have limitations. First, the method of diagnosing NAFLD varied across studies; in most studies, it was identified by ultrasonography, not liver biopsy. Because liver biopsy is the gold standard in NAFLD diagnosis, variations in the diagnostic methods used might have led to measurement error and caused underestimation of the association between SUA and NAFLD. Second, the methods for measuring SUA levels varied across studies, which likely contributed to the heterogeneity in our analysis. Third, the normal range of SUA levels remains a controversial area of research in that the cut-off values varied across studies. Moreover, the SUA levels between genders also led to errors in determining a normal SUA range, especially in mixed-gender cohort studies. Therefore, our data were markedly heterogeneous for all comparisons.

In conclusion, we have demonstrated that increased SUA levels were prevalent in NAFLD subjects, suggesting that SUA might play a role in NAFLD development. Future research should focus on investigating the effect of SUA on the pathogenesis of NAFLD and on exploring the new diagnostic and treatment strategies for NAFLD.

**AUTHOR DISCLOSURES**

The authors have declared that no competing interests exist.

**Funding disclosure**

This study was supported by the National Natural Science Fund of China (NSFC 81401617), Anhui Provincial Natural Science Foundation (1408085QH170) as well as Grants for Scientific Research of BSKY (XJ201317) from Anhui Medical University.
REFERENCES


Supplementary table 1. Search Engine up to Nov 2, 2015

PUBMED


EMBASE

'steatosis' OR "fatty liver" OR NASH OR "Non-alcoholic Fatty Liver Disease" OR "liver enzymes" OR 'transaminase' OR 'alt' OR 'bright liver' AND ("serum uric acid" OR 'serum uric acid' OR 'SUA') AND [embase]/lim

Supplementary figure 1. Flow diagram of the study.

Supplementary figure 2. Sensitivity analysis of the observational studies.