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REVIEW

Association Between Serum Uric Acid and Non-Alcoholic Fatty Liver Disease: An Updated Systematic Review and Meta-Analysis

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Objective: Recent epidemiological evidence shows that there is an association between serum uric acid (SUA) levels and nonalcoholic fatty liver disease (NAFLD). The purpose of this meta-analysis is to summarize all available evidence and assess the associations between SUA levels and NAFLD.

Methods: Using two databases, Web of Science and PubMed, observational studies were applied from the establishment of the databases to June 2022. We used a random effect model to construct the pooled odds ratio (OR) and 95% confidence interval (CI) to appraise the association between SUA levels and NAFLD. The Begg's test was conducted to appraise publication bias.

Results: A total of 50 studies were included, involving 2,079,710 participants (719,013 NAFLD patients). The prevalence and incidence rates (95% CIs) of NAFLD in the patients with hyperuricemia were 65% (57–73%) and 31% (20–41%), respectively. Compared to participants with lower levels of SUA, the pooled OR (95% CI) of NAFLD in those with higher levels of SUA was 1.88 (95% CI: 1.76–2.00). In the subgroup analyses, we found that SUA levels were positively associated with NAFLD in all subgroups, according to study design, study quality, sample size, sex, comparison, age, or country.

Conclusion: This meta-analysis shows that increased SUA levels are positively associated with NAFLD. The results suggested that reducing SUA levels can be a potential strategy for the prevention of NAFLD.

Registration Number: PROSPERO-CRD42022358431.

Keywords: serum uric acid, nonalcoholic fatty liver disease, meta-analysis, updated

Introduction

One of the most prevalent chronic liver illnesses globally is non-alcoholic fatty liver disease (NAFLD). In 2020, NAFLD evolved into metabolic dysfunction-associated fatty liver disease (MAFLD).[1] Although emerging studies have explored the associations between MAFLD and health outcomes over the past two years, there have been limited studies that investigate the associations between SUA and MAFLD. Additionally, there are differences in the definitions of NAFLD and MAFLD. MAFLD is defined as the evidence of overweight/obesity, the existence of type 2 diabetes or metabolic disorder on the basis of fatty liver.[1] NAFLD refers to liver steatosis>5% found by imaging or histology after excluding significant recent drinking and other liver diseases with known causes.[2] Therefore, based on the current available data, we summarized the associations between SUA and NAFLD in this meta-analysis. In 2018, the prevalence of NAFLD

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was about 25%.[3] NAFLD may develop into a series of advanced liver diseases such as fibrosis, cirrhosis and liver cancer.[4] Moreover, NAFLD is associated with other diseases, such as diabetes, hypertension, and cerebrovascular diseases.[5,6] Considering the disease burden caused by NAFLD and its high prevalence, it is necessary to determine its risk factors.

The primary by-product of purine metabolism in the body is serum uric acid (SUA). Previous articles found that the increase in SUA levels acts an independent risk factor for NAFLD and may be utilized as an indicator to assess the NAFLD risk,[7–10] and that the prevalence rates of NAFLD increases with an increase in the SUA concentration.[11,12] According to previous studies, a raised SUA concentration was independently associated with the existence of NAFLD even when it was within the normal range.[13–15] However, some other articles suggested that SUA levels are not associated with NAFLD risk.[12,16,17] Previous meta-analyses revealed a positive association between hyperuricemia and higher SUA levels, and NAFLD.[18–23] Based on these evidences, we believe that high SUA is a risk factor for NAFLD. The most recently meta-analysis was published in 2017, which included 11 studies and 92,725 participants.[18] In the recent years, newer studies have been published. Nonetheless, the significant heterogeneity of findings was not explored in previous meta-analyses. Despite the relative measurements (odds ratio [ORs], risk ratio [RRs], and hazard ratio [HRs]) of the associations between SUA levels and NAFLD, no previous meta-analyses had assessed and measured the prevalence and incidence rates of NAFLD in people with hyperuricemia, which is more intuitive as absolute measurements. We thus conducted this updated meta-analysis to better understand the association between SUA levels and NAFLD and summarize the pooled prevalence and incidence rates of NAFLD in patients with hyperuricemia.

Method

Search Strategy

We identified studies that were published in the English language by reviewing the PubMed and Web of Science databases. Studies that qualified for this analysis were selected on June 2022 using the following keywords: "serum uric acid", "hyperuricemia", "NAFLD", "non-alcoholic steatohepatitis", or "hepatic steatosis" (Table S1). First, studies that appeared to be irrelevant were excluded after reading the titles and abstracts of the potential papers. Complete texts of relevant articles were retrieved, and their admissibility for inclusion was evaluated by reading the whole texts. For the purpose of obtaining the most comprehensive collection of published studies, we also searched for the chosen literature in other relevant meta-analyses. The Preferred Reporting Items for Systematic Review and Meta-analyses declaration was followed in the study selection procedure.[24] The protocol of this meta-analysis has been registered in PROSPERO (CRD42022358431).

Eligibility Criteria

The following are the inclusion requirements for the chosen studies: (1) Reported an observational study; (2) Patients with a distinct NAFLD diagnosis; (3) Reporting either RRs, HRs, or ORs with 95% CIs for NAFLD (or prevalence/incidence rate of NAFLD); (4) age ≥18. The following studies were not included: (1) Those with repetitive articles or duplicate information; (2) Articles about animal experiments; (3) Subjects that were pregnant women or children (4) Conference reports, letters, or case reports. The participants included in estimating the pooled incidence rates of NAFLD in hyperuricemic population had no NAFLD at the beginning of follow-up.

Data Extraction and Quality Assessment

The following information was collected from the articles: the first author's name; age; sex proportion; edition year; country of study; study design; duration of follow-up; number of participants and cases; diagnostic methods (NAFLD and hyperuricemia); OR (95% CI), HR (95% CI), or RR (95% CI). We used the Newcastle–Ottawa Scale (NOS) and the Agency for Healthcare Research and Quality (AHRQ) for quality evaluation.[25,26] The evaluation of cohort and case-control studies used the NOS scale. The evaluation of the cross-sectional studies was performed using the AHRQ scale.

Statistical Analysis

We used the OR (95% CI) as the effect measure for pooling the associations between SUA levels and NAFLD. A random effects model was used to analyze the pooled OR if $I^2 > 50\%$, as well as the fix effects model. In estimating the pooled prevalence and incidence rates of NAFLD in the patients with hyperuricemia, a random effects model was used according to the degree of heterogeneity. Subgroup analyses were further performed according to sex, age, study quality, sample size, study design, comparison, and country. Meta-regression analysis was carried out to identify sources of heterogeneity. Possible factors include study design, study quality, sample size, country, age, and so on. We used sensitivity analysis to identify the impact of each study on the overall results. The Begg's test was conducted to appraise publication bias. All statistical analyses were conducted using Stata version 17.0 software (Stata Corp., College Station, TX, United States). A two-sided P value < 0.05 was regarded as significantly.

Results

Study Selection

Figure 1 displays the study selection procedure. From the PubMed and Web of Science databases, 8234 premier studies were retrieved. We excluded 1139 articles that included duplicates and 6923 studies that did not achieve the inclusion requirements on the basis of reading the title and abstract screening. Through thorough reading of the texts, 50 articles[7–12,14–16,27–67] conformed to the inclusion requirements and were included in the meta-analysis, which involved 2,079,710 participants (719,013 NAFLD patients). Of them, 50 studies with 54 estimates were included in the meta-analysis of the association between SUA levels and NAFLD, and 10 studies with 10 estimates were included in estimating the pooled prevalence and incidence rates of NAFLD in hyperuricemic population.

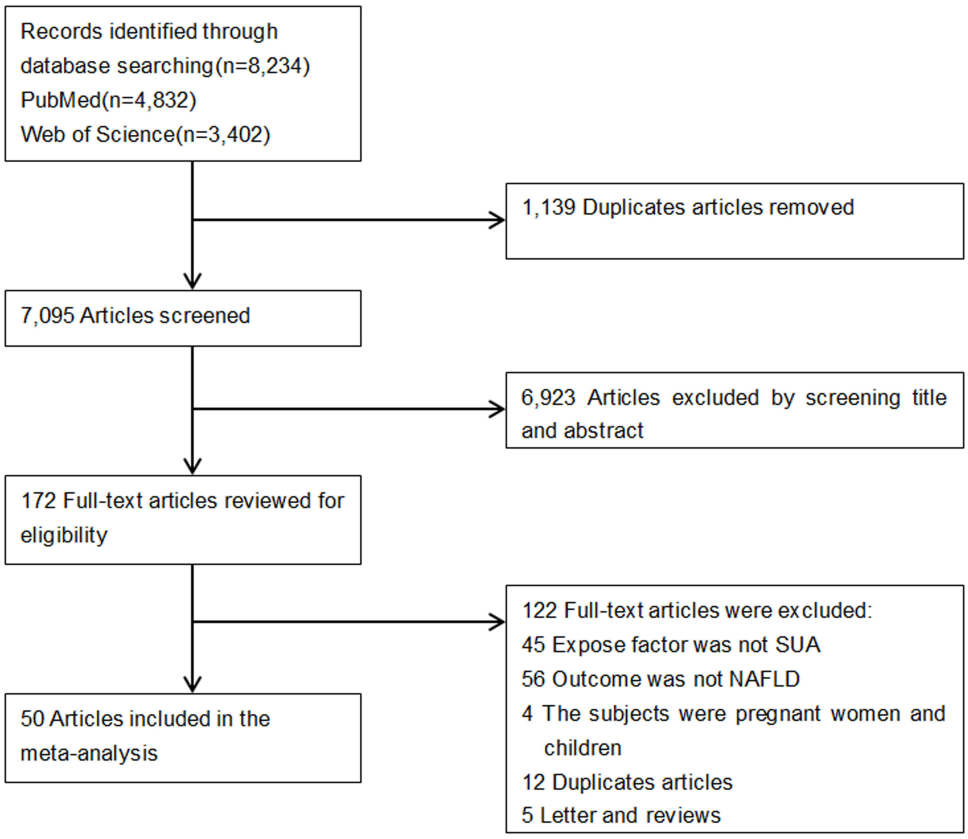

Figure 1 Flow chart of study selection in the meta-analysis.

Table 1 Summary of the Characteristics of Included Studies (Association Between SUA Levels and NAFLD)[a]

Characteristics	Overall
Number of studies	50
Sample size (median value) (N %)	
≤4149	24 (48.00)
>4149	26 (52.00)
Age (year) (N %)	
≤44	19 (38.00)
45–59	22 (44.00)
≥60	3 (6.00)
Not available	6 (12.00)
Follow-up (year) (N %)	
≤2	28 (56.00)
>2	18 (36.00)
Not available	4 (8.00)
Study design (N %)	
Cohort Study	13 (26.00)
Cross-Sectional Study	36 (72.00)
Case-Control Study	1 (2.00)
Comparison (N %)	
T3 vs T1	2 (4.00)
Q4 vs Q1	24 (48.00)
Q5 vs Q1	4 (8.00)
HUA (+) vs HUA (-)	22 (44.00)
Gout (+) vs Gout (-)	1 (2.00)
Elevated SUA vs normal SUA	1 (2.00)
Study quality (N %)	
<7	27 (54.00)
≥7	23 (46.00)
Country (N %)	
China	40 (80.00)
Korea	6 (12.00)
USA	2 (4.00)
Japan	1 (2.00)
Italy	1 (2.00)

Note: [a]A total of 50 studies were included, with 54 estimates.
Abbreviations: T3 vs T1, Highest vs lowest tertile; Q4 vs Q1, Highest vs lowest quartile; Q5 vs Q1, Highest vs lowest quintile; HUA, hyperuricemia; SUA, serum uric acid.

Study Characteristics

Table 1 summarizes the characteristics of the study. These studies were included in pooling the associations between NAFLD and SUA levels (detailed information is presented in Table S2). Among the included studies, there were 36 cross-sectional studies, 13 cohort studies, and 1 case-control study. Of them, 40 studies were from China, 6 studies were from Korea, 2 studies were from the USA, 1 study was from Japan, and 1 study was from Italy. Table S3 summarizes the characteristics of the studies included in the meta-analysis of the prevalence and incidence rates of NAFLD in hyperuricemic population. Among the included studies, there were 6 cross-sectional studies, and 4 cohort studies. Of them, 7 studies were from China, 1 study was from Korea, 1 study was from the USA, and 1 study was from Iran.

Tables S4 and S5 display the quality appraisal of the included studies according to the study designs. The mean point of cohort and case-control studies was 6.6 stars. The mean point of cross-sectional studies was 6.3 points. All studies were of medium- or high-quality.

Association Between SUA and NAFLD

Figure 2 shows the pooled OR (95% CI) of the association between SUA levels and NAFLD. The Forest plot showed that SUA was positively associated with NAFLD (OR: 1.88, 95% CI: 1.76–2.00). Table 2 shows the results of the subgroup analysis. All the studies were divided into three subgroups according to the types of study design. The ORs (95% CIs) in cross-sectional, cohort, and case-control studies were 1.91 (1.79–2.05), 1.73 (1.52–1.97), and 5.92 (3.39–10.33), respectively. We divided all the studies into five subgroups (China, Korea, USA, Japan, and Italy) according to the countries where the study was conducted. The ORs (95% CIs) in China, Korea, USA, Japan, and Italy were 1.96 (1.83–2.10), 1.57 (1.34–1.83), 1.46 (1.25–1.70), 2.00 (1.42–2.82), and 3.01 (1.40–6.48), respectively. Based on the average or median age of the study population, included studies were divided into three subgroups: young people (≤ 44 years), middle-aged people (45–59 years), or elderly people (≥ 60 years). The ORs (95% CIs) in young people, middle-aged people, and elderly people were 1.76 (1.55–2.00), 1.96 (1.77–2.17), and 3.42 (1.60–7.33), respectively. In the subgroup analysis according to sex, SUA levels was associated with NAFLD in both males and females, the ORs (95% CIs) were 1.76 (1.53–2.01) and 2.09 (1.77–2.47), respectively. All the studies were divided into two subgroups: ≤ 4149 participants (OR: 2.17, 95% CI: 1.91–2.47) or > 4149 participants (OR: 1.77, 95% CI: 1.64–1.91) based on the median sample size. The ORs (95% CIs) according to the classifications of SUA levels were as follows: Q4 vs Q1 1.95 (1.76–2.17), HUA (+) vs HUA (-) 1.73 (1.58–1.90), Q5 vs Q1 2.50 (1.57–3.99), T3 vs T1 2.26 (1.32–3.89), Gout (+) vs Gout (-) 1.42 (1.26–1.61), or

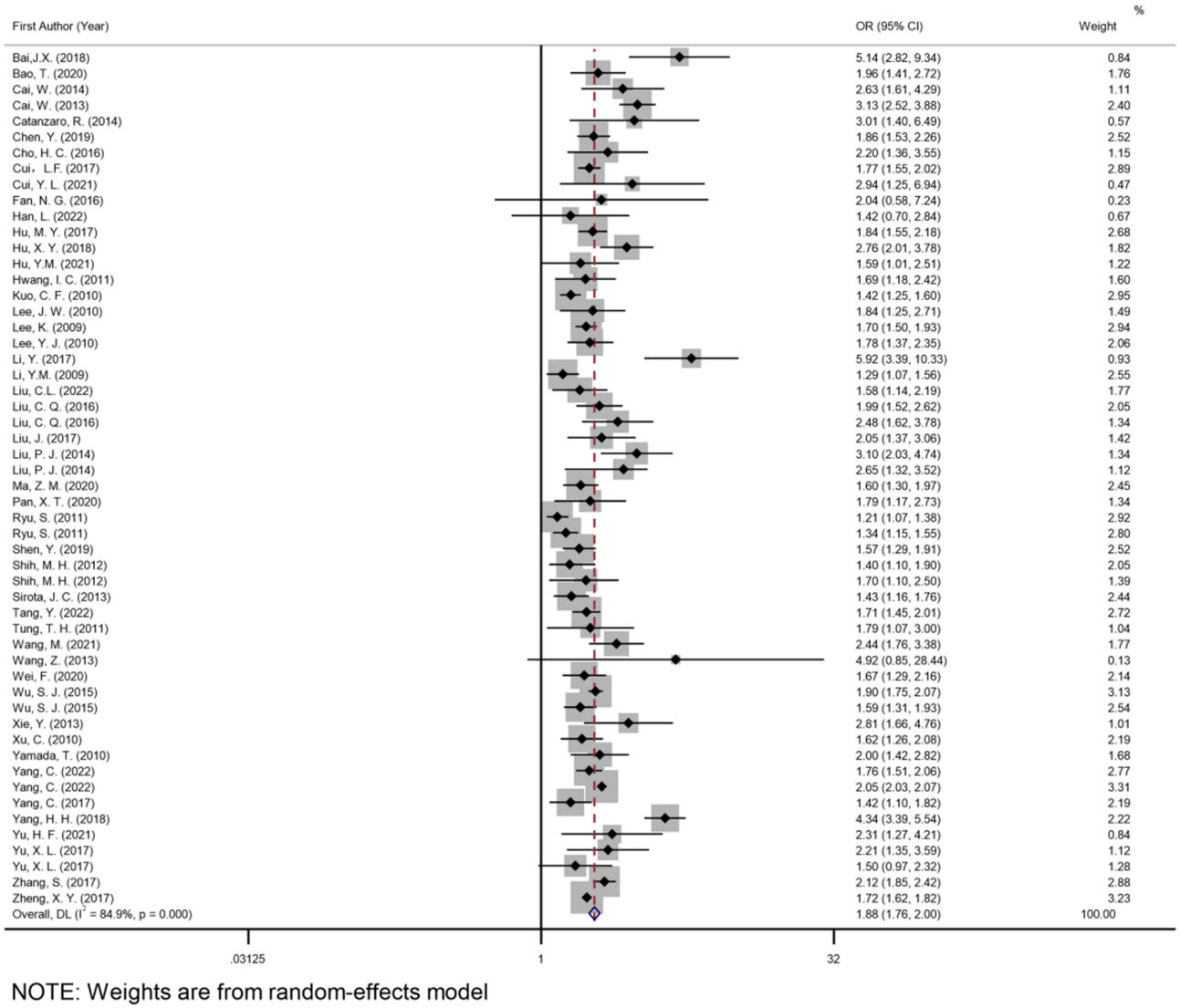

Figure 2 Overall pooled OR of association between SUA and NAFLD.

Table 2 Subgroup Analysis for Articles Included in the Meta-Analysis of Associations Between SUA Levels and NAFLD

Subgroup Analysis	Number of Estimates	OR (95% CI)	P value	I^2 (%)
Study design				
Cohort Study	14	1.73 (1.52–1.97)	<0.001	77.10%
Cross-sectional Study	39	1.91 (1.79–2.05)	<0.001	81.20%
Case-control Study	1	5.92 (3.39–10.33)	–	–
Sex				
Male	14	1.76 (1.53–2.01)	<0.001	77.60%
Female	14	2.09 (1.77–2.47)	<0.001	68.00%
Study quality				
<7	28	1.97 (1.82–2.15)	<0.001	68.10%
≥7	26	1.79 (1.61–1.99)	<0.001	89.10%
Sample size (median value)				
≤4149	26	2.17 (1.91–2.47)	<0.001	55.50%
>4149	28	1.77 (1.64–1.91)	<0.001	90.80%
Comparison				
Q4 vs Q1	24	1.95 (1.76–2.17)	<0.001	69.50%
HUA (+) vs HUA (-)	22	1.73 (1.58–1.90)	<0.001	87.50%
Q5 vs Q1	4	2.50 (1.57–3.99)	<0.001	91.90%
T3 vs T1	2	2.26 (1.32–3.89)	0.860	0.00%
Gout (+) vs Gout (-)	1	1.42 (1.26–1.61)	–	–
Elevated SUA vs Normal SUA	1	2.12 (1.85–2.42)	–	–
Age[a]				
≤44	19	1.76 (1.55–2.00)	<0.001	83.10%
45–59	22	1.96 (1.77–2.17)	<0.001	65.20%
≥60	3	3.42 (1.60–7.33)	<0.001	94.20%
Country				
China	42	1.96 (1.83–2.10)	<0.001	82.40%
Korea	7	1.57 (1.34–1.83)	0.001	73.00%
USA	3	1.46 (1.25–1.70)	0.721	0.00%
Japan	1	2.00 (1.42–2.82)	-	-
Italy	1	3.01 (1.40–6.48)	-	-

Note: [a]There are 10 estimates that do not provide age of subjects.
Abbreviations: T3 vs T1, Highest vs lowest tertile; Q4 vs Q1, Highest vs lowest quartile; Q5 vs Q1, Highest vs lowest quintile; HUA, hyperuricemia; SUA, serum uric acid; CI, confidence interval.

elevated SUA vs normal SUA 2.12 (1.85–2.42). All studies were divided into two subgroups based on the quality score of the included literature: < 7 (OR: 1.97, 95% CI: 1.82–2.15) or ≥ 7 (OR: 1.79, 95% CI: 1.61–1.99). Sensitivity analysis showed that there was no significant change in the overall results after excluding each study in sequence. The Begg's test suggested that there was no obvious publication bias ($P = 0.068$). The funnel plot is shown in Figure S1.

Meta-Regression Analysis

Because of the obvious heterogeneity ($I^2 = 84.9\%$) in the meta-analysis, a meta-regression analysis was conducted to identify the possible sources of this heterogeneity (Table 3). It was found that the study design ($P < 0.001$, study quality ($P < 0.001$), sample size ($P < 0.001$), comparison ($P = 0.004$), country ($P = 0.027$) and age ($P < 0.001$) had significant effects on the meta-analysis, which could possibly be the source of heterogeneity.

Prevalence and Incidence Rates of NAFLD in the Patients with Hyperuricemia

As shown in Figure 3, the pooled overall prevalence of NAFLD in hyperuricemic population was estimated to be 65% (95% CI: 57–73%). As shown in Figure 3, the pooled overall incidence of NAFLD in patients with hyperuricemia was estimated to be 31% (95% CI: 20–41%).

Table 3 Results of Meta-Regression Analysis

Variable	*Coef*	SE	t	P
Study design	5.920	2.163	4.87	<0.001
Study quality	2.959	0.686	4.68	<0.001
Sample size	2.171	0.145	11.57	<0.001
Comparison	2.115	0.528	3.00	0.004
Country	2.000	0.606	2.29	0.027
Age	1.852	0.131	8.70	<0.001

Abbreviations: SE, Standard error; *Coef*, coefficient.

Discussion

This meta-analysis included 50 studies, with 54 estimates, to identify the association between SUA levels and NAFLD. The study found that categorizing populations according to their SUA levels reveal that the group with the highest SUA level is about twice as likely to develop NAFLD compared to the group with the lowest SUA level. In all subgroups, SUA levels were positively associated with NAFLD. The prevalence and incidence rates of NAFLD in hyperuricemic population were 65% and 31%, respectively.

In the previous meta-analyses, two studies explored the associations between hyperuricemia and NAFLD;[19,22] three studies explored the associations between levels of SUA and NAFLD;[18,21,23] and one study combined the weighted mean difference of SUA concentration between patients with NAFLD and the control group.[20] All previous meta-analyses showed a positive association between SUA levels and NAFLD. Our results were the same as those from the published meta-analyses, showing a positive association between SUA levels and NAFLD. However, previous meta-analyses[18–23] have simply displayed the comparison between pooled ORs of the highest SUA level group and the lowest SUA level group. Subgroups were divided according to different SUA comparison methods. The high heterogeneity was also not

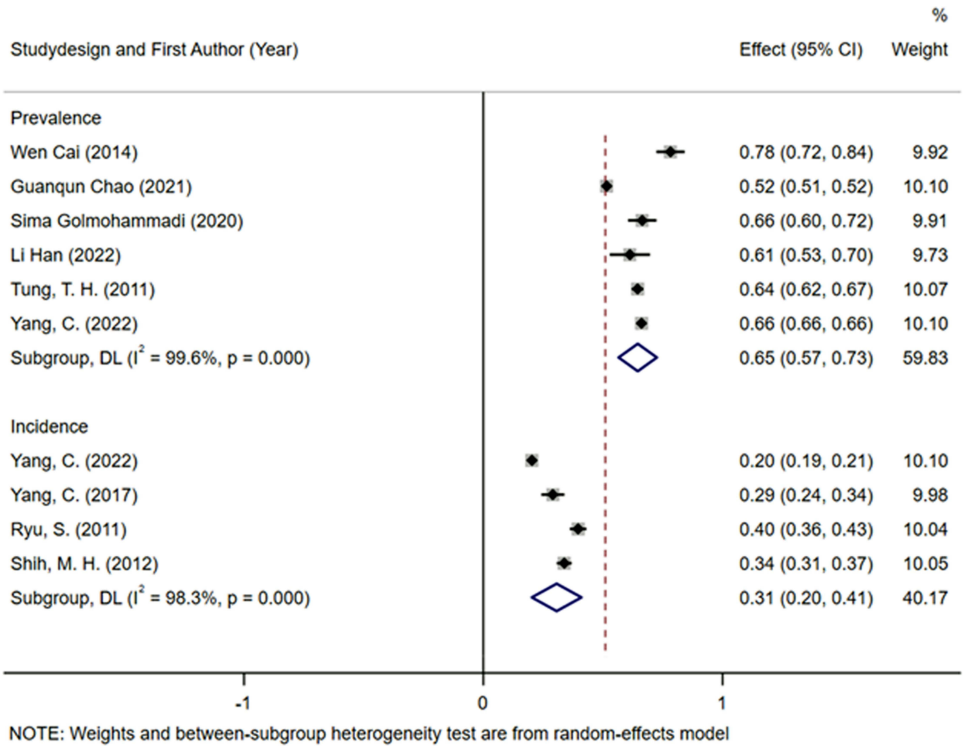

Figure 3 Prevalence and incidence rate of NAFLD in patients with hyperuricemia.

explored in previous meta-analyses. Therefore, this meta-analysis was performed with the renewed data. Meta-regression was used to explore the high heterogeneity.

Subgroup analyses of study designs, sex, study quality, age, and country suggested consistent results to the main results. Our results indicated that the associations between SUA levels and NAFLD were statistically significant in both males and females. However, the pooled OR was higher in females than in males, which is also supported by previous meta-analyses.[18,23] The cause of this result is unclear, but the difference in lifestyles and SUA production in the two sexes are considered as potential mechanisms.[16,57] Moreover, influenced by estrogen, the SUA levels of men and women are different, which can possibly affect the relationship between SUA levels and NAFLD. Compared with middle-aged and young people, the combined ORs of NAFLD in relation to SUA levels is higher in the elderly. This suggests that the association between SUA and NAFLD may be stronger in the elderly. Subgroup analysis based on the study design revealed that the same positive association was found in all study designs. Nevertheless, the association seems to be even stronger in case-control studies, which could be due to the fact that only one case-control study was included.

The specific mechanism by which higher SUA levels increase the risk of NAFLD remains unclear, but there are several possible explanations. The increase of SUA levels can lead to insulin resistance in various ways,[68,69] leading to an increase in cytotoxic substances and lipid peroxidation products in cells.[70] SUA mainly promotes liver fat synthesis and accumulation through mitochondrial oxidative stress. Mitochondrial oxidative stress, by inhibiting the activity of aconitase in the tricarboxylic acid cycle, leads to a decrease in citric acid metabolism, which generates an increase in fat deposition and synthesis in liver cells.[71] SUA can induce the expression of NLRP3 inflammatory complex, which is related to lipid accumulation in hepatocytes.[72] However, the temporal order of the correlation between NAFLD and SUA has been controversial. One cohort study showed that NAFLD significantly increased the risk of hyperuricemia, and this result was not observed in other cohorts.[73] This reverse causal pathway may be explained by a significant increase in the expression and activity of xanthine oxidase, a rate-limiting enzyme that catalyzes the production of uric acid, in NAFLD cells and mouse models, leading to a significant increase in serum uric acid levels.[73]

There are some advantages of this meta-analysis. Firstly, this meta-analysis updated new evidences that have emerged in recent years, with a larger sample size and more reliable results. Secondly, we performed subgroup analyses according to various classifications, especially the different comparison models. Finally, this meta-analysis assessed intuitive indicators, which are the prevalence and incidence rates of NAFLD in hyperuricemic population.

Some limitations also need to be noted. First, there is an obvious heterogeneity in this meta-analysis. Meta-regression analysis suggested that the study design, sample size, comparison, country, and age could be the sources of heterogeneity. Second, the criteria for SUA grouping were different for each included study. Third, a few included studies did not adjust confounding factors, like serum insulin, and metabolic syndrome. This will lead to biased estimation of the pooled ORs to some extent. Fourth, the inability to calculate incident density (person-years) stems from the fact that the vast majority of included articles fail to provide the necessary follow-up years.

In conclusion, these results indicate that there is a positive association between the increase of SUA levels and the presence of NAFLD. Moreover, the prevalence and incidence rates of NAFLD in hyperuricemic population were 65% and 31%, respectively.

Data Sharing Statement

All data generated or analysed during this study are included in this published article and its Supplementary Information File.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent

This paper did not involve patients enrolled by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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