Association between Serum Uric Acid and Non-Alcoholic Fatty Liver Disease: A Meta-Analysis

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ABSTRAK

Latar belakang: *perlemakan hati non-alkoholik (PHNA) berhubungan dengan berbagai penyakit metabolik. Penelitian terbaru menunjukkan peranan asam urat pada PHNA melalui proses oksidatif dan inflamasi. Laporan ini bertujuan mengevaluasi hubungan antara kadar asam urat serum dengan PHNA.* ***Metode:*** *tinjauan pustaka sistematik dilakukan dengan menggunakan Pubmed dan Cochrane library. Kualitas dari setiap studi dikaji dengan menggunakan the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). Semua data dianalisis dengan menggunakan REVIEW MANAGER 5.3.* ***Hasil:*** *didapatkan 11 studi dari Amerika dan Asia yang secara keseluruhan melibatkan 100.275 subjek. Pooled adjusted OR untuk NAFLD adalah 1,92 (95% CI: 1,66-2,23; p<0,00001). Analisis subgroup dilakukan berdasarkan desain studi, gender, subjek non diabetes, subjek non obese. Semua analisa subgroup menunjukkan adjusted OR yang bermakna secara statistic dan heterogenitas yang rendah hingga sedang pada mayoritas analisis subgrup. Dua studi menunjukkan hubungan antara kenaikan serum asam urat dengan tingkat keparahan PHNA. Bias publikasi tidak ditemukan pada laporan ini.* ***Kesimpulan:*** *laporan ini menunjukkan hubungan antara kadar serum asam urat dengan PHNA. Temuan ini dapat memberikan pandangan yang baru terhadap asam urat dalam praktik klinis. Peningkatan kadar serum asam urat dapat menjadi pemicu bagi dokter untuk melakukan skrining PHNA.*

Kata kunci: *asam urat, perlemakan hati non-alkoholik, meta-analisis.*

ABSTRACT

Background: *non-alcoholic fatty liver disease (NAFLD) is known to be associated with some metabolic disorders. Recent studies suggested the role of uric acid in NAFLD through oxidative stress and inflammatory process. This study is aimed to evaluate the association between serum uric acid and NAFLD.* ***Methods:*** *a systematic literature review was conducted using Pubmed and Cochrane library. The quality of all studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). All data were analyzed using REVIEW MANAGER 5.3.* ***Results:*** *eleven studies from America and Asia involving 100,275 subjects were included. The pooled adjusted OR for NAFLD was 1.92 (95% CI: 1.66-2.23; p<0.00001). Subgroup analyses were done based on study design, gender, non-diabetic subjects, non-obese subjects. All subgroup analyses showed statistically significant adjusted OR and most of which having low to moderate heterogeneity. Two studies revealed relationship between increased serum uric acid levels and severity of NAFLD. No publication bias was observed.* ***Conclusion:*** *our study demonstrated association between serum uric acid*

level and NAFLD. This finding brings a new insight of uric acid in clinical practice. Increased in serum uric acid levels might serve as a trigger for physician to screen for NAFLD.

Keywords: *uric acid, non-alcoholic fatty liver disease, meta-analysis.*

INTRODUCTION

Non alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases. The prevalence of NAFLD has doubled during last 20 years, ranging from 24% to 42% in Western countries and 5% to 30% in Asian countries, depending on the studied population.[1-5] NAFLD is diagnosed when daily alcohol consumption is ≤20 g/day in women and ≤30 g/day in men and exclude other causes of disease (autoimmune, viral, steatogenic drugs, etc).[4,5] It is pathologically characterized by excessive accumulation of triglyceride (more than 5%) in the hepatocytes, ranging from simple steatosis, non alcoholic steatohepatitis (NASH), fibrosis, and liver cirrhosis which may progress to hepatocellular carcinoma (HCC). Multiple "hits", having metabolic syndrome as a major role and inflammation process involving cytokines, adipokines, oxidative stress are hypothesized to explain the complex pathogenesis and progression of NAFLD.[3,4] NAFLD, widely considered as liver manifestation of metabolic syndrome, is associated with some clinical conditions. Obesity, hypertension, diabetes, dyslipidemia are the most reviewed factors associated with NAFLD.[4,6,7]

Uric acid, the final oxidation product of purine metabolism in humans, is allied with metabolic disorders. It is widely known that increased serum uric acid levels often co-exist with insulin resistance, atherosclerosis, hypertension, and obesity. Inflammation and oxidative stress are hypothesized to be the essential link in this relationship.[8,9] Moreover, there is an increasing of evidence that uric acid relates with NAFLD. Petta, et al.[10] showed hyperuricemia related with the severity of liver damage. Recently, many observational studies were done to explore the correlation between serum uric acid level and NAFLD.[9,11-25]

Therefore, we performed a meta-analysis study to evaluate the association between serum uric acid levels and NAFLD in adult.

METHODS

We conducted this study according to the meta-analysis PRISMA guideline (see PRISMA checklist).[26] We did systematic literature search using Cochrane and PubMed database (up to December 2015). The following search terms were used for searching relevant literature with research subjects limited to humans and adult:"uric acid" OR"serum uric acid" OR "hyperuricemia"AND "non-alcoholic fatty liver disease" OR "NAFLD" OR "non-alcoholic steatohepatitis" OR "NASH" OR "fatty liver" OR "liver steatosis" AND "observational study" OR "cross sectional" OR "prospective study" OR "retrospective study". Additional manual search was performed to look for additional relevant studies. Article selection and assessment were done by reviewers. We contacted the correspondence authors via email to obtain the required information when relevant information was not available in the published article.

Eligibility Criteria

The inclusion criteria were: (i) published observational studies with large sample size (more than 1000 subjects); (ii) study providing SUA and NAFLD risk factors; (iii) the outcome was NAFLD; (iv) the diagnostic criteria of outcome was clearly defined; (v) study had adjusted odds ratio (OR) with 95% confidence interval (CI) for NAFLD risk comparing the highest to lowest SUA. For studies with data published more than once or using the same subjects, only the article with larger number of subjects and adequate study strategy was chosen.

Data Extraction

Data were extracted independently by authors from original studies as follows: author's name, publication year; origin country, study design, participant characteristics (total number, gender, and age); category of SUA levels, NAFLD definition, incidence or prevalence of NAFLD, adjusted OR with 95% CI.

Quality Assessment

We assessed the quality of each selected study by scoring 22-item Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). The quality levels then were graded as good, fair, and poor. Only studies with good quality were included in our final analysis review. Discrepancies and disagreements were resolved by consensus.

Statistical Analysis

We used the fully adjusted OR with 95% CI and pooled it. The Mantel-Haenszel method was used to weight the studies included. A fixed-effect model approach was use if there was no heterogeneity; otherwise, a random-effect model was used. Heterogeneity was assessed using I^2. Negative value of I^2 was put equal to 0. I^2 values ranged from 0% (no observed heterogeneity) to 100%, and interpreted according to Cochrane Consumers and Communication Review Group.

For subgroup analyses, we grouped the studies based on study design, gender, non-diabetic subjects, non-obese subjects and pooled the fully adjusted OR with 95% CI. Publication bias was assessed by funnel plot. Statistical analysis was performed using Review Manager 5.3.

RESULTS

Our initial search yielded 53 studies. After the final screening, 11 studies met our criteria.[9,14-17,19-23,25] Within the 11 studies, one study by Wu, et. al. consisted of 2 sub studies with different subjects, place, and study designs (cross-sectional and longitudinal study). We further decided to include only the longitudinal sub study due to inaccurate data reporting in the cross-sectional sub study.[9] The total number of subjects in the included studies was 100,725. The flowchart showed the process of studies selection (**Figure 1**).

Study Characteristics

The studies were published between 2009 and 2015, and the characteristics of which are summarized in **Table 1**. Studies were done in various countries, including China (n=4)[9,15,16,21], Korea (n=4)[14,19,21,22], Japan (n=1)[19], India (n=1)[25],

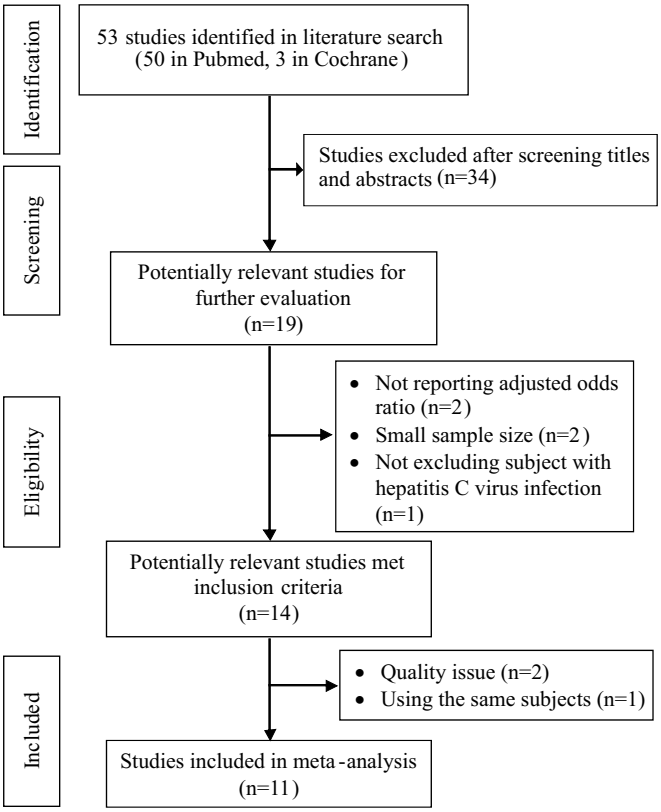

Figure 1. Flow chart of study selection process

Table 1. Study characteristic

No	Author	Year	Country	Design	Subjects	Age	Method for NAFLD diagnosis	Comparison	Prevalence/ Incidence NAFLD	Adjusted covariates	HR or OR (95% CI)
1	Hwang	2011	South Korea	Cross-sectional	M: 4632 F: 4387 Normal serum uric acid	> 20	USG	Highest tertilevs lowest tertile M: 6.4-7.2 mg/dl vs <5.1 mg/dl F: 4.6-5.7 mg/dl vs <3.5 mg/dl	23.5% (2124/9019)	Age Smoking status Regular exercise BMI BP FPG Total Cholesterol Triglyceride HDL ALT AST GGT	OR M: 1.46 (1.17-1.82) F: 2.13 (1.42-3.18)
2	Xu	2010	China, Ningbo	Prospective observational 3 years follow up	M: 4492 F: 2398	44.4 (12.7)	USG	Highest quintile vs lowest quintile M: ≥410 μmol/L vs ≤295 μmol/L F: ≥299 μmol/L vs ≤205 μmol/L	11.79% (813/6890)	Age Gender Alcohol BMI Waist circumference SBP DBP AST ALT GGT Triglyceride Total Cholesterol HDL LDL FPG Creatinine BUN	HR 1.62 (1.26-2.08: p 0.003)
3	Cai	2013	China	Cross sectional	4157 Uyghur 6448 Han	43.24 (12.91) 42.24 (12.91)	USG	Highest quintilevs lowest quintile M: ≥417 μmol/L vs ≤281.68 μmol/L F ≥357 μmol/L vs ≤194 μmol/L	36.69% (3906/10645)	Age Gender Hypertension Diabetes Dyslipidemia Obesity	OR Uyghur: 3.253 (2.304-4.594; p 0.00) Han: 3.053 (2.321-4.015; p 0.00)

Table 1. Study characteristic

No	Author	Year	Country	Design	Subjects	Age	Method for NAFLD diagnosis	Comparison	Prevalence/ Incidence NAFLD	Adjusted covariates	HR or OR (95% CI)
4	Yamada	2011	Japan	Retrospective	M: 1042 F: 3076	M: 51.4 (11.2) F: 51.82 (9.2)	USG	Highest vs lowest quartile M: >6.5 mg/dl vs ≤5.0 mg/dl F: ≥4.9 mg/dl vs <3.7 mg/dl	10.51% (433/4118)	Age BMI Increase in BMI for 5 years SBP Triglyceride FPG Smoking	OR M: 2.31 (1.34-4.01) F: 1.82 (1.17-2.84)
5	Sirota	2013	USA	Cross sectional	M: 4924 F: 5808 Non-diabetic subjects	20-74 41.81 (0.4)	USG Graded severity	Highest vs lowest quartile M: > 6.9 mg/dl vs ≤ 5.2 mg/dl F: > 5.3 mg/dl vs ≤ 3.7 mg/dl	48.85% (954/1953)	Age Race Hypertension Waist circumference Triglycerides HDL eGFR HOMA AST	OR M: 1.54 (1.11-2.13; p 0.009) F: 1.5 (1.15-1.95; p 0.003)
6	Lee	2010	South Korea	Retrospective cohort (5 years)	M: 2502 F: 2452 Non-diabetic subjects	40 (5.9)	USG	Highest vs lowest quartile 5.9-12.6 mg/dLvs 0.6-3.9 mg/dL	Incidence 13% (644/4954)	Age Gender FPG ALT Fasting insulin Bilirubin Alcohol Smoking status Regular exercise Educational background BMI	OR 1.84 (1.25-2.71; p 0.002)

Table 1. Study characteristic

No	Author	Year	Country	Design	Subjects	Age	Method for NAFLD diagnosis	Comparison	Prevalence/ Incidence NAFLD	Adjusted covariates	HR or OR (95% CI)
7	Ryu	2011	South Korea	Cohort 7 years	5741 (all men)	36.7 (4.9)	USG	Highest vs lowest quartile <5.2 mg/dl vs< ≥6.5 mg/dl	29.9% (1717/5741)	Age BMI Smoking Alcohol Exercise Total cholesterol HDL Triglycerides Glucose SBP Insulin hsCRP Metabolic syndrome	OR 1.34 (1.15-1.55; p 0.001)
8	Liang	2015	China	Cross sectional	21798	41.1 (18-90)	USG	Highest vs lowest quartile >363.6 µmol/L vs <223.7 µmol/L	23.35% (5091/21798)	Age Gender BMI SBP DBP Total Cholesterol HDL LDL Log Triglyceride Log ALT Log AST	OR 3.71 (2.83-4.88; p<0.001)
9	Wu	2015	China	Prospective (median: 23.6 months)	M: 4851 F: 6512	M: 43.5 (13.2) F: 39.1 (11.6)	USG	Highest vs lowest quartile M: ≥ 436 µmol/L vs ≤ 330 µmol/L F: ≥ 311 µmol/L vs ≤ 230 µmol/L	Pros: 8.99% (1022/11363)	Age BMI SBP FPG Albumin ALT AST BUN Creatinine Total Cholesterol Triglyceride HDL LDL	HR M: 1.249 (0.975-1.601) F: 2.355 (1.702-3.259)

Table 1. Study characteristic

No	Author	Year	Country	Design	Subjects	Age	Method for NAFLD diagnosis	Comparison	Prevalence/ Incidence NAFLD	Adjusted covariates	HR or OR (95% CI)
10	Lee	2009	Korea	Cross sectional	Non obese M: 4127 F: 4683 Obese M: 3094 F: 1717	Adult	USG	Hyperuricemiavs normal	11.9% (1045/8810)	Age BP HDL Triglycerides Glucose AST ALT GGT	OR Non obese M: 1.4 (1.1-1.7) F: 2.2 (1.1-4.2) Obese M: 1.8 (1.5-2.1) F: 2.3 (1.5-3.6)
11	Valiyakath	2015	India	Cross sectional	M: 1066 F: 818 Non diabetic, non dyslipidemia, non obese subjects	21-65	USG Graded severity	Highest vs lowest quartile M: >7 mg/dl vs ≤5 mg/dl F: >6 mg/dl vs ≤4 mg/dl	29.4% (554/1884)	Age	OR M: 2.07 (1.37-2.81) F: 1.99 (1.23-3.09)

M, male; F, female; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HDL, high density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HOMA, homeostasis model assessment; hsCRP, high sensitivity C- reactive protein; OR, odds ratio; HR, hazard ratio; CI, confidence interval

and the USA (n=1).[23] There were six cross sectional studies, three prospective studies, and two retrospective studies. Three studies had non-diabetic subjects only[20,22,23], one study separated the subjects into obese and non-obese[19], 1 study included non-obese, non-diabetic, non hypertensive, non dyslipidemia subjects only.[25]

Meta-analysis Result

The total event of NAFLD was 18,303. The pooled adjusted OR for NAFLD from 11 studies was 1.92 (95% CI: 1.66-2.23; p<0.00001) (**Figure 2**) We performed subgroup analysis based on study design, showing pooled adjusted OR was 1.55 (95% CI: 1.23-1.96; p<0.0002) in three prospective studies[9,15,22], 2.06 (95% CI: 1.70-2.51; p<0.00001) in six cross sectional studies[14,16,19,21,23,25], and 1.93 (95% CI: 1.49-2.49; p<0.00001) in two retrospective studies.[8,20] (**Figure 2**)

In subgroup analysis based on gender, the pooled adjusted OR was 1.52 (95% CI: 1.35-1.72; p<0.00001) in men[8,9,14,19,22,23,25] and 1.93 (95% CI: 1.67-2.23; p<0.00001) in women.[8,9,14,19,23,25] Moderate heterogeneity (I^2=47%) was found in men group but no heterogeneity (I^2=0%) in women group. (**Figure 3**) Four studies in non-diabetic subjects[20,22,23,25] and two studies in non-obese subjects[19,25] revealed statistically significant adjusted OR (OR 1.56; 95% CI: 1.34-1.82; p<0.0001 and OR 1.73; 95% CI: 1.36-2.2; p<0.0001, respectively) with no substantial heterogeneity (I^2=28% in both subgroup). (**Figure 4** and **Figure 5**)

For the overall 11 studies, no evidence of publication bias was observed in the funnel plot (**Figure 6**).

DISCUSSION

In our meta-analysis of 11 studies, we found a significant association between serum uric acid and NAFLD. The risk of NAFLD was increased almost 2-fold in the highest serum uric acid

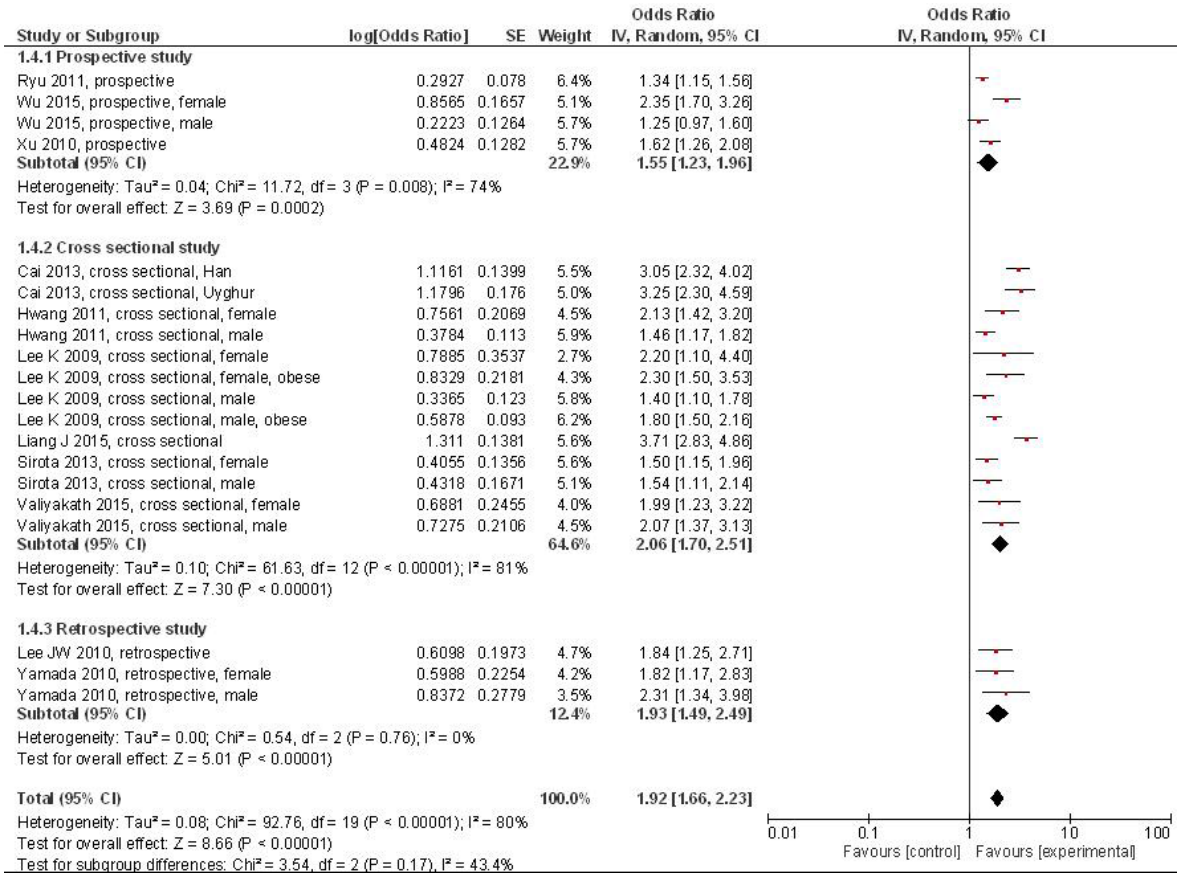

Figure 2. Forest plot describing association between serum uric acid and NAFLD in overall studies and subgroup analysis based on study method

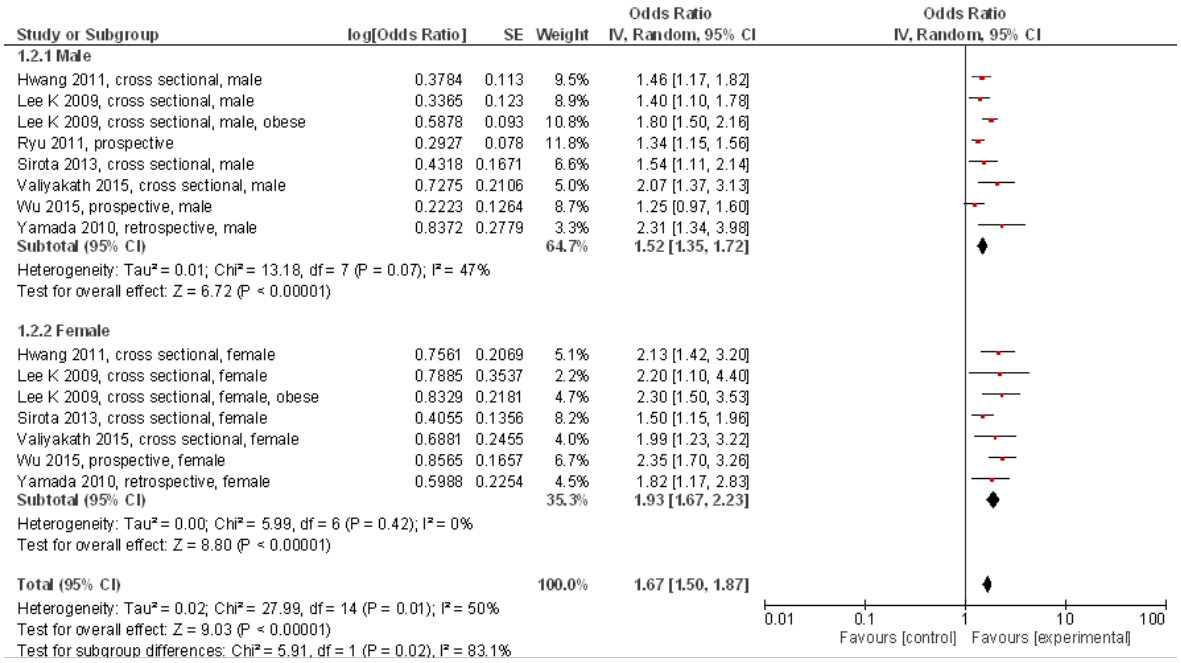

Figure 3. Forest plot describing association between serum uric acid and NAFLD based on gender

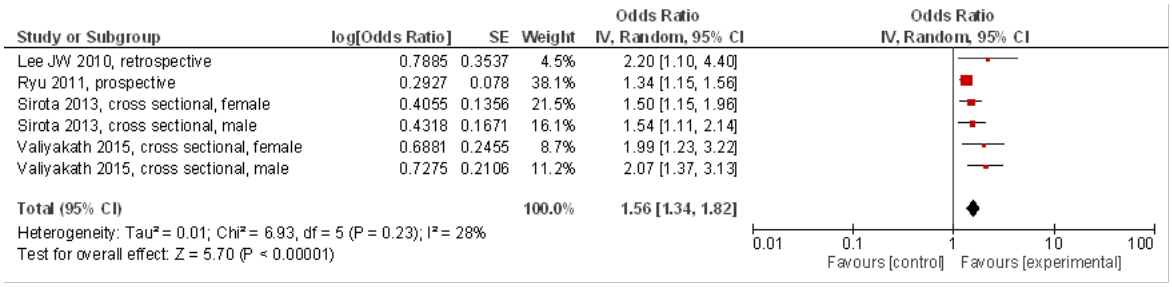

Figure 4. Forest plot describing association between serum uric acid and NAFLD in non-diabetic subjects

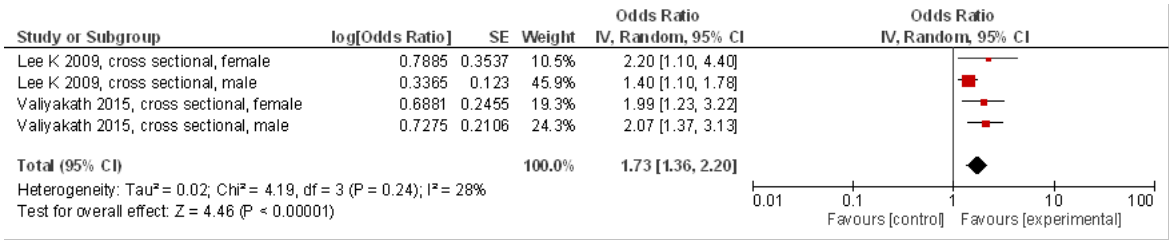

Figure 5. Forest plot describing association between serum uric acid and NAFLD in non-obese subjects

group compared to the lowest group. This finding was in line with previous meta-analysis study by Liu, showing a dose-response relationship of serum uric acid with incidence of NAFLD in two prospective studies.[27] Although the pathogenesis is still not fully understood, several mechanisms are hypothesized to explain the relationship. Uric acid stimulated inflammation through production of p38 mitogen-activated protein kinases (MAPK), cyclooxygenase-2 (COX-2), chemokinemonocyte chemoattractant protein-1. Moreover, serum uric acid within

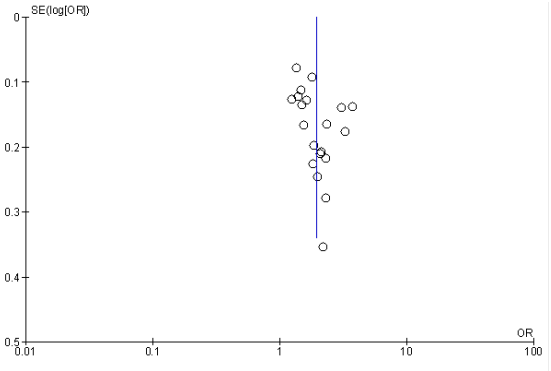

Figure 6. Funnel plot

the normal range correlated positively with interleukin-18 (IL-18), IL-6, and tumor necrosis factor-α (TNF-α). It also induced oxidative stress in adipocytes and vascular cells. Uric acid amplified the lipogenic effects of fructose by increasing ketohexokinase (KHK) expression which resulted in triglycerides accumulation in hepatocytes. The co-presence of insulin resistance in NAFLD might increase the serum uric acid through reduction of uric acid clearance in the renal proximal tubule.[17,28]

We did subgroup analyses to explore the association within the similar study design, gender and subject characteristics.Cross sectional studies showed significant association between serum uric acid and NAFLD. Longitudinal studies, intended to further investigate the causal relationship, also revealed significant association, with better value in heterogeneity. Men and women have different serum uric acid levels, influenced by the uricosuric effect of estrogens. Our study revealed that the association between serum uric acid and NAFLD were significant in both genders, with higher risk in women. The higher impact in women was in accordance with other studies observing the relationship between gender-specific hyperuricemia and the development of cardiovascular metabolic disorders.[8,29-31] Although it is still cannot be fully explained, the difference in sex hormones, gender-specific effects of uric acid production, life style are proposed to be the underlying mechanism.[9,30]

Some of the well known risk factors for NAFLD are diabetes and obesity.[3,7,32,33] Although there were adjustment for body mass index and blood glucose in the included studies, we performed two subgroup analyses evaluating studies using non-diabetic subjects and studies using non-obese subjects. Analyses of 4 studies in non-diabetic subjects using different approaches (retrospective, prospective, and cross-sectional) revealed a significant association with moderately low heterogeneity. Similar result was found in analyses of 2 studies in non-obese subjects. These, strengthen the relationship between uric acid and NAFLD regardless diabetes or obesity status.

In addition, 2 studies evaluated the relationship between serum uric acid levels and severity of hepatic steatosis by ultrasonography examination.[23,25] Both of the studies showed increasing severity of NAFLD in line with increased serum uric acid levels. This finding was in accordance with study by Lin, showing that liver fat content accumulation was associated with elevated serum uric acid.[34]

The large number of subjects from different countries included in the meta-analysis was the strength of our study. Other strength was we separately evaluated the association between serum uric acid levels and NAFLD in based on study design and subjects' characteristic. The significant association between serum uric acid levels and NAFLD as shown in our study, might bring a new insight in clinical practice as a physician. First, although the role was not totally clear (e.g. as marker or etiology), increased serum uric acid may bring the physician to screen for the risk of NAFLD. Second, there is a potential therapeutic role of xanthin oxidase inhibitor, such as allopurinol, in NAFLD. Inhibition of xanthin oxidase would lower KHK levels and amelioratethe lipogenic effects of fructose in the liver, as shown in animal study by Lanaspa.[28]

Several limitations in our study should be mentioned. First, almost all subjects were health check-up patients; therefore, selection bias might be present in the study since subjects participating in the study would be more health-conscious, having less severe disease than general population in community. Nonetheless, it would just underestimate the observed association between serum uric acid and

NAFLD. Secondly, there was no adjustment for dietary factors, such as meat and fructose intake which might influence serum uric acid levels and NAFLD. Thirdly, since alcohol intake data was taken based on self-report questionnaire, it can underestimate the exact amount of alcohol consumed. Fourthly, NAFLD was determined by ultrasonography examination in all included studies with no histologic confirmation of fatty liver. None of the studies performed either liver biopsy or liver fibroscan examination. Although liver ultrasonography is not the gold standard, it is the first-line imaging technique for NAFLD. Liver ultransonography is non-invasive, safe, has an acceptable accuracy, and able to evaluate the severity of fatty liver either qualitatively or semi-quantitatively.[39] Lastly, there is a need to consider the menstrual cycle phase in premenopausal women since serum uric acid levels may varies throughout the menstrual cycle.[40]

Further studies on community based subjects with prospective design are needed to demonstrate clearly the causal relationship between serum uric acid levels and NAFLD. Moreover, prospective studies using xanthine oxidase inhibitor as a potential treatment of NAFLD deserve should be conducted.

CONCLUSION

Our report showed an association between serum uric acid levels and NAFLD. This finding brings new insight into uric acid in clinical practice. Increase serum uric acid levels might serve as a trigger for physician to screen for NAFLD.

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