

# A combined association of serum uric acid, alanine aminotransferase and waist circumference with non-alcoholic fatty liver disease: a community-based study

Min Wang<sup>1,\*</sup>, Minxian Wang<sup>1,\*</sup>, Ru Zhang<sup>1</sup>, Liuxin Zhang<sup>2</sup>, Yajie Ding<sup>1</sup>, Zongzhe Tang<sup>1</sup>, Haozhi Fan<sup>3</sup>, Hongliang Wang<sup>4</sup>, Wei Zhang<sup>5</sup>, Yue Chen<sup>1</sup> and Jie Wang<sup>1</sup>

<sup>1</sup> School of Nursing, Nanjing Medical University, Nanjing, Jiangsu, China

<sup>2</sup> Affiliated Brain Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

<sup>3</sup> Department of Information, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

<sup>4</sup> Mofan West Road Community Health Service Center, Nanjing, Jiangsu, China

<sup>5</sup> Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

\* These authors contributed equally to this work.

## ABSTRACT

**Background:** Increasing evidence has supported that serum uric acid (SUA), alanine aminotransferase (ALT) and waist circumference (WC) are associated with the occurrence of non-alcoholic fatty liver disease (NAFLD). However, the combined role of these factors in early screening of NAFLD has not been investigated.

We aimed to delineate this role in a community-based population.

**Methods:** Binary logistic regression was used to explore the correlations of SUA, ALT and WC with NAFLD risk. The goodness of fit and discriminative ability of the model were evaluated by the Hosmer-Lemeshow test and area under the receiver operating characteristic curve (AUROC), respectively.

**Results:** Logistic regression analysis indicated that elevated SUA (adjusted odds ratio (OR) = 2.44, 95% confidence interval (CI) [1.76–3.38]), ALT (adjusted OR = 4.98, 95% CI [3.41–7.27]) and WC (adjusted OR = 3.22, 95% CI [2.01–5.16]) were facilitating factors for incident NAFLD after fully adjusted for related confounders. In addition, the risk of NAFLD followed linear trends with increasing levels of these three indicators (all  $P_{\text{trend}} < 0.001$ ). The risk assessment model consisting of SUA, ALT, WC and demographics showed useful discrimination by AUROC being 0.825 (95% CI [0.811–0.838]) and good performance of calibration ( $P = 0.561$ ).

**Conclusions:** SUA, ALT and WC were all associated with NAFLD, independent of known risk factors. The simple model composed of these indicators showed good performance in the Chinese population, which may be applicable for appraisal of NAFLD risk in primary healthcare.

Submitted 15 November 2021

Accepted 7 February 2022

Published 4 March 2022

Corresponding author

Jie Wang, wangjienjmu@126.com

Academic editor

Jose Maria Moran-Garcia

Additional Information and  
Declarations can be found on  
page 11

DOI 10.7717/peerj.13022

© Copyright

2022 Wang et al.

Distributed under

Creative Commons CC-BY 4.0

OPEN ACCESS

**Subjects** Diabetes and Endocrinology, Epidemiology, Gastroenterology and Hepatology, Metabolic Sciences, Obesity

**Keywords** Non-alcoholic fatty liver disease (NAFLD), Risk assessment model, Serum uric acid (SUA), Alanine aminotransferase (ALT), Waist circumference (WC)

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a metabolic syndrome (MetS) manifested in the liver (*Buzzetti, Pinzani & Tsochatzis, 2016*), is pathophysiologically related to adipose tissue inflammation and insulin resistance (*Tilg, Adolph & Moschen, 2021*). It has been widely established that NAFLD has bidirectional association with the components of MetS (obesity, hyperglycemia, hypertension and dyslipidemia), which leads to increased risks of liver-related and extrahepatic complications such as cirrhosis, diabetes (*Hamed et al., 2019*), cerebral stroke (*Abdeldyem et al., 2017*), cancer (*Wang et al., 2020*) and cardiovascular disease (*Targher, Byrne & Tilg, 2020*). NAFLD is currently acknowledged as the leading cause of liver disease worldwide (*Younossi et al., 2016*), and the burden of NAFLD in China has increased considerably due to the changed lifestyle and insufficient diagnostic tools in the past two decades (*Abo-Amer et al., 2020; Zhou et al., 2020*). Although liver biopsy is the gold standard for diagnosis of NAFLD, it is costly and impractical for large-scale population (*Chalasan et al., 2018; Rinella, 2015*). Thus, readily measurable biochemical and anthropometric markers of NAFLD should be pinpointed, with the purpose of early identification of this disease.

In term of biochemical parameter, serum uric acid (SUA), as the end product of purine metabolism, has been reported to lead endothelial dysfunction, release pro-inflammatory cytokines, induce insulin resistance and hepatocyte fat accumulation (*Sun et al., 2016; Zhu et al., 2014*). Large epidemiological studies have demonstrated that increased SUA was correlated with NAFLD risk (*Sirota et al., 2013; Wei et al., 2020; Zheng et al., 2017*).

In addition, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are common liver enzymes, which could be released into serum if hepatocellular injury or apoptosis occurred. However, ALT is a more liver-specific marker than AST since that AST is widely distributed not only in hepatocytes, but also in skeletal muscle, heart, kidney, and so on (*Collier & Bassendine, 2002*). In fact, ALT has been globally regarded as a reliable biomarker of the liver disease. Studies have suggested that even a mild or no serum ALT elevation can also indicate the existence of liver damage (*Fracanzani et al., 2008; Kang et al., 2018; Omagari et al., 2011*).

A simple anthropometric parameter, waist circumference (WC) is widely used as an indicator for central obesity (including subcutaneous and visceral fat). Evidence has indicated that NAFLD is primarily caused by visceral fat deposition (*Abdelmoemen et al., 2019; Casagrande et al., 2020*). Although having limited precision in differentiating subcutaneous fat from visceral fat, WC has been proven highly correlated with visceral fat (*Al-Radaideh et al., 2019; Eloi et al., 2017*). Indeed, insulin resistance and metabolic disorders, the important factors in the pathogenesis of NAFLD, may be partially indicated by elevated WC (*Jiang et al., 2019*).

In spite of the evidence that SUA, ALT and WC all contribute to the onset of NAFLD, using the combination of these three indicators to assess NAFLD risk has rarely been discussed. Therefore, we conducted the community-based study to verify the association of SUA, ALT and WC with NAFLD occurrence, and evaluate the joint validity of them for NAFLD risk assessment.

## MATERIALS AND METHODS

### Design and participants

Participants who underwent physical check-ups in a community in Nanjing (Jiangsu, China) were enrolled in this cross-sectional study from July to September 2018.

The exclusion criteria of our study were as follows: (1) younger than 18 years old; (2) with other liver diseases, such as viral hepatitis, liver cancer and cirrhosis; (3) excessive alcohol intake ( $\geq 30$  g/d for males and  $\geq 20$  g/d for females); (4) with history of liver transplant in the past year, multi-system illness or malignancy; (5) history of psychiatric illness.

Diagnosis of NAFLD followed the “*Guideline of prevention and treatment for nonalcoholic fatty liver disease: a 2018 update*” (*National Workshop on Fatty Liver & Alcoholic Liver Disease CSoH, Chinese Medical Association & Fatty Liver Expert Committee CMDA, 2018*), including evidence of hepatic steatosis in images or histology and absence of secondary causes of liver fat accumulation (e.g., heavy alcohol intake, medication and autoimmune hepatitis). With the prevalence of NAFLD in Asia estimated as 30% (*Li et al., 2019; Younossi et al., 2018; Younossi et al., 2019*), confidence level  $1-\alpha$  set at 0.95 and two-sided confidence interval width set at 0.06, we obtained a minimal sample size of 928 by NCSS-PASS (version 15.0, Dawson edition; Kaysville, UT, USA). In fact, a total of 3,311 participants were recruited in our study, fulfilling the required sample size. To confirm the validity of the study, *post-hoc* power analyses were performed by G\*power (version 3.1.9.6), showing that the statistical power of the study exceeded 99%. The study protocol was approved by the Institutional Ethics Review Committee of the Nanjing Medical University (Nanjing, China) with approval number (2018) 596, and all participants provided written informed consents.

### Data collection

Questionnaires and electronic medical record system were used to collect demographic data and medical history. Trained physicians were responsible for the measurement of height, weight, WC and blood pressure. Blood pressure was measured twice with a 5-min interval by a mercury sphygmomanometer and a stethoscope, then averaged for analysis. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters ( $\text{kg}/\text{m}^2$ ). Abdominal ultrasonography was operated for imaging diagnosis of NAFLD by technicians using a Logiq E9 ultrasound system (General Electric (GE) Healthcare, Milwaukee, WI, USA). Moreover, venous blood samples were collected from all participants after an overnight fast for biochemical assessments of ALT, AST, SUA, fasting plasma glucose (FPG), triacylglycerol (TG) and total cholesterol (TC). All the laboratory parameters were analyzed by an automatic biochemical analyzer (Mindray BC-860; Mindray, Shenzhen, China).

### Statistical analysis

Continuous variables were presented as mean  $\pm$  standard deviation (normal distribution) or median and interquartile range (non-normal distribution); categorical variables were presented as frequencies. Baseline characteristics of subjects between NAFLD and non-NAFLD groups were compared by Chi-square test, independent-samples T test or

Mann-Whitney U test, wherever appropriate. To facilitate the interpretation of associations between SUA, ALT and WC levels with NAFLD risk and screen factors influencing them, all participants were categorized according to SUA quartiles (Q1,  $\leq 280$   $\mu\text{mol/L}$ ; Q2, 281–337  $\mu\text{mol/L}$ ; Q3, 338–394  $\mu\text{mol/L}$ ; Q4,  $\geq 395$   $\mu\text{mol/L}$ ), ALT quartiles (Q1,  $\leq 13$  IU/L; Q2, 14–19 IU/L; Q3, 20–29 IU/L; Q4,  $\geq 30$  IU/L) and WC quartiles (Q1,  $\leq 75$  cm; Q2, 76–82 cm; Q3, 83–89 cm; Q4,  $\geq 90$  cm) for further analysis.

The comparisons among quartile groups were conducted by Chi-square test, univariate analysis of variance (ANOVA) or Welch's test. For differences in NAFLD prevalence among quartiles, the Chi-square linear trend test was used. Multivariate logistic regression was employed to investigate the correlations of SUA, ALT and WC with NAFLD risk, and screen predictors to build a model for NAFLD risk assessment. Moreover, the assumed linearity between logits of the dependent variable and the continuous predictors was assessed by Box-Tidwell Test (*Thompson, Xie & White, 2003*). Tolerance and variance inflation factor (VIF) were calculated by linear regression analysis and applied for collinearity diagnostics. Discrimination and calibration of the model were analyzed by the area under receiver operating characteristic curve (AUROC) and Hosmer–Lemeshow test, respectively. All the statistical analyses were based on the software SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 19.1 (MedCalc Inc., Ostend, Belgium). Two-tailed  $P$  values less than 0.05 were considered statistically significant.

## RESULTS

### Baseline characteristics of subjects

Among the 3,311 subjects included in our study, 1,233 (37.2%) had NAFLD. As shown in [Table 1](#), participants with NAFLD were more likely to be male, older and showed significant differences in BMI, WC, SBP, DBP, ALT, AST, SUA, FPG, TG, TC compared with non-NAFLD subjects (all  $P < 0.001$ ).

### Comparison of characteristics among different SUA, ALT and WC groups respectively

After separated by SUA quartiles, significant differences were observed in the distribution of gender, BMI, WC, SBP, DBP, ALT, AST, TG, TC (all  $P < 0.001$ ) and age ( $P = 0.030$ ) among the four groups, but not found in FPG ( $P = 0.197$ ) ([Table 2](#)). As shown in [Table 3](#), variations across ALT quartile groups in terms of gender, age, BMI, WC, SBP, DBP, AST, SUA, TG, TC (all  $P < 0.001$ ) and FPG ( $P = 0.001$ ) were statistically significant. Similarly, comparison among the four groups of WC quartiles showed remarkable differences in gender, age, BMI, SBP, DBP, ALT, AST, SUA, FPG, TG, TC (all  $P < 0.001$ ) ([Table 4](#)). Moreover, we compared characteristics between high level and normal level groups divided according to the clinical cutoff points for SUA, ALT and WC, whose results further strengthened the reliability of the results above ([Tables S1–S3](#)).

As illustrated in [Fig.1](#), the prevalence of NAFLD increased progressively with increasing SUA quartiles (15.7% in Q1, 31.2% in Q2, 42.4% in Q3 and 59.8% in Q4;  $P_{\text{trend}} < 0.001$ ), ALT

**Table 1** Baseline characteristics of subjects with and without NAFLD.

Variables	non-NAFLD (n = 2,078)	NAFLD (n = 1,233)	t/ $\chi^2$ /Z	P
Gender (male), n (%)	1,379 (66.4)	1,065 (86.4)	160.348	<0.001 <sup>a</sup>
Age (years)	38.92 ± 9.31	42.04 ± 9.29	-9.331	<0.001 <sup>b</sup>
BMI (kg/m <sup>2</sup> )	22.25 ± 2.45	25.43 ± 2.56	-35.576	<0.001 <sup>b</sup>
WC (cm)	79.35 ± 8.44	89.03 ± 7.95	-32.705	<0.001 <sup>b</sup>
SBP (mmHg)	122.28 ± 14.11	130.99 ± 15.48	-16.172	<0.001 <sup>b</sup>
DBP (mmHg)	73.50 ± 9.51	79.75 ± 10.77	-16.851	<0.001 <sup>b</sup>
ALT (IU/L) <sup>†</sup>	16.0 (12.0, 23.0)	27.0 (19.0, 39.0)	-23.962	<0.001 <sup>c</sup>
AST (IU/L)	19.22 ± 7.24	22.83 ± 8.51	-12.453	<0.001 <sup>b</sup>
SUA (μmol/L)	317.83 ± 77.93	378.18 ± 80.78	-21.251	<0.001 <sup>b</sup>
FPG (mmol/L)	3.44 ± 1.43	4.01 ± 1.84	-9.290	<0.001 <sup>b</sup>
TG (mmol/L) <sup>†</sup>	0.97 (0.74, 1.29)	1.65 (1.19, 2.25)	-27.637	<0.001 <sup>c</sup>
TC (mmol/L)	4.48 ± 0.80	4.78 ± 0.90	-9.917	<0.001 <sup>b</sup>

**Notes:**

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SUA, serum uric acid; FPG, fasting plasma glucose; TG, triacylglycerol; TC, total cholesterol.

<sup>†</sup> Non-normally distributed variables.

<sup>a</sup> Chi square test.

<sup>b</sup> Independent-samples T-test.

<sup>c</sup> Mann-Whitney U-test.

Results in bold type indicate statistically significant.

**Table 2** Comparison of characteristics according to SUA quartiles.

Variables	Q1 (n = 829) SUA ≤ 280	Q2 (n = 827) 281 ≤ SUA ≤ 337	Q3 (n = 830) 338 ≤ SUA ≤ 394	Q4 (n = 825) SUA ≥ 395	P
Gender (male), n (%)	250 (30.2)	618 (74.7)	768 (92.5)	808 (97.9)	<0.001 <sup>a</sup>
Age (years) <sup>§</sup>	40.55 ± 8.36	40.57 ± 9.51	39.50 ± 9.83	39.69 ± 9.89	0.030 <sup>c</sup>
BMI (kg/m <sup>2</sup> )	21.80 ± 2.62	22.98 ± 2.69	23.93 ± 2.78	25.03 ± 2.64	<0.001 <sup>b</sup>
WC (cm) <sup>§</sup>	76.19 ± 8.61	81.83 ± 8.48	85.48 ± 8.35	88.52 ± 7.77	<0.001 <sup>c</sup>
SBP (mmHg)	119.35 ± 14.90	124.63 ± 14.54	127.60 ± 14.74	130.52 ± 14.47	<0.001 <sup>b</sup>
DBP (mmHg)	72.01 ± 9.83	75.46 ± 10.32	76.58 ± 9.76	79.26 ± 10.56	<0.001 <sup>b</sup>
ALT (IU/L) <sup>†§</sup>	14.0 (11.0, 19.0)	18.0 (13.0, 25.0)	22.0 (16.0, 32.25)	27.0 (18.0, 40.0)	<0.001 <sup>c</sup>
AST (IU/L) <sup>§</sup>	17.98 ± 7.46	19.41 ± 6.95	21.19 ± 7.11	23.68 ± 8.89	<0.001 <sup>c</sup>
FPG (mmol/L)	3.59 ± 1.65	3.75 ± 1.67	3.62 ± 1.61	3.64 ± 1.54	0.197 <sup>b</sup>
TG (mmol/L) <sup>†§</sup>	0.91 (0.67, 1.22)	1.07 (0.81, 1.46)	1.24 (0.90, 1.78)	1.57 (1.10, 2.24)	<0.001 <sup>c</sup>
TC (mmol/L)	4.47 ± 0.83	4.53 ± 0.85	4.62 ± 0.80	4.76 ± 0.88	<0.001 <sup>b</sup>

**Notes:**

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; TG, triacylglycerol; TC, total cholesterol.

<sup>†</sup> Non-normally distributed variables after lg transformation.

<sup>§</sup> Variables with heteroscedastic variances among the four groups.

<sup>a</sup> Chi square test.

<sup>b</sup> Univariate analysis of variance (ANOVA).

<sup>c</sup> Welch's test.

Results in bold type indicate statistically significant.

quartiles (12.6% in Q1, 27.0% in Q2, 45.9% in Q3 and 64.5% in Q4;  $P_{\text{trend}} < 0.001$ ), and WC quartiles (6.9% in Q1, 23.8% in Q2, 42.9% in Q3 and 71.3% in Q4;  $P_{\text{trend}} < 0.001$ ), respectively.

**Table 3** Comparison of characteristics according to ALT quartiles.

Variables	Q1 (n = 810) ALT ≤ 13	Q2 (n = 884) 14 ≤ ALT ≤ 19	Q3 (n = 809) 20 ≤ ALT ≤ 29	Q4 (n = 808) ALT ≥ 30	P
Gender (male), n (%)	344 (42.5)	663 (75.0)	692 (85.5)	745 (92.2)	<0.001 <sup>a</sup>
Age (years)	39.22 ± 9.00	40.90 ± 9.52	40.68 ± 9.42	39.44 ± 9.64	<0.001 <sup>b</sup>
BMI (kg/m <sup>2</sup> ) <sup>§</sup>	21.67 ± 2.44	22.95 ± 2.64	23.97 ± 2.69	25.19 ± 2.75	<0.001 <sup>c</sup>
WC (cm)	76.22 ± 8.17	82.01 ± 8.43	85.00 ± 8.46	88.83 ± 8.28	<0.001 <sup>b</sup>
SBP (mmHg)	120.08 ± 14.46	124.17 ± 14.34	127.01 ± 15.20	130.96 ± 14.88	<0.001 <sup>b</sup>
DBP (mmHg) <sup>§</sup>	72.27 ± 9.41	74.85 ± 9.90	76.66 ± 10.75	79.62 ± 10.35	<0.001 <sup>c</sup>
AST (IU/L) <sup>§</sup>	15.23 ± 2.42	17.62 ± 2.88	20.52 ± 3.61	29.17 ± 10.85	<0.001 <sup>c</sup>
SUA (μmol/L)	291.06 ± 72.52	327.73 ± 78.07	356.02 ± 75.27	387.70 ± 79.80	<0.001 <sup>b</sup>
FPG (mmol/L) <sup>§</sup>	3.48 ± 1.48	3.62 ± 1.50	3.73 ± 1.59	3.77 ± 1.88	0.001 <sup>c</sup>
TG (mmol/L) <sup>†§</sup>	0.88 (0.67, 1.16)	1.07 (0.80, 1.44)	1.27 (0.92, 1.92)	1.59 (1.13, 2.25)	<0.001 <sup>c</sup>
TC (mmol/L)	4.41 ± 0.81	4.54 ± 0.80	4.60 ± 0.82	4.83 ± 0.92	<0.001 <sup>b</sup>

**Notes:**

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; SUA, serum uric acid; FPG, fasting plasma glucose; TG, triacylglycerol; TC total cholesterol.

<sup>†</sup> Non-normally distributed variables after lg transformation.

<sup>§</sup> Variables with heteroscedastic variances among the four groups.

<sup>a</sup> Chi square test.

<sup>b</sup> Univariate analysis of variance (ANOVA).

<sup>c</sup> Welch's test.

Results in bold type indicate statistically significant.

**Table 4** Comparison of characteristics according to WC quartiles.

Variables	Q1 (n = 725) WC ≤ 75	Q2 (n = 780) 76 ≤ WC ≤ 82	Q3 (n = 905) 83 ≤ WC ≤ 89	Q4 (n = 818) WC ≥ 90	P
Gender (male), n (%)	212 (29.2)	546 (70.0)	825 (91.2)	790 (96.6)	<0.001 <sup>a</sup>
Age (years) <sup>§</sup>	38.51 ± 8.61	39.69 ± 9.27	40.57 ± 9.27	42.48 ± 9.58	<0.001 <sup>b</sup>
BMI (kg/m <sup>2</sup> ) <sup>§</sup>	20.37 ± 1.83	22.38 ± 1.78	24.05 ± 1.76	26.52 ± 2.29	<0.001 <sup>b</sup>
SBP (mmHg) <sup>§</sup>	117.25 ± 14.46	122.83 ± 13.39	127.31 ± 13.51	133.36 ± 15.25	<0.001 <sup>b</sup>
DBP (mmHg) <sup>§</sup>	70.98 ± 9.39	73.90 ± 9.37	76.94 ± 9.95	81.05 ± 10.37	<0.001 <sup>b</sup>
ALT (IU/L) <sup>†§</sup>	13.0 (10.0, 18.0)	16.5 (13.0, 23.0)	22.0 (16.0, 31.0)	27.5 (19.0, 41.0)	<0.001 <sup>b</sup>
AST (IU/L) <sup>§</sup>	18.02 ± 6.04	19.15 ± 6.78	21.06 ± 8.29	23.40 ± 8.66	<0.001 <sup>b</sup>
SUA (μmol/L) <sup>§</sup>	275.00 ± 65.23	326.78 ± 73.56	357.80 ± 73.96	389.54 ± 79.64	<0.001 <sup>b</sup>
FPG (mmol/L) <sup>§</sup>	3.28 ± 1.29	3.56 ± 1.46	3.74 ± 1.60	4.09 ± 1.94	<0.001 <sup>b</sup>
TG (mmol/L) <sup>†§</sup>	0.83 (0.64, 1.11)	1.05 (0.80, 1.45)	1.27 (0.94, 1.79)	1.65 (1.15, 2.26)	<0.001 <sup>b</sup>
TC (mmol/L) <sup>§</sup>	4.42 ± 0.79	4.54 ± 0.81	4.61 ± 0.81	4.80 ± 0.96	<0.001 <sup>b</sup>

**Notes:**

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SUA, serum uric acid; FPG, fasting plasma glucose; TG, triacylglycerol; TC, total cholesterol.

<sup>†</sup> Non-normally distributed variables after lg transformation.

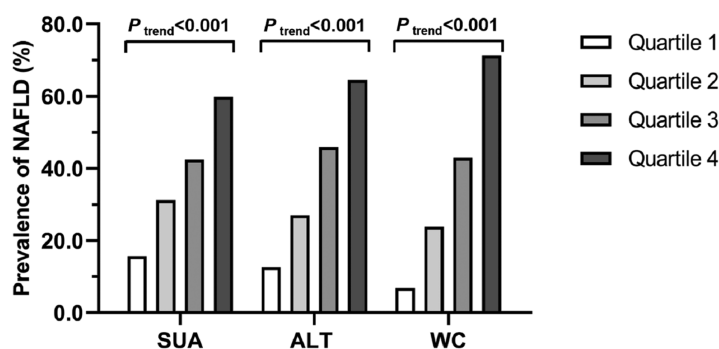
<sup>§</sup> Variables with heteroscedastic variances among the four groups.

<sup>a</sup> Chi square test.

<sup>b</sup> Welch's test.

Results in bold type indicate statistically significant.





**Figure 1** Prevalence of NAFLD in quartiles of SUA, ALT and WC, respectively. SUA: Q1,  $\leq 280$   $\mu\text{mol/L}$ ; Q2, 281–337  $\mu\text{mol/L}$ ; Q3, 338–394  $\mu\text{mol/L}$ ; Q4,  $\geq 395$   $\mu\text{mol/L}$ . ALT: Q1,  $\leq 13$  IU/L; Q2, 14–19 IU/L; Q3, 20–29 IU/L; Q4,  $\geq 30$  IU/L. WC: Q1,  $\leq 75$  cm; Q2, 76–82 cm; Q3, 83–89 cm; Q4,  $\geq 90$  cm.

Full-size DOI: [10.7717/peerj.13022/fig-1](https://doi.org/10.7717/peerj.13022/fig-1)

### Associations of SUA, ALT and WC with NAFLD risk respectively

The associations of SUA, ALT and WC with NAFLD risk were assessed through multivariate logistic regression (Table 5). Considering that gender, age, BMI, SBP, DBP, AST, FPG, TG and TC were all significantly different among quartile groups of SUA, ALT or WC, we adjusted them as covariates for further analyses.

SUA Q2 (crude OR = 2.44, 95% CI [1.92–3.09]), Q3 (crude OR = 3.96, 95% CI [3.14–5.00]), and Q4 (crude OR = 7.98, 95% CI [6.32–10.08]) were associated with higher odds of NAFLD compared to Q1, and this association was dose-dependent ( $P_{\text{trend}} < 0.001$ ). After adjustment for gender, age, BMI, SBP, DBP (model 2), the NAFLD risk increased significantly with the increases of SUA quartiles ( $P_{\text{trend}} < 0.001$ ). Similar associations between SUA levels and NAFLD risk were obtained after further adjusted for AST, FPG, TG and TC (Q2 vs Q1: adjusted OR = 1.66, 95% CI [1.23–2.22]; Q3 vs Q1: adjusted OR = 1.92, 95% CI [1.40–2.63]; Q4 vs Q1: adjusted OR = 2.44, 95% CI [1.76–3.38];  $P_{\text{trend}} < 0.001$ ).

Positive associations existed between ALT quartiles and NAFLD risk, with ORs significantly increasing from 2.57 (95% CI [1.99–3.32]) to 12.60 (95% CI [9.79–16.22]) as the ALT quartiles elevated from Q2 to Q4 (Q1 served as reference) (model 1). Subjects in ALT Q2 (adjusted OR = 1.62, 95% CI [1.21–2.17]), Q3 (adjusted OR = 3.03, 95% CI [2.26–4.05]) and Q4 (adjusted OR = 4.83, 95% CI [3.57–6.52]) had significantly increased risk of NAFLD compared to Q1 after adjusted for gender, age, BMI, SBP and DBP ( $P_{\text{trend}} < 0.001$ ). Further adjustment for other covariates did not change the positive associations and linear trend (model 3).

Significant correlations between WC quartiles and NAFLD were observed without adjustment of factors (model 1). When adjusting for gender, age, BMI, SBP and DBP, the ORs of NAFLD for WC Q2, Q3, Q4 compared to Q1 were 2.21 (95% CI [1.53–3.20]), 3.00 (95% CI [2.01–4.48]) and 4.31 (95% CI [2.73–6.81]) respectively, which increased progressively with the elevation of WC levels ( $P_{\text{trend}} < 0.001$ ). Progressive increases in the odds of NAFLD with elevated WC quartiles persisted after further adjusted for AST, FPG, TG and TC ( $P_{\text{trend}} < 0.001$ ) (model 3).

**Table 5** Associations of SUA, ALT and WC levels with the prevalence of NAFLD.

Quartiles	Model 1			Model 2			Model 3		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
SUA									
Q1	1			1			1		
Q2	2.44	[1.92–3.09]	<b>&lt;0.001</b>	1.81	[1.36–2.42]	<b>&lt;0.001</b>	1.66	[1.23–2.22]	<b>0.001</b>
Q3	3.96	[3.14–5.00]	<b>&lt;0.001</b>	2.39	[1.77–3.23]	<b>&lt;0.001</b>	1.92	[1.40–2.63]	<b>&lt;0.001</b>
Q4	7.98	[6.32–10.08]	<b>&lt;0.001</b>	3.46	[2.54–4.73]	<b>&lt;0.001</b>	2.44	[1.76–3.38]	<b>&lt;0.001</b>
$P_{\text{trend}}$			<b>&lt;0.001*</b>			<b>&lt;0.001*</b>			<b>&lt;0.001*</b>
ALT									
Q1	1			1			1		
Q2	2.57	[1.99–3.32]	<b>&lt;0.001</b>	1.62	[1.21–2.17]	<b>0.001</b>	1.66	[1.23–2.24]	<b>0.001</b>
Q3	5.88	[4.58–7.55]	<b>&lt;0.001</b>	3.03	[2.26–4.05]	<b>&lt;0.001</b>	2.84	[2.08–3.88]	<b>&lt;0.001</b>
Q4	12.60	[9.79–16.22]	<b>&lt;0.001</b>	4.83	[3.57–6.52]	<b>&lt;0.001</b>	4.98	[3.41–7.27]	<b>&lt;0.001</b>
$P_{\text{trend}}$			<b>&lt;0.001*</b>			<b>&lt;0.001*</b>			<b>&lt;0.001*</b>
WC									
Q1	1			1			1		
Q2	4.23	[3.04–5.89]	<b>&lt;0.001</b>	2.21	[1.53–3.20]	<b>&lt;0.001</b>	2.01	[1.38–2.93]	<b>&lt;0.001</b>
Q3	10.13	[7.39–13.90]	<b>&lt;0.001</b>	3.00	[2.01–4.48]	<b>&lt;0.001</b>	2.45	[1.62–3.70]	<b>&lt;0.001</b>
Q4	33.49	[24.21–46.34]	<b>&lt;0.001</b>	4.31	[2.73–6.81]	<b>&lt;0.001</b>	3.22	[2.01–5.16]	<b>&lt;0.001</b>
$P_{\text{trend}}$			<b>&lt;0.001*</b>			<b>&lt;0.001*</b>			<b>&lt;0.001*</b>

**Notes:**

SUA, serum uric acid; ALT, alanine aminotransferase; WC, waist circumference; OR, odds ratio; CI, confidence interval.

For SUA: Q1,  $\leq 280$   $\mu\text{mol/L}$ ; Q2, 281–337  $\mu\text{mol/L}$ ; Q3, 338–94  $\mu\text{mol/L}$ ; Q4,  $\geq 395$   $\mu\text{mol/L}$ .

For ALT: Q1,  $\leq 13$  IU/L; Q2, 14–19 IU/L; Q3, 20–29 IU/L; Q4,  $\geq 30$  IU/L.

For WC: Q1,  $\leq 75$  cm; Q2, 76–82 cm; Q3, 83–89 cm; Q4,  $\geq 90$  cm.

Model 1: unadjusted.

Model 2: adjusted for gender, age, BMI, SBP, DBP.

Model 3: adjusted for gender, age, BMI, SBP, DBP, AST, FPG, TG, TC.

\* P for trend.

Results in bold type indicate statistically significant.

### Validity of SUA, ALT and WC in NAFLD risk assessment

To further verify whether SUA, ALT and WC were independent risk factors of NAFLD or not, we constructed binary logistic regression (forward:LR) with the three variables and demographics (gender and age) included in the continuous form. The Box-Tidwell Test suggested that linearity assumption was met in SUA, WC and age but not in ALT, we therefore transformed ALT into the categorical variable. No collinearity among the included variables was observed in collinearity diagnostics (tolerance  $> 0.1$ ; VIF  $< 10$ ). As shown in Table 6, female (OR = 2.355, 95% CI [1.799–3.084]), age (OR = 1.033, 95% CI [1.023–1.042]), ALT  $> 40$  (OR = 2.338, 95% CI [1.791–3.052]), SUA (OR = 1.006, 95% CI [1.005–1.008]) and WC (OR = 1.140, 95% CI [1.125–1.156]) all played significant roles in facilitating the occurrence of NAFLD.

Moreover, a model was developed including these identified predictors, and was calculated as:  $(-16.229) + 0.857 \times \text{Gender (male = 1, female = 2)} + 0.032 \times \text{Age} + 0.849 \times \text{ALT (ALT = 1 if } > 40, 0 \text{ if } \leq 40 \text{ IU/L)} + 0.006 \times \text{SUA} + 0.131 \times \text{WC}$ . Insignificant result in Hosmer-Lemeshow test of the model represented agreement between predictive



**Table 6** Logistic regression for NAFLD risk assessment based on ALT, SUA, WC and demographics.

Variables	Unstandardized $\beta$	OR	95% CI	P
Gender (female vs male)	0.857	2.355	[1.799–3.084]	<0.001
Age	0.032	1.033	[1.023–1.042]	<0.001
ALT (>40 vs $\leq$ 40)	0.849	2.338	[1.791–3.052]	<0.001
SUA	0.006	1.006	[1.005–1.008]	<0.001
WC	0.131	1.140	[1.125–1.156]	<0.001
Constant	-16.229	-	-	-

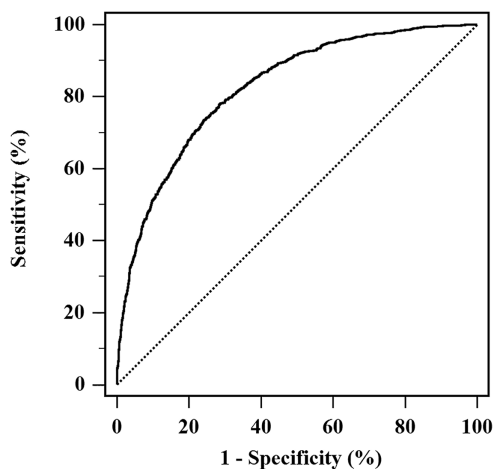
Hosmer-Lemeshow test:  $\chi^2 = 6.779$ ,  $P^* = 0.561$

**Notes:**

ALT, alanine aminotransferase; SUA, serum uric acid; WC, waist circumference; OR, odds ratio; CI, confidence interval.

\* P for Hosmer-Lemeshow test.

Results in bold type indicate statistically significant.



**Figure 2** AUROC of the model for NAFLD risk assessment. The model developed with NAFLD occurrence as a response variable, and combination of ALT, SUA, WC, age and gender as independent variables. The AUROC of the model was 0.825 (95% CI [0.811–0.838]).

Full-size  DOI: 10.7717/peerj.13022/fig-2

and actual NAFLD probability ( $P = 0.561$ ). The model had good discrimination capability for NAFLD risk, with AUROC being 0.825 (95% CI [0.811–0.838]) (Fig. 2).

## DISCUSSION

The present study evidenced strong and positive associations between SUA, ALT, WC and NAFLD occurrence, irrespective of multiple metabolic factors. The prevalence of NAFLD increased with the increasing levels of SUA, ALT and WC. Moreover, a simple model composed of these three indicators and demographics (gender and age) showed good capability in NAFLD risk assessment.

Participants with NAFLD accounted for a large proportion (37.2%) in our study, roughly paralleling with the global high prevalence of it (Younossi et al., 2018). The huge economic and health burdens carried by the epidemic prompt strong interest in identification of simple, readily measurable biomarkers for early detection of NAFLD. Consequently, we

pooled common biochemical and anthropometric parameters (SUA, ALT, WC) into this study to seek targets of screening strategy.

The independent correlation between serum SUA levels and NAFLD risk has been highlighted by multiple studies (*Liu et al., 2015; Shih et al., 2015; Sirota et al., 2013; Wei et al., 2020; Zhou, Wei & Fan, 2016*), which is in accordance with the findings of our study. The pathogenic mechanisms responsible for the association between SUA and NAFLD are essential. *Wan et al. (2016)* have proposed that uric acid may induce liver steatosis and insulin resistance, mediated by the activation of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. The activation of NLRP3 has been identified essential for the development of liver fibrosis (*Wree et al., 2014*). Moreover, SUA could induce fat accumulation in liver through hepatic endoplasmic reticulum stress (*Choi et al., 2014*) and aldose reductase activation (*Sanchez-Lozada et al., 2019*). SUA reduction has been suggested as a new therapeutic target for NAFLD, though more clinical data are needed to determine its effectiveness (*Paschos et al., 2018; Sun et al., 2016*).

A positive relationship between ALT levels (even in a normal range) and NAFLD risk was observed in our study, demonstrating that ALT is an independent risk factor for the occurrence of NAFLD. Moreover, some previous studies taking ALT as a serum marker for predicting NAFLD have suggested ALT could be applied to the detection of hepatic diseases (*Omagari et al., 2011*), but others reported ALT as poor predictor (*Verma et al., 2013*). The inconsistent results implicate that the predictive reliability of ALT might be further strengthened by combining with multi-indicators.

It has been recognized that abdominal obesity, manifested by WC, causes more obesity-related health risks than total adiposity evaluated by BMI (*Tian et al., 2020; Walls et al., 2011*). Obesity-related diseases, such as metabolic syndrome, insulin resistance, cardiovascular disorders, and NAFLD, are all reported to be associated with WC levels (*Dogan et al., 2019; Ge et al., 2021; Jiang et al., 2019*). Liver has a central role in lipid metabolism, and free fatty acids generated from the huge amount of visceral adiposity tissue lead to the accumulation of lipid in the liver (*Milic, Lulic & Stimac, 2014*). However, there is no approved medication for NAFLD treatment currently, and the most effective treatment is lifestyle modifications including weight loss and diet regulation (*Younossi et al., 2019*). The dose-response relationship between WC levels and NAFLD risk in our study may provide a clue for candidate therapeutic targets.

Results in our study indicated that SUA, ALT and WC were all independent risk factors, which could be potentially modified through behaviour modification for NAFLD treatment and prevention (*Romero-Gomez, Zelber-Sagi & Trenell, 2017*). It has been well acknowledged that gender and age appear to be predictive for NAFLD risk. We further integrated a combination of SUA, ALT, WC, gender and age into a model, which exhibited high prediction ability with useful discrimination and excellent calibration towards NAFLD occurrence. Recent studies (*Hanafy et al., 2019; Klisic, Kavarić & Ninic, 2019*) also reported that the combination of ALT and SUA together with many complicated parameters had a higher discrimination to fatty liver. Of note, our model was based on easily accessible biochemical and anthropometric predictors, which may be applicable for screening in primary healthcare settings.

Our study has some limitations. First, individuals with NAFLD in our study were imaging diagnosed by ultrasonography, which is not the gold standard for diagnosis of NAFLD. Though used in more than 99% diagnosis of NAFLD cases in China (*Zhou et al., 2020*), ultrasonography could not provide data about hepatic inflammation or fibrosis. Second, WC is not a good proxy for abdominal visceral fat, and better surrogates for visceral fat accumulation should be included in the future. Third, the cross-sectional study failed to evaluate the changes of relationship between the three predictors and NAFLD risk over time. Fourth, there may be problems in extrapolating the model developed in our study due to the lack of external verification. Hence, we will conduct further studies to verify risk assessment performance of this noninvasive model in other populations.

## CONCLUSIONS

This study found that elevated SUA, ALT and WC were all independent risk factors of NAFLD. A combination of these three indicators and demographics constituted a easy-to-use and efficient model in primary healthcare, which may provide a new approach for early risk appraisal of NAFLD in the Chinese population.

## ACKNOWLEDGEMENTS

We thank Dr. Yongke Cao for providing English language polishing support.

## ADDITIONAL INFORMATION AND DECLARATIONS

### Funding

This work was supported by the Natural Science Foundation of Jiangsu Province (grant number BK20181369), the Six Talent Peak Project in Jiangsu Province (grant number 2019-WSN-049), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (grant number PAPD [2018] 87). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Grant Disclosures

The following grant information was disclosed by the authors:  
Natural Science Foundation of Jiangsu Province: BK20181369.  
Six Talent Peak Project in Jiangsu Province: 2019-WSN-049.  
Jiangsu Higher Education Institutions: PAPD [2018] 87.

### Competing Interests

The authors declare that they have no competing interests.

### Author Contributions

- Min Wang conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Minxian Wang performed the experiments, prepared figures and/or tables, and approved the final draft.

- Ru Zhang conceived and designed the experiments, analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.
- Liuxin Zhang performed the experiments, prepared figures and/or tables, and approved the final draft.
- Yajie Ding performed the experiments, prepared figures and/or tables, and approved the final draft.
- Zongzhe Tang performed the experiments, prepared figures and/or tables, and approved the final draft.
- Haozhi Fan conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Hongliang Wang conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Wei Zhang conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Yue Chen conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Jie Wang conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.

### Human Ethics

The following information was supplied relating to ethical approvals (*i.e.*, approving body and any reference numbers):

The study protocol was approved by the Institutional Ethics Review Committee of the Nanjing Medical University [Ethics Approval Number (2018) 596].

### Data Availability

The following information was supplied regarding data availability:

The raw measurements are available in the [Supplemental File](#).

### Supplemental Information

Supplemental information for this article can be found online at <http://dx.doi.org/10.7717/peerj.13022#supplemental-information>.

## REFERENCES

- Abdeldyem SM, Goda T, Khodeir SA, Abou Saif S, Abd-Elsalam S. 2017.** Nonalcoholic fatty liver disease in patients with acute ischemic stroke is associated with more severe stroke and worse outcome. *Journal of Clinical Lipidology* **11**(4):915–919 DOI [10.1016/j.jacl.2017.04.115](https://doi.org/10.1016/j.jacl.2017.04.115).
- Abdelmoemen G, Khodeir SA, Zaki AN, Kassab M, Abou-Saif S, Abd-Elsalam S. 2019.** Overexpression of hepassocin in diabetic patients with nonalcoholic fatty liver disease may facilitate increased hepatic lipid accumulation. *Endocrine, Metabolic & Immune Disorders-Drug Targets* **19**(2):185–188 DOI [10.2174/1871530318666180716100543](https://doi.org/10.2174/1871530318666180716100543).
- Abo-Amer YE, Sabal A, Ahmed R, Hasan NFE, Refaie R, Mostafa SM, Mohamed AA, Khalil M, Elagawy W, Abd-Elsalam S. 2020.** Relationship between helicobacter pylori infection and nonalcoholic fatty liver disease (NAFLD) in a developing Country: a cross-sectional study.

*Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 13:619–625  
DOI 10.2147/DMSO.

- Al-Radaideh A, Tayyem R, Al-Fayomi K, Nimer N, Almomani A, Alhajjaj S, Agraib L, Hijawi N. 2019. The association of hepatic fat percentage with selected anthropometric and biochemical parameters at 3-Tesla magnetic resonance imaging. *British Journal of Biomedical Science* 76(2):70–76 DOI 10.1080/09674845.2019.1571555.
- Buzzetti E, Pinzani M, Tsochatzis EA. 2016. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism-Clinical and Experimental* 65(8):1038–1048 DOI 10.1016/j.metabol.2015.12.012.
- Casagrande BP, de Souza DV, Ribeiro DA, Medeiros A, Pisani LP, Estadella D. 2020. Hepatic inflammation precedes steatosis and is mediated by visceral fat accumulation. *Journal of Endocrinology* 245(3):369–380 DOI 10.1530/JOE-20-0073.
- Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. 2018. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. *Hepatology* 67(1):328–357 DOI 10.1002/hep.29367.
- Choi YJ, Shin HS, Choi HS, Park JW, Jo I, Oh ES, Lee KY, Lee BH, Johnson RJ, Kang DH. 2014. Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes. *Laboratory Investigation* 94(10):1114–1125 DOI 10.1038/labinvest.2014.98.
- Collier J, Bassendine M. 2002. How to respond to abnormal liver function tests. *Clinical Medicine* 2(5):406–409 DOI 10.7861/clinmedicine.2-5-406.
- Dogan T, Ozturk K, Celikkanat S, Aykan MB, Uygun A. 2019. Comparison of anthropometric measurements for prediction of the atherosclerosis and liver histology in young adults with nonalcoholic fatty liver disease. *European Journal of Gastroenterology & Hepatology* 31(11):1460–1466 DOI 10.1097/MEG.0000000000001431.
- Eloi JC, Epifanio M, de Goncalves MM, Pellicoli A, Vieira PF, Dias HB, Bruscatto N, Soder RB, Santana JC, Mouzaki M, Baldisserotto M. 2017. Quantification of abdominal fat in obese and healthy adolescents using 3 Tesla magnetic resonance imaging and free software for image analysis. *PLOS ONE* 12(1):e0167625 DOI 10.1371/journal.pone.0167625.
- Fracanzani AL, Valenti L, Bugianesi E, Andreoletti M, Colli A, Vanni E, Bertelli C, Fatta E, Bignamini D, Marchesini G, Fargion S. 2008. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. *Hepatology* 48(3):792–798 DOI 10.1002/hep.22429.
- Ge Q, Qi Z, Xu Z, Li M, Zheng H, Duan X, Chu M, Zhuang X. 2021. Comparison of different obesity indices related with hypertension among different sex and age groups in China. *Nutrition, Metabolism and Cardiovascular Diseases* 31(3):793–801 DOI 10.1016/j.numecd.2020.11.022.
- Hamed AE, Elwan N, Naguib M, Elwakil R, Esmat G, El Kassas M, Abd-Elsalam S, Moussa S. 2019. Diabetes association with liver diseases: an overview for clinicians. *Endocrine, Metabolic & Immune Disorders-Drug Targets* 19(3):274–280 DOI 10.2174/1871530318666181116111945.
- Hanafy AS, Seleem WM, El-Kalla F, AbdAlkhalik Basha M, Abd-Elsalam S. 2019. Efficacy of a non-invasive model in predicting the cardiovascular morbidity and histological severity in non-alcoholic fatty liver disease. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 13(3):2272–2278 DOI 10.1016/j.dsx.2019.05.032.

- Jiang B, Chen Y, Zhou K, Zheng Y, Chen Y, Li Q, Zhu C, Xia F, Gu T, Guo Y, Lu Y. 2019. Comparison of abdominal obesity and fatty liver and their association with insulin resistance and metabolic syndrome in Chinese adults. *Obesity* 27:707–715 DOI 10.1002/oby.22432.
- Kang Y, Park S, Kim S, Koh H. 2018. Normal serum alanine aminotransferase and non-alcoholic fatty liver disease among Korean adolescents: a cross-sectional study using data from KNHANES 2010–2015. *BMC Pediatrics* 18(1):215 DOI 10.1186/s12887-018-1202-z.
- Klasic A, Kavaric N, Ninic A. 2019. Predictive values of serum uric acid and alanine-aminotransferase for fatty liver index in montenegrin population. *Journal of Medical Biochemistry* 38(4):407–417 DOI 10.2478/jomb-2019-0001.
- Li J, Zou B, Yeo YH, Feng Y, Xie X, Lee DH, Fujii H, Wu Y, Kam LY, Ji F, Li X, Chien N, Wei M, Ogawa E, Zhao C, Wu X, Stave CD, Henry L, Barnett S, Takahashi H, Furusyo N, Eguchi Y, Hsu Y-C, Lee T-Y, Ren W, Qin C, Jun DW, Toyoda H, Wong VW-S, Cheung R, Zhu Q, Nguyen MH. 2019. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology* 4(5):389–398 DOI 10.1016/S2468-1253(19)30039-1.
- Liu Z, Que S, Zhou L, Zheng S. 2015. Dose-response relationship of serum uric acid with metabolic syndrome and non-alcoholic fatty liver disease incidence: a meta-analysis of prospective studies. *Scientific Reports* 5(1):14325 DOI 10.1038/srep14325.
- Milic S, Lulic D, Stimac D. 2014. Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. *World Journal of Gastroenterology* 20:9330–9337 DOI 10.3748/wjg.v20.i28.9330.
- National Workshop on Fatty Liver and Alcoholic Liver Disease CSoH, Chinese Medical Association and Fatty Liver Expert Committee CMDA. 2018. Guidelines of prevention and treatment for nonalcoholic fatty liver disease: a 2018 update. *Chinese Journal of Hepatology* 26:195–203 DOI 10.3760/cma.j.issn.1007-3418.2018.03.008.
- Omagari K, Takamura R, Matsutake S, Ichimura M, Kato S, Morikawa S, Nagaoka S, Osabe M. 2011. Serum alanine aminotransferase concentration as a predictive factor for the development or regression of fatty liver. *Journal of Clinical Biochemistry and Nutrition* 49(3):200–206 DOI 10.3164/jcfn.11-27.
- Paschos P, Athyros VG, Tsimperidis A, Katsoula A, Grammatikos N, Giouleme O. 2018. Can serum uric acid lowering therapy contribute to the prevention or treatment of nonalcoholic fatty liver disease? *Current Vascular Pharmacology* 16(3):269–275 DOI 10.2174/1570161115666170621082237.
- Rinella ME. 2015. Nonalcoholic fatty liver disease: a systematic review. *JAMA* 313(22):2263–2273 DOI 10.1001/jama.2015.5370.
- Romero-Gomez M, Zelber-Sagi S, Trenell M. 2017. Treatment of NAFLD with diet, physical activity and exercise. *Journal of Hepatology* 67(4):829–846 DOI 10.1016/j.jhep.2017.05.016.
- Sanchez-Lozada LG, Andres-Hernando A, Garcia-Arroyo FE, Cicerchi C, Li N, Kuwabara M, Roncal-Jimenez CA, Johnson RJ, Lanaspa MA. 2019. Uric acid activates aldose reductase and the polyol pathway for endogenous fructose and fat production causing development of fatty liver in rats. *Journal of Biological Chemistry* 294(11):4272–4281 DOI 10.1074/jbc.RA118.006158.
- Shih MH, Lazo M, Liu SH, Bonekamp S, Hernaez R, Clark JM. 2015. Association between serum uric acid and nonalcoholic fatty liver disease in the US population. *Journal of the Formosan Medical Association* 114(4):314–320 DOI 10.1016/j.jfma.2012.11.014.
- Sirota JC, McFann K, Targher G, Johnson RJ, Chonchol M, Jalal DI. 2013. Elevated serum uric acid levels are associated with non-alcoholic fatty liver disease independently of metabolic syndrome features in the United States: liver ultrasound data from the National Health and



- Nutrition Examination Survey. *Metabolism-Clinical and Experimental* **62(3)**:392–399 DOI [10.1016/j.metabol.2012.08.013](https://doi.org/10.1016/j.metabol.2012.08.013).
- Sun DQ, Wu SJ, Liu WY, Lu QD, Zhu GQ, Shi KQ, Braddock M, Song D, Zheng MH. 2016. Serum uric acid: a new therapeutic target for nonalcoholic fatty liver disease. *Expert Opinion on Therapeutic Targets* **20(3)**:375–387 DOI [10.1517/14728222.2016.1096930](https://doi.org/10.1517/14728222.2016.1096930).
- Targher G, Byrne CD, Tilg H. 2020. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. *Gut* **69(9)**:1691–1705 DOI [10.1136/gutjnl-2020-320622](https://doi.org/10.1136/gutjnl-2020-320622).
- Thompson WK, Xie M, White HR. 2003. Transformations of covariates for longitudinal data. *Biostatistics* **4(3)**:353–364 DOI [10.1093/biostatistics/4.3.353](https://doi.org/10.1093/biostatistics/4.3.353).
- Tian T, Zhang J, Zhu Q, Xie W, Wang Y, Dai Y. 2020. Predicting value of five anthropometric measures in metabolic syndrome among Jiangsu Province, China. *BMC Public Health* **20(1)**:1317 DOI [10.1186/s12889-020-09423-9](https://doi.org/10.1186/s12889-020-09423-9).
- Tilg H, Adolph TE, Moschen AR. 2021. Multiple parallel hits hypothesis in nonalcoholic fatty liver disease: revisited after a decade. *Hepatology* **73(2)**:833–842 DOI [10.1002/hep.31518](https://doi.org/10.1002/hep.31518).
- Verma S, Jensen D, Hart J, Mohanty SR. 2013. Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). *Liver International* **33(9)**:1398–1405 DOI [10.1111/liv.12226](https://doi.org/10.1111/liv.12226).
- Walls HL, Stevenson CE, Mannan HR, Abdullah A, Reid CM, McNeil JJ, Peeters A. 2011. Comparing trends in BMI and waist circumference. *Obesity* **19(1)**:216–219 DOI [10.1038/oby.2010.149](https://doi.org/10.1038/oby.2010.149).
- Wan X, Xu C, Lin Y, Lu C, Li D, Sang J, He H, Liu X, Li Y, Yu C. 2016. Uric acid regulates hepatic steatosis and insulin resistance through the NLRP3 inflammasome-dependent mechanism. *Journal of Hepatology* **64(4)**:925–932 DOI [10.1016/j.jhep.2015.11.022](https://doi.org/10.1016/j.jhep.2015.11.022).
- Wang Z, Zhao X, Chen S, Wang Y, Cao L, Liao W, Sun Y, Wang X, Zheng Y, Wu S, Wang L. 2020. Associations between nonalcoholic fatty liver disease and cancers in a large cohort in China. *Clinical Gastroenterology and Hepatology* **19(4)**:788–796 DOI [10.1016/j.cgh.2020.05.009](https://doi.org/10.1016/j.cgh.2020.05.009).
- Wei F, Li J, Chen C, Zhang K, Cao L, Wang X, Ma J, Feng S, Li WD. 2020. Higher serum uric acid level predicts non-alcoholic fatty liver disease: a 4-year prospective cohort study. *Frontiers in Endocrinology* **11**:179 DOI [10.3389/fendo.2020.00179](https://doi.org/10.3389/fendo.2020.00179).
- Wree A, McGeough MD, Peña CA, Schlattjan M, Li H, Inzaugarat ME, Messer K, Canbay A, Hoffman HM, Feldstein AE. 2014. NLRP3 inflammasome activation is required for fibrosis development in NAFLD. *Journal of Molecular Medicine* **92(10)**:1069–1082 DOI [10.1007/s00109-014-1170-1](https://doi.org/10.1007/s00109-014-1170-1).
- Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. 2018. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nature Reviews Gastroenterology & Hepatology* **15(1)**:11–20 DOI [10.1038/nrgastro.2017.109](https://doi.org/10.1038/nrgastro.2017.109).
- Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. 2016. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* **64(1)**:73–84 DOI [10.1002/hep.28431](https://doi.org/10.1002/hep.28431).
- Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, Wai-Sun Wong V, Yilmaz Y, George J, Fan J, Vos MB. 2019. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology* **69(6)**:2672–2682 DOI [10.1002/hep.30251](https://doi.org/10.1002/hep.30251).
- Zheng X, Gong L, Luo R, Chen H, Peng B, Ren W, Wang Y. 2017. Serum uric acid and non-alcoholic fatty liver disease in non-obesity Chinese adults. *Lipids in Health and Disease* **16(1)**:202 DOI [10.1186/s12944-017-0531-5](https://doi.org/10.1186/s12944-017-0531-5).

- Zhou Y, Wei F, Fan Y. 2016.** High serum uric acid and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Clinical Biochemistry* **49**(7-8):636-642  
[DOI 10.1016/j.clinbiochem.2015.12.010](https://doi.org/10.1016/j.clinbiochem.2015.12.010).
- Zhou J, Zhou F, Wang W, Zhang XJ, Ji YX, Zhang P, She ZG, Zhu L, Cai J, Li H. 2020.** Epidemiological features of NAFLD from 1999 to 2018 in China. *Hepatology* **71**(5):1851-1864  
[DOI 10.1002/hep.311150](https://doi.org/10.1002/hep.311150).
- Zhu Y, Hu Y, Huang T, Zhang Y, Li Z, Luo C, Luo Y, Yuan H, Hisatome I, Yamamoto T, Cheng J. 2014.** High uric acid directly inhibits insulin signalling and induces insulin resistance. *Biochemical and Biophysical Research Communications* **447**(4):707-714  
[DOI 10.1016/j.bbrc.2014.04.080](https://doi.org/10.1016/j.bbrc.2014.04.080).