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Prevalence and risk factors of hyperuricemia in non-obese Chinese population: a cross-sectional study

Jinghua Wang[1,#], Yishu Chen[1,#], Shenghui Chen[1], Xinyu Wang[1], Yuwei Zhang[1], Chengfu Xu[1,*]

[1] Department of Gastroenterology, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

***Corresponding author:**

Chengfu Xu, M.D.

Department of Gastroenterology,

The First Affiliated Hospital, Zhejiang University School of Medicine

79 Qingchun Road, Hangzhou 310003, China

Tel: 0086-571-87236863

E-mail: xiaofu@zju.edu.cn

# Jinhua Wang and Yishu Chen contributed equally to this work.

Key words: Hyperuricemia; non-obese; Risk factor; Cross-sectional study; Nonalcoholic fatty liver disease;

Abstract

Objectives: Hyperuricemia is closely related to metabolic diseases and has become a major public health problem. This study aims to investigate the prevalence and risk factors of hyperuricemia in non-obese Chinese population.

Design: Cross-sectional study

Setting: Large general hospital can provide health checkups in Hangzhou, China.

Participants: 5731 apparently healthy Chinese adults (2349 men and 3382 women) who took their health checkups during the year of 2019. Excluded criteria: (1) those with BMI $\geqslant$24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; and (3) those with a history of malignancy.

Primary and secondary outcome measures: The prevalence and risk factors of hyperuricemia in Chinese adults.

Results: Of the 5731 non-obese participants enrolled, 538 (9.4%) were diagnosed as hyperuricemia, with 16.3% in men and 4.6% in women. The prevalence of hyperuricemia increased greatly in women elder than 50 years old. The prevalence of hyperuricemia increased significantly in metabolically unhealthy normal weight participants than that in metabolically healthy normal weight participants. Hyperuricemic participants had higher prevalence of metabolic syndrome and fatty liver disease than hyperuricemia-free participants. Age, waist circumference, creatinine, blood urea nitrogen, excessive drinking and fatty liver were associated with risk of hyperuricemia in both genders.

Conclusion: The prevalence of hyperuricemia was 9.4% in non-obese Chinese adults. Non-obese hyperuricemic participants also had many metabolic disorders. Clinicians should pay attention to serum uric acid levels in non-obese individuals, especially in metabolically unhealthy individuals.

Strengths and limitations of this study

The prevalence of hyperuricemia was 9.4% in non-obese Chinese adults.

The prevalence of hyperuricemia increased significantly in metabolically unhealthy normal weight participants compared with metabolically healthy normal weight participants.

Hyperuricemia in non-obese people was also accompanied by many metabolic disorders.

It is a single-center cross-sectional study, and further multi-center cohort studies are needed.

Introduction

Uric acid is the end-product of purine metabolism in humans and it has the ability to scavenge oxygen radicals and protect the erythrocyte membrane from lipid oxidation[1]. Hyperuricemia is a common metabolic disease that closely related to gout[2]. Over the last decade, more and more studies have found that hyperuricemia is related to obesity, hypertension, dyslipidemia, chronic kidney disease, and nonalcoholic fatty liver disease (NAFLD)[3-7]. The prevalence of hyperuricemia varies across different populations and different areas. In the United States, approximately 21.4% adults met the criteria for hyperuricemia in the first decade of the 21th century[8]. A previous nationally representative survey showed that the prevalence of hyperuricemia was 6.4% among middle-aged and elderly Chinese[9]. A recent meta-analysis reported that the pooled prevalence of hyperuricemia was 13.3% in China[10].

Many metabolic-related indicators are independent risk factors for hyperuricemia. A study from the United States reported that serum levels of triglycerides, total cholesterol, apolipoprotein-B, and low-density lipoprotein cholesterol (LDL-C), and ratio of triglycerides to high-density lipoprotein cholesterol (HDL-C) were strongly positively associated with serum uric acid levels, whereas serum HDL-C levels were significantly inversely associated[11]. Juraschek *et al.* found that individuals with uncontrolled blood pressure and additional cardiovascular disease risk factors had a 4-fold or greater prevalence of hyperuricemia[12].

It is generally believed that obesity is closely related to metabolic related

diseases, and increased the risk of diabetes, NAFLD and hyperuricemia. Recently, more and more studies focus on the metabolic disorders in non-obese people. Some studies have shown that non-obese people also have a high prevalence of NAFLD. For example, we previously reported that the prevalence of NAFLD in the non-obese Chinese population was 7.3%[13]. A study from Japan warned that more than 60% of Japanese diabetic subjects are non-obese[14]. This means that it is important to assess metabolic abnormalities in non-obese people. So far, there is still a paucity of studies about the assessment of hyperuricemia in non-obese people.

In this study, we conducted a cross-sectional analysis in a non-obese Chinese population to evaluate the prevalence of hyperuricemia and determine its associated risk factors.

Methods

Study population

We conducted a cross-sectional study among adults who took their health checkups at First Affiliated Hospital, Zhejiang University School of Medicine from January 1 to December 31, 2019. We excluded the following participants: (1) those with BMI $\geqslant$24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; and (3) those with a history of malignancy. A total of 5731 participants (2349 men and 3382 women) were qualified for the cross-sectional study.

Clinical evaluations

We collected the standing height, body weight, waist circumference and blood pressure for all participants. Height and weight were measured while participants were wearing light clothing without shoes. BMI (kg/m^2) is calculated as the body weight (kg) divided by the standing height (m) squared. Blood pressure was measured using a standard protocol. Fasting serum samples were obtained for the analysis of biochemical values. The values were measured by Hitachi 7600 clinical analyzer (Hitachi, Tokyo, Japan) using standard methods. Questions about alcohol intake included the frequency of alcohol consumption per week and the usual amount per day. Questions about smoking history included the daily smoking count and years of smoking.

Diagnostic criteria and definitions

BMI is the only criterion that defines obesity. Non-obese is defined as BMI < 24 kg/m^2, and obesity is defined as BMI ≥24 kg/m^2. Excessive drinking was defined as alcohol consumption >210 g/week for men or >70 g/week for women. Hyperuricemia was defined as serum uric acid levels >420 μmol/L for men or >360 μmol/L for women, and/or taking medication for hyperuricemia.

Fatty liver was diagnosed by abdominal ultrasound examination. Trained ultrasonographists performed abdominal ultrasound examinations with a Toshiba Nemio 20 ultrasound system (Toshiba, Tokyo, Japan). The ultrasonographists were blinded to the study design and the clinical data. The criteria for ultrasonic diagnosis of fatty liver were based on those suggested by the Chinese Liver Disease Association[15].

Metabolic syndrome was defined by the modified National Cholesterol Education Program Adult Treatment Panel III report. For a participant to be defined as having metabolic syndrome they must have three or more of the following factors: (1) central obesity, defined as waist circumference ＞ 102 cm for men or ＞ 88 cm for women; (2) raised triglyceride level, defined as triglycerides ⩾ 1.7 mmol/L or specific treatment for this lipid abnormality; (3) reduced HDL cholesterol, defined as HDL cholesterol <1.03 mmol/L for men or <1.29 mmol/L for women; (4) elevated blood pressure, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and (5) raised fasting blood sugar, defined as fasting blood sugar ≥6.1 mmol/L, or previously diagnosed type 2 diabetes. Metabolically unhealthy were defined as participants met

the criterion of metabolic syndrome.

Statistical analysis

The statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL). Continuous variables were presented as medians and interquartile range. They were compared by Student's *t* test or Mann-Whitney *U* test, one-way ANOVA with post hoc Tukey's test, or Kruskal-Wallis test with Bonferroni correction as appropriate. Categorical variables were compared using the χ^2 test. A stepwise logistic regression analysis was performed to examine the relationship between hyperuricemia and anthropometric or biochemical variables (probability to enter = 0.05 and probability to remove = 0.10). A *P* value <0.05 (two-tailed) was considered to be statistically significant.

Ethics

All participants were verbally informed about the study's aim and procedures, and voluntarily consented to participant. The subject information was anonymized at collection and prior to analysis. All methods were performed in accordance with the approved guidelines. The study was approved by Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No.2021015).

Results

Prevalence of hyperuricemia in non-obese population

A total of 5731 non-obese participants (2349 men and 3382 women) with a median age of 49.0 were included in this study. The overall prevalence of hyperuricemia was 9.4%, and were 16.3% and 4.6% in males and females, respectively. In non-obese males, the prevalence of hyperuricemia was stable under the age of 50, and gradually decreased after 50 years of age. Conversely, in non-obese females, the prevalence of hyperuricemia was decreased under the age of 50, and gradually increased after 50 years of age. An interesting finding is that the prevalence of hyperuricemia in females even higher than that in males after the ages of 65 (Figure 1).

We compared the clinical characteristics of participants with or without hyperuricemia in both genders (Table 1). We found that hyperuricemic participants had greater BMI and waist circumference, higher diastolic blood pressure, and worse lipid profiles than those without hyperuricemia. Hyperuricemic participants also had higher serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), and creatinine than hyperuricemia-free participants.

Association of hyperuricemia with metabolic disorders in non-obese population

We classified all non-obese participants into metabolically healthy normal weight (MHNW) and metabolically unhealthy normal weight (MUHNW), according to their metabolic status. We found that MUHNW participants had significantly higher

prevalence of hyperuricemia than MHNW participants. In detail, the prevalence of hyperuricemia increased from 15.6% in MHNW participants to 26.7% in MUHNW participants in males. Similarly, the prevalence of hyperuricemia increased from 4.1% in MHNW participates to 16.3% in MUHNW participants in females (Figure 2).

We were also analyzed the prevalence of metabolic disorders in non-obese with or without hyperuricemia. We found that the prevalence of metabolic syndrome and fatty liver disease were significantly higher in hyperuricemic participants than in hyperuricemia-free participates. Male hyperuricemic participants had higher prevalence of raised triglyceride level and reduced HDL-C than hyperuricemia-free participants. Female hyperuricemic participants had higher prevalence of raised triglyceride level, reduced HDL-C, elevated blood pressure, and raised fasting blood sugar than hyperuricemia-free participants (Table 2). However, the prevalence of diabetes was not different between the two groups (Table 2).

Risks of hyperuricemia among non-obese population

We analyzed the risk factors of hyperuricemia by stepwise logistic regression analysis. The multivariable model showed that age, waist circumference, creatinine, BUN, excessive drinking and presence of fatty liver were associated with increased risks of hyperuricemia in both genders. Elevated serum levels of AST, total cholesterol, HDL-C and LDL-C were associated with increased risks of hyperuricemia in males. Elevated diastolic blood pressure, ALT, and triglyceride were associated with increased risks of hyperuricemia in females (Table 3).

Discussion

This study investigated the prevalence and risks of hyperuricemia in non-obese Chinese adults. We found that the prevalence of hyperuricemia was 9.4% in non-obese adults, with 16.3% in men and 4.6% in women. Age, waist circumference, creatinine, BUN, excessive drinking and presence of fatty liver were associated with risk of hyperuricemia in both genders.

The prevalence of hyperuricemia in non-obese individuals was 9.4%, which is lower than that in the previously reported general population in East Asia [10, 16]. We found that among non-obese individuals, the overall prevalence of hyperuricemia in men was higher than that in women. However, the prevalence of hyperuricemia increased greatly in women older than 50 years, and the prevalence even exceeded that in men after the age of 65 years. This phenomenon was also found in other studies[17, 18]. This is primarily attributable to sex hormone effects on renal urate transport. It has been reported that estrogen affected serum uric acid levels through renal clearance, secretion and reabsorption. Young adult women have lower serum urate levels than young adult men, but the onset of menopause is associated with increased serum urate levels[19].

Some studies have reported the interaction between hyperuricemia and NAFLD. We previously reported that hyperuricemia is independently associated with risk of NAFLD[7]. Our previous prospective study also found that NAFLD was strongly associated with increased risk of incident hyperuricemia[20]. In this study, we found fatty liver is an independent risk factor for hyperuricemia in non-obese population.

These evidences indicated that hyperuricemia and NAFLD could cause and worsen each other. This interaction still existed in non-obese population and resulted in a more deteriorated metabolic status.

MUHNW generally defined as normal-weight with metabolic syndrome and it has raised considerable scientific interest[21]. Individuals with a metabolically unhealthy profile were associated with several health issues and a higher healthcare and loss-of-productivity costs[22]. The risk of CVD in MUHNW individuals was 1.5–3-fold higher than that in MHNW individuals, and the risk was higher than the relative risk in those with metabolically healthy obesity (MHO) [23]. It is not rare to find MUHNW individuals who have a worse prognosis of diabetes than MHO individuals[24]. In this study, we found that the prevalence of hyperuricemia increased significantly in MUHNW participants compared with that in MHNW participants. This phenomenon was more obvious in women. This reminds us that we should pay more attention to the serum uric acid levels in MUHNW individuals.

We next assessed the comorbidity of other metabolic disorders in non-obese hyperuricemia patients. We found that the prevalence of metabolic syndrome and fatty liver disease in non-obese hyperuricemic participants were higher than that in hyperuricemia-free controls. This indicated that hyperuricemia in non-obese people is also accompanied by many metabolic disorders. Non-obese hyperuricemic individuals also need to intervene in uric acid levels actively to reduce the risk of comorbid metabolic disorders.

Several limitations are acknowledged in this study. First, it is a single-center

cross-sectional study. Our sample size may be insufficient to represent the entire Chinese adult population, and further multi-center cohort studies are needed. Second, dietary information was not collected, although dietary intake could be a cofactor associated with hyperuricemia. Some studies have showed that fructose-enriched food and drink could increase serum UA levels[25]. Meanwhile, this study diagnosed non-obese participants by the BMI but did not include waist circumference and waist-to-hip ratio. Some central obese patients would be mixed in non-obese participants.

In conclusion, our cross-sectional study showed that the prevalence of hyperuricemia was 9.4% in non-obese Chinese adults. The prevalence of hyperuricemia increased significantly in MUHNW participants compared with MHNW participants. Hyperuricemia in non-obese people was also accompanied by many metabolic disorders. Therefore, clinicians need to pay attention to serum uric acid levels in non-obese patients, especially in metabolically unhealthy individuals.

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Conflicts of interest

The authors declare no conflicts of interest.

Author Contributions:

Conceived and designed the experiment: X.C.F. Collected the clinical information: W.J.H, C.Y.S. and C.S.H. Analyzed the data: W.J.H, W.X.Y. and Z.Y.W. Wrote the paper: W.J.H. and C.Y.S. All authors reviewed the manuscript.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Data Availability Statement

Data are available upon reasonable request

References

1. Ichida K, Matsuo H, Takada T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. Nat Commun 2012; 3: 764.
2. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology (Oxford) 2019; 58(12): 2177-80.
3. Zheng R, Chen C, Yang T, Chen Q, Lu R, Mao Y. Serum Uric Acid Levels and the Risk of Obesity: a Longitudinal Population-Based Epidemiological Study. Clin Lab 2017; 63(10): 1581-87.
4. Son M, Seo J, Yang S. Association between dyslipidemia and serum uric acid levels in Korean adults: Korea National Health and Nutrition Examination Survey 2016-2017. PLoS One 2020; 15(2): e0228684.
5. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol 2013; 25(2): 210-6.
6. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, Hypertension, and Chronic Kidney Disease: an Emerging Association. Curr Hypertens Rep 2016; 18(10): 74.
7. Li Y, Xu C, Yu C, Xu L, Miao M. Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. J Hepatol 2009; 50(5): 1029-34.
8. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011; 63(10): 3136-41.
9. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. Sci Rep 2018; 8(1): 4314.
10. Liu R, Han C, Wu D, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. Biomed Res Int 2015; 2015: 762820.
11. Peng TC, Wang CC, Kao TW, et al. Relationship between hyperuricemia and lipid profiles in US adults. Biomed Res Int 2015; 2015: 127596.
12. Juraschek SP, Kovell LC, Miller ER, Gelber AC. Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. PLoS One 2013; 8(2): e56546.
13. Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 2013; 108(8): 1299-304.
14. Kashima S, Inoue K, Matsumoto M, Akimoto K. Prevalence and characteristics of non-obese diabetes in Japanese men and women: the Yuport Medical Checkup Center Study. J Diabetes 2015; 7(4): 523-30.
15. Fan JG, Wei L, Zhuang H, National Workshop on Fatty L, Alcoholic Liver Disease CSOHCMA, Fatty Liver Disease Expert Committee CMDA. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis 2019; 20(4): 163-73.
16. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018; 37(9): 2529-38.
17. Gaffo AL, Jacobs DR, Jr., Lewis CE, Mikuls TR, Saag KG. Association between being African-American, serum urate levels and the risk of developing hyperuricemia: findings from the

Coronary Artery Risk Development in Young Adults cohort. Arthritis Res Ther 2012; 14(1): R4.
18. Mcadams-Demarco MA, Law A, Maynard JW, Coresh J, Baer AN. Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. BMC Musculoskelet Disord 2013; 14: 347.
19. Koga M, Saito H, Mukai M, Kasayama S, Yamamoto T. Factors contributing to increased serum urate in postmenopausal Japanese females. Climacteric 2009; 12(2): 146-52.
20. Xu C, Wan X, Xu L, et al. Xanthine oxidase in non-alcoholic fatty liver disease and hyperuricemia: One stone hits two birds. J Hepatol 2015; 62(6): 1412-9.
21. Lonardo A, Mantovani A, Lugari S, Targher G. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. Ann Hepatol 2020; 19(4): 359-66.
22. Samouda H, Ruiz-Castell M, Karimi M, et al. Metabolically healthy and unhealthy weight statuses, health issues and related costs: Findings from the 2013-2015 European Health Examination Survey in Luxembourg. Diabetes Metab 2019; 45(2): 140-51.
23. Schulze MB. Metabolic health in normal-weight and obese individuals. Diabetologia 2019; 62(4): 558-66.
24. Buscemi S, Chiarello P, Buscemi C, et al. Characterization of Metabolically Healthy Obese People and Metabolically Unhealthy Normal-Weight People in a General Population Cohort of the ABCD Study. J Diabetes Res 2017; 2017: 9294038.
25. Caliceti C, Calabria D, Roda A, Cicero AFG. Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: A Critical Review. Nutrients 2017; 9(4).

Table 1. Clinical characteristics of the study population

Variables	Male		P value	Female		P value
	Without hyperuricemia (n =1967)	With hyperuricemia (n =382)		Without hyperuricemia (n =3226)	With hyperuricemia (n =156)	
Age (year)	47.0(18.0)	45.0(17.0)	0.004	43.0(16.0)	47.5(21.0)	0.004
WC (cm)	82.0(7.0)	84.0(7.0)	<0.001	74.0(8.0)	76.0(9.0)	<0.001
BMI (kg/m^2)	22.29(2.21)	22.73(1.93)	<0.001	21.09(2.72)	21.96(2.67)	<0.001
SBP (mmHg)	121.0(22.0)	123.0(23.0)	0.086	112.0(21.0)	119.0(27.0)	<0.001
DBP (mmHg)	75.0(15.0)	77.0(15.3)	<0.001	68.0(14.0)	72.5(16.8)	<0.001
ALT (U/L)	18.0(11.0)	21.0(15.0)	<0.001	13.0(7.0)	15.0(10.8)	<0.001
AST (U/L)	19.0(6.0)	20.0(8.0)	<0.001	17.0(5.0)	19.0(8.5)	<0.001
GGT (U/L)	21.0(18.0)	30.0(28.0)	<0.001	13.0(7.0)	16.0(13.0)	<0.001
Creatinine (μmol/L)	80.0(14.0)	84.0(13.3.0)	<0.001	59.0(11.0)	63.0(12.0)	<0.001
BUN (mmol/L)	4.94(1.5)	5.22(1.65)	0.001	4.43(1.49)	4.88(1.78)	<0.001
TG (mmol/L)	1.17(0.74)	1.56(1.26)	<0.001	0.89(0.56)	1.17(0.94)	<0.001
TC (mmol/L)	4.45(1.11)	4.65(1.14)	<0.001	4.45(1.17)	4.69(1.27)	0.003
HDL-C (mmol/L)	1.17(0.38)	1.10(0.34)	<0.001	1.42(0.44)	1.31(0.52)	0.001
LDL-C (mmol/L)	2.58(0.91)	2.69(1.01)	0.02	2.45(0.91)	2.62(0.98)	0.032
VLDL-C (mmol/L)	0.6(0.34)	0.73(0.46)	<0.001	0.5(0.29)	0.62(0.40)	<0.001
FBS (mmol/L)	4.84(0.65)	4.9(0.63)	0.139	4.75(0.57)	4.92(0.73)	<0.001
Excessive drinking (%)	14.0%	19.4%	0.007	1.4%	3.8%	0.016
Smoking history (%)	39.0%	42.9%	0.15	1.4%	1.3%	0.906
SUA (μmol/L)	336.0(70.0)	452.5(57.0)	<0.001	256.0(61.0)	388.0(38.5)	<0.001

Data are expressed as the medians (IQR) because the data were not normally distributed.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; DBP: diastolic blood pressure; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SUA: serum uric acid; TG: triglycerides; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; WC: waist circumference.

Table 2. Prevalence of metabolic disease according to hyperuricemia

	Male			Female		
	Without hyperuricemia	With hyperuricemia	*P*-value	Without hyperuricemia	With hyperuricemia	*P*-value
Metabolic syndrome	5.4%	10.2%	<0.001	4%	16%	<0.001
Metabolic syndrome components						
Waist circumference (> 102 cm in men, >88 cm in women)	0%	0%	/	1.4%	3.2%	0.06
Fasting blood glucose (≥ 6.1 mmol/L)	6.4%	6.5%	0.890	2%	10.9%	<0.001
Triglyceride (≥1.7mmol/L)	21.9%	45%	<0.001	10.8%	26.3%	<0.001
HDL-C (<1.04 mmol/L in men, <1.30 mmol/L in women)	28.9%	37.7%	0.001	35.2%	48.1%	0.001
Blood pressure (≥130/85 mmHg)	33.7%	38%	0.105	19.3%	35.9%	<0.001
Diabetes mellitus	3.4%	2.9%	0.599	1%	2.6%	0.062
NAFLD	13.8%	30.4%	<0.001	6.4%	20.5%	<0.001

NAFLD: nonalcoholic fatty liver disease;

Table 3. Multivariable analysis for factors associated with hyperuricemia

Variables	Male		Female	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (year)	0.971 (0.960-0.981)	<0.001	0.970 (0.952-0.988)	0.001
WC (cm)	1.056 (1.030-1.084)	<0.001	1.038 (1.006-1.071)	0.019
DBP (mmHg)	/		1.032 (1.015-1.049)	<0.001
ALT (U/L)	/		1.023 (1.013-1.033)	<0.001
AST (U/L)	1.012 (1.002-1.022)	0.013	/	
Creatinine (μmol/L)	1.026 (1.016-1.037)	<0.001	1.046 (1.027-1.065)	<0.001
BUN (mmol/L)	1.112 (1.006-1.228)	0.037	1.290 (1.116-1.490)	0.001
TG (mmol/L)	/		1.403 (1.183-1.664)	<0.001
TC (mmol/L)	2.681 (1.902-3.777)	<0.001	/	
HDL-C (mmol/L)	0.381 (0.242-0.598)	<0.001	/	
LDL-C (mmol/L)	0.398 (0.265-0.597)	<0.001	/	
Excessive drinking	1.486 (1.089-2.029)	0.013	3.324 (1.328-8.319)	0.010
NAFLD	1.918 (1.445-2.547)	<0.001	1.861 (1.140-3.037)	0.013

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; DBP: diastolic blood pressure; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; TG: triglycerides; TC: total cholesterol; WC: waist circumference

Figure Legend

Figure 1. Prevalence of hyperuricemia(A) and Serum uric acid(B) in participants

Figure 2. Prevalence of hyperuricemia (A) and Serum uric acid (B) in metabolically healthy or metabolically unhealthy participants. **p<0.01, ***p<0.001.

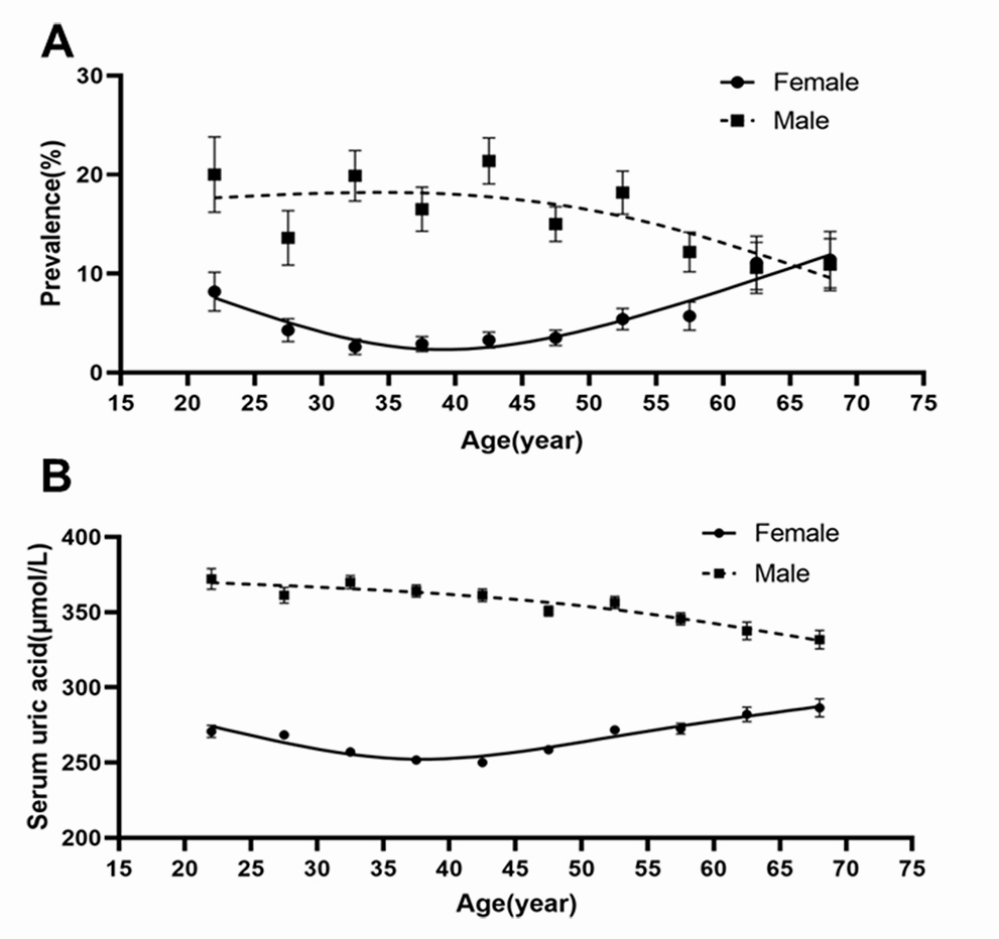

Figure 1

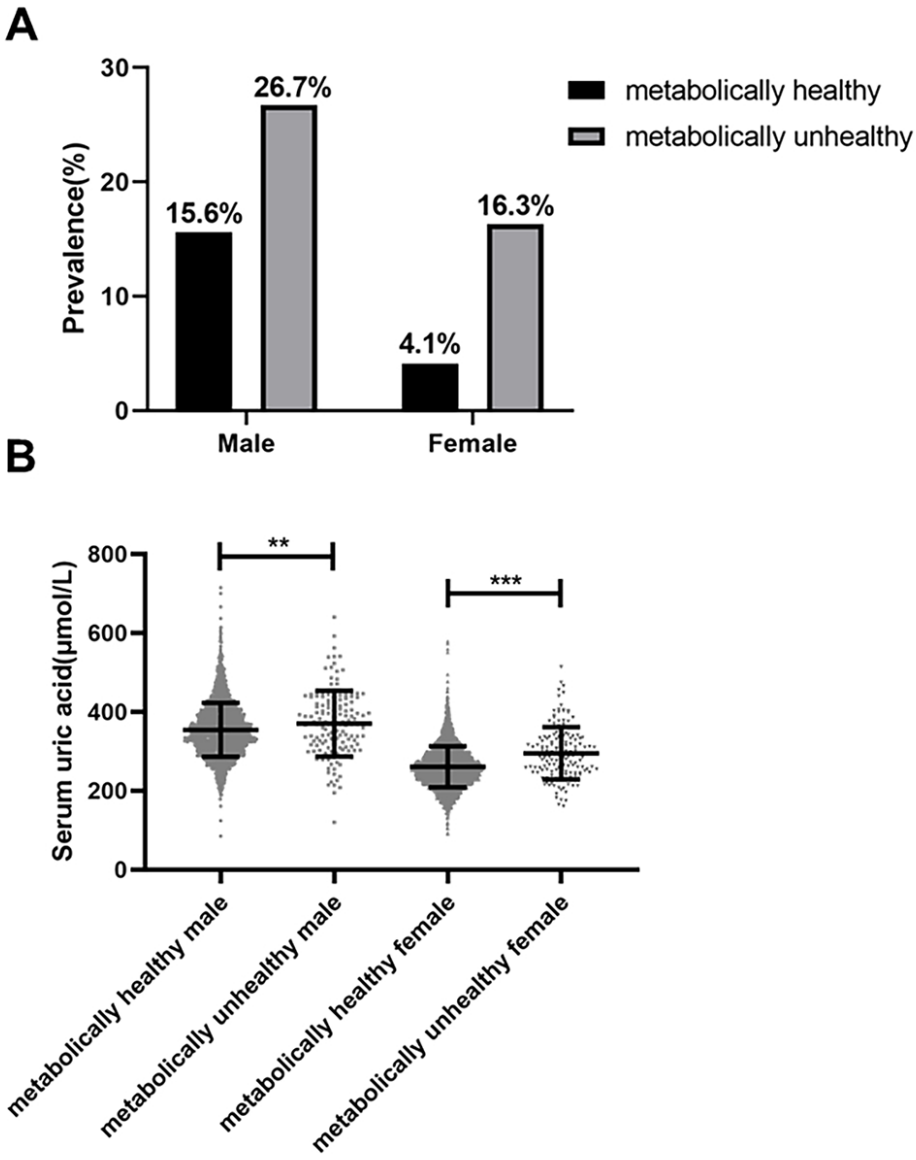

Figure 2

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of hyperuricemia in non-obese Chinese: a single-center cross-sectional study

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Prevalence and risk factors of hyperuricemia in non-obese Chinese: a single-center cross-sectional study

Jinghua Wang[1,#], Yishu Chen[1,#], Shenghui Chen[1], Xinyu Wang[1], Yuwei Zhang[1], Chengfu Xu[1,*]

[1] Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

***Corresponding author:**

Chengfu Xu, M.D.

Department of Gastroenterology,

The First Affiliated Hospital, Zhejiang University School of Medicine

79 Qingchun Road, Hangzhou 310003, China

Tel: 0086-571-87236863

E-mail: xiaofu@zju.edu.cn

# Jinghua Wang and Yishu Chen contributed equally to this work.

Key words: Hyperuricemia; Non-obese; Risk factor; Cross-sectional study; Nonalcoholic fatty liver disease;

Abstract

Objectives: Hyperuricemia is closely related to metabolic diseases and is receiving increasing attention from all over the world. This study aimed to investigate the prevalence and factors associated with hyperuricemia in non-obese Chinese population.

Design: Cross-sectional study

Setting: Large general hospital can provide health checkups in Hangzhou, China.

Participants: A total of 5731 apparently healthy Chinese adults (2349 men and 3382 women) who took their health checkups during the year of 2019. Exclusion criteria: (1) those with BMI $\geqslant$ 24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy, and (4) those under urate lowering treatment.

Primary and secondary outcome measures: The prevalence and factors associated with hyperuricemia in Chinese adults.

Results: Of the 5731 non-obese participants enrolled, 538 (9.4%) were diagnosed as hyperuricemia, specifically 16.3% in men and 4.6% in women. The prevalence of hyperuricemia increased greatly in women older than 50 years old. The prevalence of hyperuricemia was significantly higher in metabolically unhealthy participants with normal weight than that in metabolically healthy participants with normal weight. Hyperuricemic participants showed higher prevalence of metabolic syndrome and fatty liver disease than hyperuricemia-free participants. Age, waist circumference,

eGFR, blood urea nitrogen, excessive drinking and fatty liver were associated with hyperuricemia in both genders.

Conclusion: The prevalence of hyperuricemia was 9.4% in non-obese Chinese adults. Non-obese hyperuricemic participants also showed multiple metabolic disorders. Clinicians should pay attention to serum uric acid levels in non-obese population, especially in metabolically unhealthy individuals.

Strengths and limitations of this study

This study included a large sample size of participants (more than 5000 adults), which made our findings more convincible.

This study first estimated the prevalence of hyperuricemia among non-obese adults in China.

The multivariate logistic model was used to correct selection biases by adjusting for potential confounders.

It is a single-center cross-sectional study, and further multi-center cohort studies are needed.

Patients currently undergoing uric acid treatment were excluded, which may cause a certain bias in the prevalence of hyperuricemia in this study.

Introduction

Hyperuricemia, defined as elevated uric acid level in blood, is a metabolic disorder that is commonly recognized to be closely related to gout and CKD[1]. Over the last decade, more and more studies have found that hyperuricemia is related to other metabolic diseases, such as obesity, hypertension, dyslipidemia, and nonalcoholic fatty liver disease (NAFLD)[2-6]. Some studies also suggested hyperuricemia as an independent risk factor for metabolic syndrome and non-alcoholic fatty liver disease[7, 8]. Moreover, the prevalence of hyperuricemia varies across populations and areas. In the United States, approximately 21.4% of adults met the criteria for hyperuricemia in the first decade of the 21st century, which was 3.2% higher than that of NHANES 1988–1994[9]. A recent meta-analysis reported that the pooled prevalence of hyperuricemia was 13.3% in China[10]. A study from Wuhan suggested that the prevalence of hyperuricemia in men rose from 26.1% in 2010 to 34.4% in 2019, and the prevalence of hyperuricemia in women rose from 5.8% in 2010 to 10.1% in 2019[11]. The findings above all call for more attention on the health problem of hyperuricemia from a metabolic perspective.

Many metabolism-related indicators are independent risk factors for hyperuricemia. A study from the United States reported that serum levels of triglycerides, total cholesterol, apolipoprotein-B, and low-density lipoprotein cholesterol (LDL-C), and ratio of triglycerides to high-density lipoprotein cholesterol (HDL-C) were strongly positively associated with serum uric acid level, whereas serum HDL-C level was significantly inversely associated[12]. Juraschek *et al.* found

that individuals with uncontrolled blood pressure and additional cardiovascular disease risk factors had a 4-fold or greater prevalence of hyperuricemia[13].

It is generally believed that obesity is closely related to metabolism-related diseases, and it increases the risk of developing diabetes, NAFLD and hyperuricemia. Recently, more and more studies shifted their attention to metabolic disorders in non-obese people. Some studies have shown that non-obese people also present a high prevalence of NAFLD. For example, as we previously reported, the prevalence of NAFLD in non-obese Chinese population was 7.3%[14]. A study from Japan warned that more than 60% of Japanese diabetic subjects are non-obese[15]. The findings suggest that it be important to assess metabolic abnormalities in non-obese people. So far, there is still a paucity of studies on hyperuricemia in non-obese people.

In this study, we conducted a cross-sectional analysis in a non-obese Chinese population to evaluate the prevalence of hyperuricemia and determine its associated factors.

Methods

Study population

We conducted a cross-sectional study among adults who took their health checkups at the First Affiliated Hospital, Zhejiang University School of Medicine from January 1 to December 31, 2019. All participants received medical history collection, anthropometric testing, blood examination, and abdominal ultrasound examination. We excluded the following participants: (1) those with BMI $\geqslant$24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate lowering treatment. A total of 10908 participants were enrolled in this study, 4120 of whom had a BMI greater than 24 kg/m^2, 684 had incomplete data, 114 had a history of malignancy, and 259 took urate-lowering drugs. Finally, a total of 5731 participants (2349 men and 3382 women) were qualified for the cross-sectional study (Figure S1).

Clinical evaluations

We collected standing height, body weight, waist circumference and blood pressure from all participants. Height and weight were measured while participants were wearing light clothes without shoes. BMI (kg/m^2) was calculated as the body weight (kg) divided by the standing height (m) squared. Blood pressure was measured using a standard protocol. Fasting serum samples were obtained for the analysis of biochemical parameters. The values were measured by Hitachi 7600 clinical analyzer (Hitachi, Tokyo, Japan) using standard methods. Questions about alcohol intake

included frequency of alcohol consumption (per week) and usual amount per day. Questions about smoking history included daily smoking count and years of smoking.

Diagnostic criteria and definitions

BMI was adopted to define obesity. Non-obese was defined as BMI < 24 kg/m^2, and obesity is defined as BMI ≥24 kg/m^2. Excessive drinking was defined as alcohol consumption >210 g/week for men or >70 g/week for women. Hyperuricemia was defined as serum uric acid level >420 μmol/L for men or >360 μmol/L for women, and/or taking medication for hyperuricemia. The factor eGFR (estimated glomerular filtration rate) was calculated using the modified MDRD formula[16].

All individuals included in the study underwent abdominal ultrasound examination, which was performed by trained ultrasonographists with a Toshiba Nemio 20 ultrasound system (Toshiba, Tokyo, Japan). The ultrasonographists were blinded to the study design and the clinical data. The criteria for ultrasonic diagnosis of fatty liver were based on those suggested by the Chinese Liver Disease Association[17].

Metabolic syndrome was defined by the modified National Cholesterol Education Program Adult Treatment Panel III report[18]. Participants diagnosed with metabolic syndrome must have three or more of the following factors: (1) central obesity, defined as waist circumference ＞ 102 cm for men or ＞ 88 cm for women; (2) raised serum triglyceride level, defined as triglycerides ≥ 1.7 mmol/L or specific treatment for this lipid abnormality; (3) reduced HDL cholesterol, defined as HDL

cholesterol <1.03 mmol/L for men or <1.29 mmol/L for women; (4) elevated blood pressure, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and (5) raised fasting blood sugar, defined as fasting blood sugar ≥6.1 mmol/L, or previously diagnosed type 2 diabetes. Metabolically unhealthy was defined as participants met the criterion of metabolic syndrome.

Statistical analysis

The statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL). Continuous variables were presented as mean and 95% confidence interval (CI) and compared by Student's *t* test or Mann-Whitney *U* test as appropriate. Categorical variables were compared using the χ^2 test. A stepwise logistic regression analysis was performed to examine the relationship between hyperuricemia and anthropometric or biochemical variables (probability to enter = 0.05 and probability to remove = 0.10). A *P* value <0.05 (two-tailed) was considered to be statistically significant.

Ethics

All participants were verbally informed about the study's aim and procedures, and gave voluntary consent. The subject information was anonymized at collection and prior to analysis. All methods were performed in accordance with the approved guidelines. The study was approved by Clinical Research Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine (No.2021015).

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or report, or dissemination plan of our research.

Results

Prevalence of hyperuricemia in non-obese population

A total of 5731 non-obese participants (2349 men and 3382 women) with a mean age of 44.6±12.0 years were included in this study. The overall prevalence of hyperuricemia was 9.4%, and 16.3% and 4.6% in males and females, respectively. In non-obese males, the prevalence of hyperuricemia was stable under the age of 50, and gradually decreased after 50. Conversely, in non-obese females, the prevalence of hyperuricemia decreased under the age of 50, and gradually increased after 50. An interesting finding was that the prevalence of hyperuricemia in females was even higher than that in males after the age of 65 (Figure 1).

We compared the clinical characteristics of participants with or without hyperuricemia in both genders (Table 1). We found that hyperuricemic participants had greater BMI and waist circumference, higher diastolic blood pressure, and worse lipid profiles than those without hyperuricemia. Hyperuricemic participants also had higher serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), creatinine and eGFR than hyperuricemia-free participants.

Association of hyperuricemia with metabolic disorders in non-obese population

We classified all non-obese participants into metabolically healthy normal weight (MHNW) and metabolically unhealthy normal weight (MUHNW), according to their metabolic status. We found that MUHNW participants had significantly higher

prevalence of hyperuricemia than MHNW participants. In detail, the prevalence of hyperuricemia increased from 15.6% in MHNW participants to 26.7% in MUHNW participants in males (p<0.001). Similarly, the prevalence of hyperuricemia increased from 4.1% in MHNW participates to 16.3% in MUHNW participants in females (p<0.001) (Figure 2).

We also analyzed the prevalence of metabolic disorders in non-obese individuals with or without hyperuricemia. We found that the prevalence of metabolic syndrome and that of fatty liver disease were significantly higher in hyperuricemic participants than in hyperuricemia-free participates. Male hyperuricemic participants had higher prevalence of raised triglyceride level and reduced HDL-C than hyperuricemia-free participants. Female hyperuricemic participants had higher prevalence of raised triglyceride level, reduced HDL-C, elevated blood pressure, and raised fasting blood sugar than hyperuricemia-free participants (Table 2). However, the prevalence of diabetes was not different between the two groups (Table 2).

Factors associated with hyperuricemia among non-obese population

We analyzed the factors associated with hyperuricemia by stepwise logistic regression analysis. The multivariable model showed that age, waist circumference, eGFR, BUN, excessive drinking and presence of fatty liver were associated with increased prevalence of hyperuricemia in both genders. Elevated serum levels of AST, total cholesterol, HDL-C and LDL-C were associated with increased prevalence

of hyperuricemia in males. Elevated diastolic blood pressure, ALT, and triglyceride were associated with increased prevalence of hyperuricemia in females (Table 3).

Discussion

This study investigated the prevalence and factors associated with hyperuricemia in non-obese Chinese adults. We found that the prevalence of hyperuricemia was 9.4% in non-obese adults, with 16.3% in men and 4.6% in women. Age, waist circumference, eGFR, BUN, excessive drinking and presence of fatty liver were associated with hyperuricemia in both genders.

The prevalence of hyperuricemia in non-obese individuals was 9.4%, which is lower than that previously reported in general population in East Asia [10, 19], which included both non-obese and obese individuals as a whole, not separately. We found that among non-obese individuals, the overall prevalence of hyperuricemia in men was higher than that in women. However, the prevalence of hyperuricemia increased greatly in women older than 50 years. This phenomenon was also found in other studies[20, 21]. This is primarily attributable to sex hormone effects on renal urate transport. It was reported that estrogen affected serum uric acid level through renal clearance, secretion and reabsorption. Young adult women have lower serum urate level than young adult men, but the onset of menopause is associated with increased serum urate level[22].

At the same time, we found that the prevalence of hyperuricemia gradually decreased with age in male non-obese patients, which was inconsistent with previous studies[23, 24]. One possible reason was that we excluded patients undergoing uric acid-lowering treatment in our study. Nowadays, as the prevalence of gout increases

significantly with age, number of patients taking uric acid-lowering treatment is also on the rise as age grows, which may lead to a bias in our research.

Some studies have reported the interaction between hyperuricemia and NAFLD. We previously reported that hyperuricemia is independently associated with risk of NAFLD[6]. Our previous prospective study also found that NAFLD was strongly associated with increased risk of incident hyperuricemia[8]. In this study, we identified fatty liver as a factor associated with hyperuricemia in non-obese population. Our results suggested that the interaction between hyperuricemia and metabolic disorders should also be paid attention to in non-obese population, to prevent further progression to deteriorated metabolic status.

MUHNW, generally defined as normal weight with metabolic syndrome, has raised considerable scientific interest[25]. Individuals with a metabolically unhealthy profile were associated with several health issues and higher healthcare and loss-of-productivity costs[26]. The risk of CVD in MUHNW individuals was 1.5–3-fold higher than that in MHNW individuals, and the risk was higher than the relative risk in those with metabolically healthy obesity (MHO) [27]. It is not rare to find that MUHNW individuals have a worse prognosis of diabetes than MHO individuals[28]. In this study, we found that the prevalence of hyperuricemia increased significantly in MUHNW participants compared with that in MHNW participants. This phenomenon was more obvious in women. This reminds us that we should pay more attention to serum uric acid level in MUHNW individuals. As they are more likely to suffer from hyperuricemia, early intervention in uric acid level may benefit these patients by

protecting them from developing further metabolic disorders.

We next assessed the comorbidity of other metabolic disorders in non-obese hyperuricemic patients. We found that the prevalence of metabolic syndrome and that of fatty liver disease in non-obese hyperuricemic participants were higher than those in hyperuricemia-free controls. This indicated that hyperuricemia in non-obese people is also accompanied by multiple metabolic disorders. Studies have reported hyperuricemia as a cause of metabolic syndrome. Our previous studies also found that hyperuricemia could promote the occurrence and development of NAFLD, and uric acid-lowering treatment could alleviate NAFLD. Therefore, non-obese hyperuricemic individuals also need active intervention in uric acid level to reduce the risk of comorbid metabolic disorders.

Several limitations are acknowledged in this study. First, it is a single-center cross-sectional study. Our sample size may be insufficient to represent the entire Chinese adult population, and further multi-center cohort studies are needed. Second, in our study, patients currently undergoing uric acid treatment were excluded, which may cause a certain bias in the prevalence of the disease. In our research, some factors related to uric acid were not included, such as gout, renal disease, and treatment with diuretics, etc. Third, dietary information was not collected, though dietary intake could be a cofactor associated with hyperuricemia. Some studies have shown that fructose-enriched food and drink could increase serum UA levels[29]. Meanwhile, this study diagnosed non-obese participants by the BMI but did not include waist circumference and waist-to-hip ratio. Some central obese patients could be mixed in

non-obese participants.

In conclusion, our cross-sectional study showed that the prevalence of hyperuricemia was 9.4% in non-obese Chinese adults. The prevalence of hyperuricemia increased significantly in MUHNW participants compared with MHNW participants. Hyperuricemia in non-obese people was also accompanied by multiple metabolic disorders. Therefore, clinicians need to pay attention to serum uric acid level in non-obese patients, especially in metabolically unhealthy individuals.

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Conflicts of interest

The authors declare no conflicts of interest.

Author Contributions:

Conceived and designed the experiment: X.C.F. Collected the clinical information: W.J.H, C.Y.S. and C.S.H. Analyzed the data: W.J.H, W.X.Y. and Z.Y.W. Wrote the paper: W.J.H. and C.Y.S. All authors reviewed the manuscript.

Data Availability Statement

Data are available upon reasonable request

References

1. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology (Oxford) 2019; 58(12): 2177-80.
2. Zheng R, Chen C, Yang T, Chen Q, Lu R, Mao Y. Serum Uric Acid Levels and the Risk of Obesity: a Longitudinal Population-Based Epidemiological Study. Clin Lab 2017; 63(10): 1581-87.
3. Son M, Seo J, Yang S. Association between dyslipidemia and serum uric acid levels in Korean adults: Korea National Health and Nutrition Examination Survey 2016-2017. PLoS One 2020; 15(2): e0228684.
4. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol 2013; 25(2): 210-6.
5. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, Hypertension, and Chronic Kidney Disease: an Emerging Association. Curr Hypertens Rep 2016; 18(10): 74.
6. Li Y, Xu C, Yu C, Xu L, Miao M. Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. J Hepatol 2009; 50(5): 1029-34.
7. King C, Lanaspa MA, Jensen T, Tolan DR, Sanchez-Lozada LG, Johnson RJ. Uric Acid as a Cause of the Metabolic Syndrome. Contrib Nephrol 2018; 192: 88-102.
8. Xu C, Wan X, Xu L, et al. Xanthine oxidase in non-alcoholic fatty liver disease and hyperuricemia: One stone hits two birds. J Hepatol 2015; 62(6): 1412-9.
9. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011; 63(10): 3136-41.
10. Liu R, Han C, Wu D, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. Biomed Res Int 2015; 2015: 762820.
11. Wan Z, Song L, Hu L, Lei X, Huang Y, Lv Y. Temporal trends in hyperuricaemia among adults in Wuhan city, China, from 2010 to 2019: a cross-sectional study. BMJ Open 2021; 11(3): e043917.
12. Peng TC, Wang CC, Kao TW, et al. Relationship between hyperuricemia and lipid profiles in US adults. Biomed Res Int 2015; 2015: 127596.
13. Juraschek SP, Kovell LC, Miller ER, Gelber AC. Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. PLoS One 2013; 8(2): e56546.
14. Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 2013; 108(8): 1299-304.
15. Kashima S, Inoue K, Matsumoto M, Akimoto K. Prevalence and characteristics of non-obese diabetes in Japanese men and women: the Yuport Medical Checkup Center Study. J Diabetes 2015; 7(4): 523-30.
16. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006; 17(10): 2937-44.
17. Fan JG, Wei L, Zhuang H, National Workshop on Fatty L, Alcoholic Liver Disease CSOHCMA, Fatty Liver Disease Expert Committee CMDA. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis 2019; 20(4): 163-73.
18. Expert Panel on Detection E, Treatment of High Blood Cholesterol In A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection,

Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-97.

19. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018; 37(9): 2529-38.

20. Gaffo AL, Jacobs DR, Jr., Lewis CE, Mikuls TR, Saag KG. Association between being African-American, serum urate levels and the risk of developing hyperuricemia: findings from the Coronary Artery Risk Development in Young Adults cohort. Arthritis Res Ther 2012; 14(1): R4.

21. Mcadams-Demarco MA, Law A, Maynard JW, Coresh J, Baer AN. Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. BMC Musculoskelet Disord 2013; 14: 347.

22. Koga M, Saito H, Mukai M, Kasayama S, Yamamoto T. Factors contributing to increased serum urate in postmenopausal Japanese females. Climacteric 2009; 12(2): 146-52.

23. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. Sci Rep 2018; 8(1): 4314.

24. Cui L, Meng L, Wang G, et al. Prevalence and risk factors of hyperuricemia: results of the Kailuan cohort study. Mod Rheumatol 2017; 27(6): 1066-71.

25. Lonardo A, Mantovani A, Lugari S, Targher G. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. Ann Hepatol 2020; 19(4): 359-66.

26. Samouda H, Ruiz-Castell M, Karimi M, et al. Metabolically healthy and unhealthy weight statuses, health issues and related costs: Findings from the 2013-2015 European Health Examination Survey in Luxembourg. Diabetes Metab 2019; 45(2): 140-51.

27. Schulze MB. Metabolic health in normal-weight and obese individuals. Diabetologia 2019; 62(4): 558-66.

28. Buscemi S, Chiarello P, Buscemi C, et al. Characterization of Metabolically Healthy Obese People and Metabolically Unhealthy Normal-Weight People in a General Population Cohort of the ABCD Study. J Diabetes Res 2017; 2017: 9294038.

29. Caliceti C, Calabria D, Roda A, Cicero AFG. Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: A Critical Review. Nutrients 2017; 9(4).

Table 1. Clinical characteristics of the study population

Variables	Male		P value	Female		P value
	Without hyperuricemia (n =1967)	With hyperuricemia (n =382)		Without hyperuricemia (n =3226)	With hyperuricemia (n =156)	
Age (year)	46.5(46.0-47.1)	44.5(43.3-45.7)	0.004	43.4(43.0-43.8)	46.6(44.3-49.0)	0.009
WC (cm)	81.3(81.1-81.5)	83.1(82.6-83.6)	<0.001	74.0(73.8-74.2)	76.6(75.5-77.7)	<0.001
BMI (kg/m^2)	21.87(21.80-21.94)	22.33(22.19-22.47)	<0.001	20.94(20.88-21.00)	21.64(21.36-21.92)	<0.001
SBP (mmHg)	122.8(122.1-123.5)	124.1(122.4-125.8)	0.159	115.0(114.4-115.6)	122.2(119.0-125.4)	<0.001
DBP (mmHg)	75.6(75.1-76.1)	77.2(76.1-78.3)	0.009	69.2(68.8-69.6)	73.9(72.1-75.7)	<0.001
ALT (U/L)	21.4(20.6-22.3)	26.5(24.7-28.4)	<0.001	15.2(14.9-15.6)	23.2(18.4-28.0)	0.001
AST (U/L)	20.6(20.1-21.0)	22.5(21.6-23.5)	0.001	18.4(18.1-18.6)	23.1(20.5-25.7)	0.001
GGT (U/L)	30.1(29.1-32.9)	41.6(37.7-45.6)	<0.001	16.8(16.2-17.5)	22.9(19.5-26.3)	<0.001
Creatinine (μmol/L)	81.2(80.6-81.8)	86.5(84.6-88.4)	<0.001	59.5(59.2-59.8)	63.8(62.2-65.4)	<0.001
BUN (mmol/L)	5.12(5.07-5.17)	5.37(5.21-5.53)	0.003	4.55(4.51-4.59)	5.07(4.84-5.30)	<0.001
eGFR	101.1(100.4-101.8)	95.3(93.5-97.1)	<0.001	188.7(188.0-189.4)	109(105.4-112.6)	<0.001
TG (mmol/L)	1.38(1.34-1.42)	1.88(1.76-2.00)	<0.001	1.05(1.03-1.07)	1.60(1.28-1.92)	0.001
TC (mmol/L)	4.49(4.45-4.53)	4.71(4.62-4.80)	<0.001	4.52(4.49-4.55)	4.76(4.62-4.90)	0.001
HDL-C (mmol/L)	1.21(1.20-1.22)	1.14(1.11-1.17)	<0.001	1.44(1.43-1.45)	1.36(1.30-1.42)	0.003
LDL-C (mmol/L)	2.62(2.59-2.65)	2.72(2.65-2.79)	0.012	2.53(2.51-2.55)	2.65(2.53-2.77)	0.026
VLDL-C (mmol/L)	0.65(0.64-0.66)	0.84(0.80-0.88)	<0.001	0.55(0.54-0.56)	0.73(0.65-0.81)	<0.001
FBS (mmol/L)	5.02(4.97-5.07)	5.01(4.93-5.09)	0.815	4.81(4.79-4.83)	5.07(4.93-5.21)	<0.001
Excessive drinking (%)	14.0%(12.5%-15.5%)	19.4%(15.4%-23.4%)	0.007	1.4%(1.0%-1.8%)	3.8%(0.8%-6.8%)	0.016
Smoking history (%)	39.0%(36.8%-41.2%)	42.9%(37.9%-47.9%)	0.15	1.4%(1.0%-1.8%)	1.3%(0%-3.1%)	0.906
SUA (μmol/L)	333.8(331.6-336.0)	467.9(463.2-472.6)	<0.001	260.0(258.5-261.5)	397.1(390.8-403.4)	<0.001

Data are expressed as the mean (95% CI)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate;FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SUA: serum uric acid; TG: triglycerides; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; WC: waist circumference.

Table 2. Prevalence of metabolic disease according to hyperuricemia

	Male			Female		
	Without hyperuricemia	With hyperuricemia	*P*-value	Without hyperuricemia	With hyperuricemia	*P*-value
Metabolic syndrome	5.4%	10.2%	<0.001	4%	16%	<0.001
Metabolic syndrome components						
Waist circumference (> 102 cm in men, >88 cm in women)	0%	0%	/	1.4%	3.2%	0.06
Fasting blood glucose (≥ 6.1 mmol/L)	6.4%	6.5%	0.890	2%	10.9%	<0.001
Triglyceride (≥1.7mmol/L)	21.9%	45%	<0.001	10.8%	26.3%	<0.001
HDL-C (<1.04 mmol/L in men, <1.30 mmol/L in women)	28.9%	37.7%	0.001	35.2%	48.1%	0.001
Blood pressure (≥130/85 mmHg)	33.7%	38%	0.105	19.3%	35.9%	<0.001
Diabetes mellitus	3.4%	2.9%	0.599	1%	2.6%	0.062
NAFLD	13.8%	30.4%	<0.001	6.4%	20.5%	<0.001

HDL-C: high-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease;

Table 3. Multivariable analysis for factors associated with hyperuricemia

Variables	Male		Female	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (year)	0.961(0.950-0.972)	<0.001	0.958 (0.939-0.977)	<0.001
WC (cm)	1.057 (1.030-1.084)	<0.001	1.038 (1.006-1.071)	0.020
DBP (mmHg)	/		1.033(1.016-1.050)	<0.001
ALT (U/L)	/		1.023 (1.013-1.033)	<0.001
AST (U/L)	1.014 (1.004-1.024)	0.005	/	
eGFR (μmol/L)	0.973 (0.965-0.980)	<0.001	0.976 (0.966-0.985)	<0.001
BUN (mmol/L)	1.114 (1.014-1.223)	0.025	1.308 (1.137-1.505)	<0.001
TG (mmol/L)	/		1.423 (1.199-1.690)	<0.001
TC (mmol/L)	2.717 (1.921-3.843)	<0.001	/	
HDL-C (mmol/L)	0.378 (0.240-0.594)	<0.001	/	
LDL-C (mmol/L)	0.386 (0.256-0.583)	<0.001	/	
Excessive drinking	1.501 (1.097-2.055)	0.011	3.562 (1.408-9.011)	0.007
NAFLD	1.959 (1.472-2.607)	<0.001	1.900 (1.164-3.102)	0.010

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; TG: triglycerides; TC: total cholesterol; WC: waist circumference

Figure Legend

Figure 1. Prevalence of hyperuricemia(A) and Serum uric acid(B) in participants

Data was expressed as mean with 95% confidence interval (error bars)

Figure 2. Prevalence of hyperuricemia (A) and Serum uric acid (B) in metabolically healthy or metabolically unhealthy participants. Data was expressed as mean±SD. $^{**}p<0.01$, $^{***}p<0.001$.

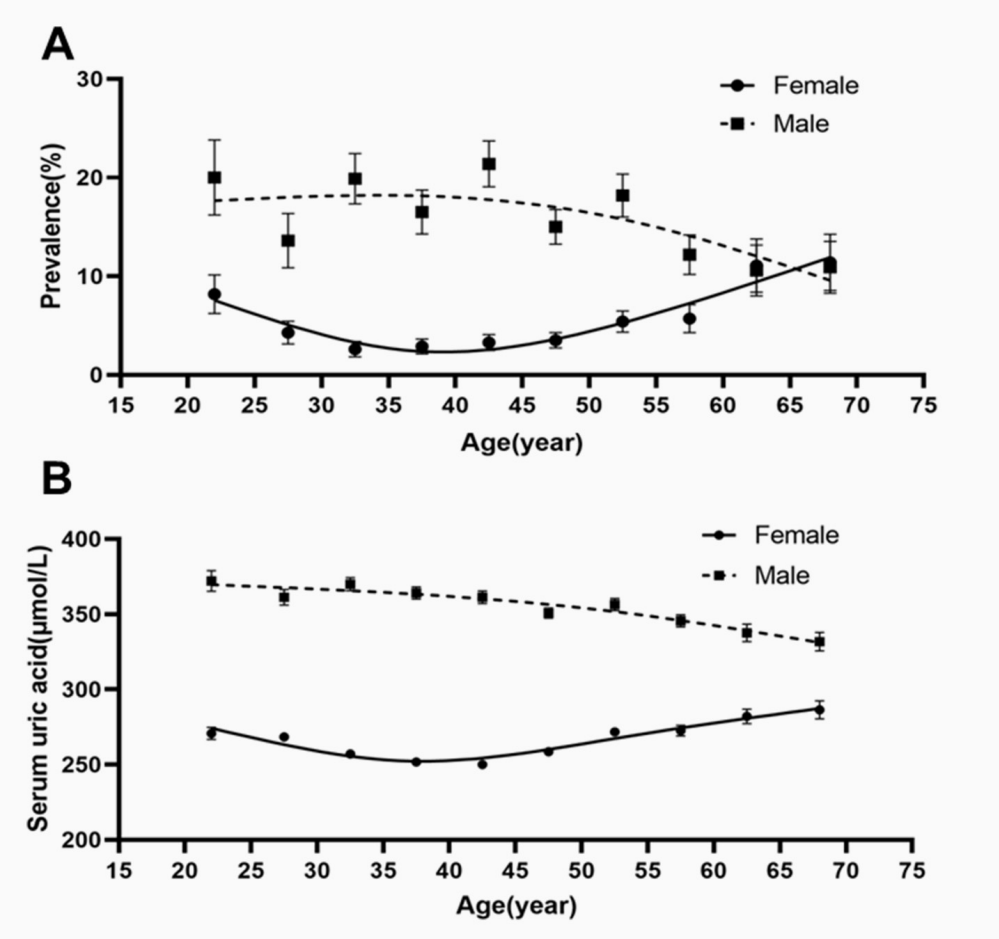

Figure 1

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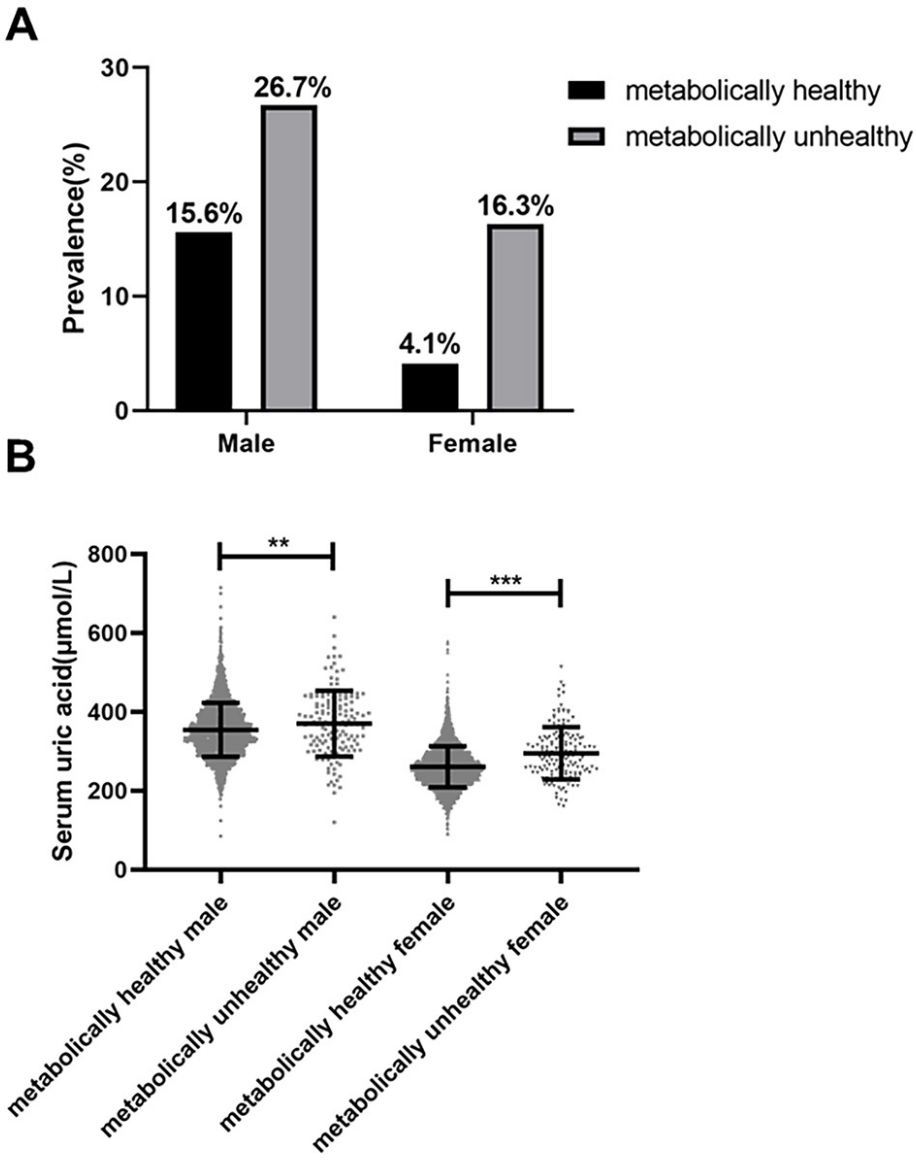

Figure 2

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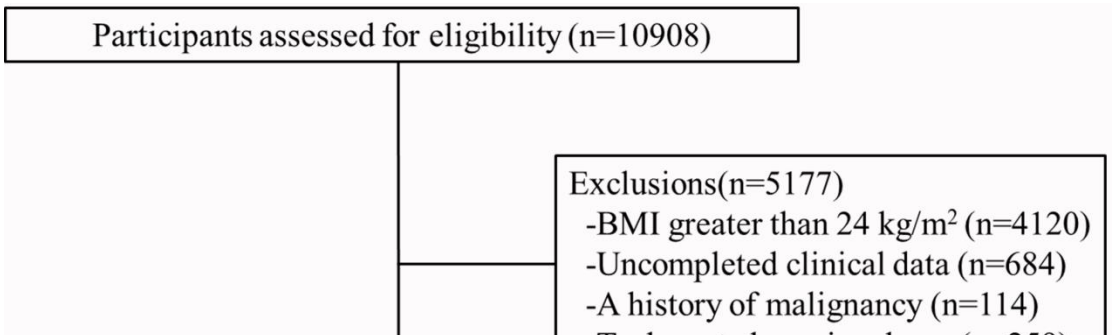

Figure S1. Inclusion and exclusion flow chart of this study

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of hyperuricemia in non-obese Chinese: a single-center cross-sectional study

Jinghua Wang[1,#], Yishu Chen[1,#], Shenghui Chen[1], Xinyu Wang[1], Yuwei Zhang[1], Chengfu Xu[1,*]

[1] Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

***Corresponding author:**

Chengfu Xu, M.D.

Department of Gastroenterology,

The First Affiliated Hospital, Zhejiang University School of Medicine

79 Qingchun Road, Hangzhou 310003, China

Tel: 0086-571-87236863

E-mail: xiaofu@zju.edu.cn

# Jinghua Wang and Yishu Chen contributed equally to this work.

Key words: Hyperuricemia; Non-obese; Risk factor; Cross-sectional study; Nonalcoholic fatty liver disease

Abstract

Objectives: Hyperuricemia is closely related to metabolic diseases and is receiving increasing attention from all over the world. This study aimed to investigate the prevalence and factors associated with hyperuricemia in non-obese Chinese population.

Design: Cross-sectional study

Setting: A large general hospital that can provide health checkups in Hangzhou, China.

Participants: A total of 5731 apparently healthy Chinese adults (2349 men and 3382 women) who took their health checkups during the year of 2019. Exclusion criteria: (1) those with BMI $\geqslant$ 24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate lowering treatment.

Primary and secondary outcome measures: The prevalence and factors associated with hyperuricemia in non-obese Chinese adults.

Results: Of the 5731 non-obese participants enrolled, 538 (9.4%) were diagnosed as hyperuricemia, specifically 16.3% in men and 4.6% in women. The prevalence of hyperuricemia increased greatly in women older than 50 years old. The prevalence of hyperuricemia was significantly higher in metabolically unhealthy participants with normal weight than in metabolically healthy participants with normal weight. Hyperuricemic participants showed a higher prevalence of metabolic syndrome and fatty liver disease than hyperuricemia-free participants. Age, waist circumference,

eGFR, blood urea nitrogen, excessive drinking and fatty liver were associated with hyperuricemia in both genders.

Conclusion: The prevalence of hyperuricemia was 9.4% in non-obese Chinese adults. Non-obese hyperuricemic participants also showed multiple metabolic disorders. Clinicians should pay attention to serum uric acid level in the non-obese population, especially in metabolically unhealthy individuals.

Strengths and limitations of this study

This study included a large sample size of participants (more than 5000 adults), which made our findings more convincible.

This is the first study that has evaluated the prevalence of hyperuricemia among non-obese adults in China.

A multivariate logistic model was used to correct selection biases by adjusting for potential confounders.

It is a single-center cross-sectional study, and further multi-center cohort studies are needed.

Patients currently undergoing uric acid treatment were excluded, which might cause a certain bias in the prevalence of hyperuricemia in this study.

Introduction

Hyperuricemia, defined as elevated uric acid level in blood, is a metabolic disorder that is commonly recognized to be closely related to gout and CKD[1]. Over the last decade, more and more studies have found that hyperuricemia is also associated with other metabolic diseases, such as obesity, hypertension, dyslipidemia, and nonalcoholic fatty liver disease (NAFLD)[2-6]. Some studies also suggested hyperuricemia as an independent risk factor for metabolic syndrome and non-alcoholic fatty liver disease[7, 8]. Moreover, the prevalence of hyperuricemia varies across populations and regions. In the United States, approximately 21.4% of adults met the criteria for hyperuricemia in the first decade of the 21st century, which was 3.2% higher than that of NHANES 1988–1994[9]. A recent meta-analysis reported that the pooled prevalence of hyperuricemia was 13.3% in China[10]. A study from Wuhan, China suggested that the prevalence of hyperuricemia in men rose from 26.1% in 2010 to 34.4% in 2019, and the prevalence of hyperuricemia in women rose from 5.8% in 2010 to 10.1% in 2019[11]. The findings above all call for more attention on the health problem of hyperuricemia from a metabolic perspective.

Many metabolism-related indicators are independent risk factors for hyperuricemia. A study from the United States reported that serum levels of triglycerides, total cholesterol, apolipoprotein-B, and low-density lipoprotein cholesterol (LDL-C), and ratio of triglycerides to high-density lipoprotein cholesterol (HDL-C) were strongly positively associated with serum uric acid level, whereas serum HDL-C level was significantly inversely associated[12]. Juraschek *et al.* found

that individuals with uncontrolled blood pressure and additional cardiovascular disease risk factors had a 4-fold or greater prevalence of hyperuricemia[13].

It is generally believed that obesity is closely related to metabolism-related diseases, and it increases the risk of developing diabetes, NAFLD and hyperuricemia. Recently, more and more studies have shifted their attention to metabolic disorders in the non-obese population. Some studies showed that the non-obese population could also present a high prevalence of NAFLD. For example, as we previously reported, the prevalence of NAFLD in a non-obese Chinese population was 7.3%[14]. A study from Japan warned that more than 60% of Japanese diabetic subjects are non-obese[15]. The findings suggest that it be important to assess metabolic abnormalities in non-obese individuals. So far, there has still been a paucity of studies on hyperuricemia in the non-obese population.

In this study, we conducted a cross-sectional analysis on a non-obese Chinese population to evaluate the prevalence of hyperuricemia and determine its associated factors.

Methods

Study population

We conducted a cross-sectional study on adults who took their health checkups at the First Affiliated Hospital, Zhejiang University School of Medicine from January 1 to December 31, 2019. All participants received medical history collection, anthropometric testing, blood examination, and abdominal ultrasound examination. We excluded the following participants: (1) those with BMI $\geqslant$24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate-lowering treatment. A total of 10908 participants were enrolled in this study, 4120 of whom had BMI greater than 24 kg/m^2, 684 had incomplete data, 114 had a history of malignancy, and 259 took urate-lowering drugs. Finally, a total of 5731 participants (2349 men and 3382 women) were qualified for the cross-sectional study (Figure S1).

Clinical evaluations

We collected standing height, body weight, waist circumference and blood pressure from all participants. Height and weight were measured while participants were wearing light clothes without shoes. BMI (kg/m^2) was calculated as the body weight (kg) divided by the standing height (m) squared. Blood pressure was measured using a standard protocol. Fasting serum samples were obtained for the analysis of biochemical parameters. The values were measured by Hitachi 7600 clinical analyzer (Hitachi, Tokyo, Japan) using standard methods. Questions about alcohol intake

included frequency of alcohol consumption (per week) and usual amount per day. Questions about smoking history included daily smoking count and years of smoking.

Diagnostic criteria and definitions

BMI was adopted to define obesity. Non-obese was defined as BMI < 24 kg/m^2, and obesity is defined as BMI ≥24 kg/m^2. Excessive drinking was defined as alcohol consumption >210 g/week for men or >70 g/week for women. Hyperuricemia was defined as serum uric acid level >420 μmol/L for men or >360 μmol/L for women. The factor eGFR (estimated glomerular filtration rate) was calculated using the modified MDRD formula[16].

All individuals included in the study underwent abdominal ultrasound examination, which was performed by trained ultrasonographists with a Toshiba Nemio 20 ultrasound system (Toshiba, Tokyo, Japan). The ultrasonographists were blinded to the study design and the clinical data. The criteria for ultrasonic diagnosis of fatty liver were based on those suggested by the Chinese Liver Disease Association[17].

Metabolic syndrome was defined by the modified National Cholesterol Education Program Adult Treatment Panel III report[18]. Participants diagnosed with metabolic syndrome must have three or more of the following factors: (1) central obesity, defined as waist circumference >102 cm for men or >88 cm for women; (2) raised serum triglyceride level, defined as triglycerides ⩾ 1.7 mmol/L or specific treatment for this lipid abnormality; (3) reduced HDL cholesterol, defined as HDL

cholesterol <1.03 mmol/L for men or <1.29 mmol/L for women; (4) elevated blood pressure, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and (5) raised fasting blood sugar, defined as fasting blood sugar ≥6.1 mmol/L, or previously diagnosed type 2 diabetes. Metabolically unhealthy participants were defined as those who met the criteria of metabolic syndrome.

Statistical analysis

The statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL). Continuous variables were presented as mean and 95% confidence interval (CI) and compared by Student's *t* test or Mann-Whitney *U* test as appropriate. Categorical variables were compared using the χ^2 test. A stepwise logistic regression analysis was performed to examine the relationship between hyperuricemia and anthropometric or biochemical variables (probability to enter = 0.05 and probability to remove = 0.10). A *P* value <0.05 (two-tailed) was considered statistically significant.

Ethics

All participants were verbally informed of the study's aim and procedures, and gave voluntary consent. The subject information was anonymized at collection and prior to analysis. All methods were performed in accordance with the approved guidelines. The study was approved by Clinical Research Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine (No.2021015).

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or report, or dissemination plan of our research.

Results

Prevalence of hyperuricemia in the non-obese population

A total of 5731 non-obese participants (2349 men and 3382 women) with a mean age of 44.6±12.0 years were included in this study. The overall prevalence of hyperuricemia was 9.4% (16.3% in males and 4.6% in females). In non-obese males, the prevalence of hyperuricemia was stable before the age of 50, and gradually decreased after 50. Conversely, in non-obese females, the prevalence of hyperuricemia decreased before the age of 50, and gradually increased after 50. An interesting finding was that the prevalence of hyperuricemia in females was even higher than that in males after the age of 65 (Figure 1).

We compared the clinical characteristics of participants with or without hyperuricemia in both genders (Table 1). We found that hyperuricemic participants had greater BMI (22.33 (22.19—22.47) versus 21.87 (21.80—21.94) kg/m^2, p<0.001 in males; 21.64 (21.36–21.92) versus 20.94 (20.88–21.00) kg/m^2, p<0.001 in females) and waist circumference (83.1 (82.6–83.6) versus 81.3 (81.1–81.5) cm, p<0.001 in males; 76.6 (75.5–77.7) versus 74.0 (73.8–74.2) cm, p<0.001 in females), higher diastolic blood pressure (77.2 (76.1–78.3) versus 75.6 (75.1–76.1) mmHg, p=0.006 in males; 73.9 (72.1–75.7) versus 69.2 (68.8–69.6) mmHg, p<0.001 in females), and worse lipid profiles than those without hyperuricemia. Hyperuricemic participants also had higher serum levels of alanine aminotransferase (ALT) (26.5 (24.7–28.4) versus 21.4 (20.6 - 22.3) U/L, p<0.001 in males; 23.2 (18.4 - 28.0) versus 15.2 (14.9 - 15.6) U/L, p=0.001 in females), aspartate aminotransferase (AST) (22.5

(21.6 – 23.5) versus 20.6 (20.1 – 21.0) U/L, p=0.001 in males; 23.1 (20.5 – 25.7) versus 18.4 (18.1 – 18.6) U/L, p=0.001 in females), gamma–glutamyl transpeptidase (GGT) (41.6 (37.7 – 45.6) versus 30.1 (29.1 – 32.9) U/L, p<0.001 in males; 22.9 (19.5 – 26.3) versus 16.8 (16.2 – 17.5) U/L, p<0.001 in females), blood urea nitrogen (BUN) (5.37 (5.21 – 5.53) versus 5.12 (5.07 – 5.17) mmol/L, p=0.003 in males; 5.07 (4.84 – 5.30) versus 4.55 (4.51 – 4.59) mmol/L, p<0.001 in females), and creatinine (86.5 (84.6 – 88.4) versus 81.2 (80.6 – 81.8) μmol/L, p<0.001 in males; 63.8 (62.2 – 65.4) versus 59.5 (59.2 – 59.8) μmol/L, p<0.001 in females) than hyperuricemia-free participants.

Association of hyperuricemia with metabolic disorders in the non-obese population

We classified all the non-obese participants into metabolically healthy normal weight (MHNW) group and metabolically unhealthy normal weight (MUHNW) group, according to their metabolic status. We found that MUHNW participants had a significantly higher prevalence of hyperuricemia than MHNW participants. In detail, the prevalence of hyperuricemia increased from 15.6% in MHNW participants to 26.7% in MUHNW participants in males (p<0.001). Similarly, the prevalence of hyperuricemia increased from 4.1% in MHNW participates to 16.3% in MUHNW participants in females (p<0.001) (Figure 2).

We also analyzed the prevalence of metabolic disorders in non-obese individuals with or without hyperuricemia. We found that the prevalence of metabolic syndrome

(male 10.2%, female 16%) were significantly higher in hyperuricemic participants than in hyperuricemia-free participates (male 5.4%, female 4%; $p<0.001$ in both genders). We also found that the prevalence of fatty liver disease (male 30.4%, female 20.5%) were significantly higher in hyperuricemic participants than in hyperuricemia-free participates (male 13.8%, female 6.4%; $p<0.001$ in both genders). Male hyperuricemic participants had a higher prevalence of raised triglyceride level and reduced HDL-C than hyperuricemia-free participants. Female hyperuricemic participants had a higher prevalence of raised triglyceride level, reduced HDL-C, elevated blood pressure, and raised fasting blood sugar than hyperuricemia-free participants (Table 2). However, the prevalence of diabetes was not different between the two groups (Table 2).

Factors associated with hyperuricemia among the non-obese population

We analyzed the factors associated with hyperuricemia by stepwise logistic regression analysis. The multivariable model showed that greater waist circumference values (1.057 (1.030–1.084) in males and 1.038 (1.006–1.071) in females), elevated BUN levels (1.114 (1.014–1.223) in males and 1.308 (1.137–1.505) in females), excessive drinking (1.501 (1.097–2.055) in males and 3.562 (1.408–9.011) in females) and presence of fatty liver (1.959 (1.472–2.607) in males and 1.900 (1.164–3.102) in females) were associated with an increased prevalence of hyperuricemia in both genders. Greater age (0.961 (0.950–0.972) in males and 0.958 (0.939–0.977) in females) and elevated eGFR levels (0.973 (0.965–0.980) in males and 0.976 (0.966–

0.985) in females) were associated with a decreased prevalence of hyperuricemia in both genders. Elevated serum levels of AST (1.014 (1.004–1.024)) and total cholesterol (2.717 (1.921–3.843)) were associated with an increased prevalence of hyperuricemia in males. Elevated serum levels of HDL-C (0.378 (0.240–0.594)) and LDL-C (0.386 (0.256–0.583)) were associated with a decreased prevalence of hyperuricemia in males. Elevated diastolic blood pressure (1.033 (1.016–1.050)), higher ALT (1.023 (1.013–1.033)) and triglyceride (1.423 (1.199–1.690)) levels were associated with an increased prevalence of hyperuricemia in females (Table 3).

Discussion

This study investigated the prevalence and factors associated with hyperuricemia in a non-obese Chinese population. We found that the prevalence of hyperuricemia was 9.4% in the non-obese adults, with 16.3% in men and 4.6% in women. Age, waist circumference, eGFR, BUN, excessive drinking and presence of fatty liver were associated with hyperuricemia in both genders.

The prevalence of hyperuricemia in non-obese individuals was 9.4%, lower than the value previously reported in the general population in East Asia [10, 19], which included both non-obese and obese individuals as a whole, not separately. We found that in the non-obese individuals, the overall prevalence of hyperuricemia was higher in men than in women. However, the prevalence of hyperuricemia increased greatly in women older than 50, which can also be corroborated by other studies[20, 21]. This is primarily attributable to the sex hormone effects on renal urate transport. It has been reported that estrogen affects serum uric acid level through renal clearance, secretion and reabsorption. Young adult women have a lower serum urate level than young adult men, while the onset of menopause is associated with an increased serum urate level[22].

At the same time, we found that the prevalence of hyperuricemia gradually decreased with age in male non-obese patients, which was inconsistent with previous studies[23, 24]. One possible reason was that we havd excluded patients undergoing uric acid-lowering treatment in our study. Nowadays, as the prevalence of gout increases

significantly with age, the number of patients taking uric acid-lowering treatment is also on the rise as age grows, which may lead to a bias in our research[25, 26].

Some studies have reported the interaction between hyperuricemia and NAFLD. We previously reported that hyperuricemia is independently associated with the risk of NAFLD[6]. Our previous prospective study also found that NAFLD was strongly associated with an increased risk of incident hyperuricemia[8]. In this study, we identified fatty liver as a factor associated with hyperuricemia in the non-obese population. Our results suggested that the interaction between hyperuricemia and metabolic disorders should also be paid attention to in the non-obese population, to prevent further progression to deteriorated metabolic status.

MUHNW, generally defined as normal weight with metabolic syndrome, has raised considerable scientific interest[27]. Individuals with a metabolically unhealthy profile were associated with several health issues and higher healthcare and loss-of-productivity costs[28]. The risk of CVD in MUHNW individuals was 1.5–3-fold higher than that in MHNW individuals, and higher than the relative risk in those with metabolically healthy obesity (MHO) [29]. It is not rare to find that MUHNW individuals have a worse prognosis of diabetes than MHO individuals[30]. In this study, we found that the prevalence of hyperuricemia increased significantly in MUHNW participants compared with that in MHNW participants. This phenomenon was more obvious in women, which reminds us that we should pay more attention to serum uric acid level in MUHNW individuals. As they are more likely to suffer from hyperuricemia, early intervention in uric acid level may benefit these patients by

protecting them from developing further metabolic disorders[31].

We next assessed the comorbidity of other metabolic disorders in non-obese hyperuricemic patients. We found that the prevalence of metabolic syndrome and that of fatty liver disease in non-obese hyperuricemic participants were higher than those in hyperuricemia-free controls. This indicated that hyperuricemia in the non-obese population is also accompanied by multiple metabolic disorders. Studies have reported hyperuricemia as a cause of metabolic syndrome. Our previous studies also found that hyperuricemia could promote the occurrence and development of NAFLD, and uric acid-lowering treatment could alleviate NAFLD[8]. Therefore, non-obese hyperuricemic individuals also need active intervention in uric acid level to reduce the risk of comorbid metabolic disorders[32].

Several limitations are acknowledged in this study. First, it is a single-center cross-sectional study. Our sample size may be insufficient to represent the entire Chinese adult population, and further multi-center cohort studies are needed. Second, in our study, patients currently undergoing uric acid treatment were excluded, which may cause a certain bias in the prevalence of the disease. In our research, some factors related to uric acid were not included, such as gout, renal disease, and treatment with diuretics, etc. Third, dietary information was not collected, though dietary intake could be a cofactor associated with hyperuricemia. Some studies have shown that fructose-enriched food and drink could increase serum UA levels[33]. Meanwhile, this study defined the non-obese participants by BMI without including waist circumference or waist-to-hip ratio. Some central obese patients could be mixed in the

non-obese participants.

In conclusion, our cross-sectional study showed that the prevalence of hyperuricemia was 9.4% in the non-obese Chinese population. The prevalence of hyperuricemia increased significantly in MUHNW participants compared with MHNW participants. Hyperuricemia in non-obese people was also accompanied by multiple metabolic disorders. Therefore, clinicians need to pay attention to serum uric acid level in non-obese patients, especially in metabolically unhealthy individuals.

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Conflicts of interest

The authors declare no conflicts of interest.

Author Contributions:

Conceived and designed the experiment: X.C.F. Collected the clinical information: W.J.H, C.Y.S. and C.S.H. Analyzed the data: W.J.H, W.X.Y. and Z.Y.W. Wrote the paper: W.J.H. and C.Y.S. All authors reviewed the manuscript.

Data Availability Statement

Data are available upon reasonable request

References

1. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology (Oxford) 2019; 58(12): 2177-80.
2. Zheng R, Chen C, Yang T, Chen Q, Lu R, Mao Y. Serum Uric Acid Levels and the Risk of Obesity: a Longitudinal Population-Based Epidemiological Study. Clin Lab 2017; 63(10): 1581-87.
3. Son M, Seo J, Yang S. Association between dyslipidemia and serum uric acid levels in Korean adults: Korea National Health and Nutrition Examination Survey 2016-2017. PLoS One 2020; 15(2): e0228684.
4. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol 2013; 25(2): 210-6.
5. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, Hypertension, and Chronic Kidney Disease: an Emerging Association. Curr Hypertens Rep 2016; 18(10): 74.
6. Li Y, Xu C, Yu C, Xu L, Miao M. Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. J Hepatol 2009; 50(5): 1029-34.
7. King C, Lanaspa MA, Jensen T, Tolan DR, Sanchez-Lozada LG, Johnson RJ. Uric Acid as a Cause of the Metabolic Syndrome. Contrib Nephrol 2018; 192: 88-102.
8. Xu C, Wan X, Xu L, et al. Xanthine oxidase in non-alcoholic fatty liver disease and hyperuricemia: One stone hits two birds. J Hepatol 2015; 62(6): 1412-9.
9. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011; 63(10): 3136-41.
10. Liu R, Han C, Wu D, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. Biomed Res Int 2015; 2015: 762820.
11. Wan Z, Song L, Hu L, Lei X, Huang Y, Lv Y. Temporal trends in hyperuricaemia among adults in Wuhan city, China, from 2010 to 2019: a cross-sectional study. BMJ Open 2021; 11(3): e043917.
12. Peng TC, Wang CC, Kao TW, et al. Relationship between hyperuricemia and lipid profiles in US adults. Biomed Res Int 2015; 2015: 127596.
13. Juraschek SP, Kovell LC, Miller ER, Gelber AC. Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. PLoS One 2013; 8(2): e56546.
14. Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 2013; 108(8): 1299-304.
15. Kashima S, Inoue K, Matsumoto M, Akimoto K. Prevalence and characteristics of non-obese diabetes in Japanese men and women: the Yuport Medical Checkup Center Study. J Diabetes 2015; 7(4): 523-30.
16. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006; 17(10): 2937-44.
17. Fan JG, Wei L, Zhuang H, National Workshop on Fatty L, Alcoholic Liver Disease CSOHCMA, Fatty Liver Disease Expert Committee CMDA. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis 2019; 20(4): 163-73.
18. Expert Panel on Detection E, Treatment of High Blood Cholesterol In A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection,

Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-97.
19. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018; 37(9): 2529-38.
20. Gaffo AL, Jacobs DR, Jr., Lewis CE, Mikuls TR, Saag KG. Association between being African-American, serum urate levels and the risk of developing hyperuricemia: findings from the Coronary Artery Risk Development in Young Adults cohort. Arthritis Res Ther 2012; 14(1): R4.
21. Mcadams-Demarco MA, Law A, Maynard JW, Coresh J, Baer AN. Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. BMC Musculoskelet Disord 2013; 14: 347.
22. Koga M, Saito H, Mukai M, Kasayama S, Yamamoto T. Factors contributing to increased serum urate in postmenopausal Japanese females. Climacteric 2009; 12(2): 146-52.
23. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. Sci Rep 2018; 8(1): 4314.
24. Cui L, Meng L, Wang G, et al. Prevalence and risk factors of hyperuricemia: results of the Kailuan cohort study. Mod Rheumatol 2017; 27(6): 1066-71.
25. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020; 16(7): 380-90.
26. Robinson PC, Taylor WJ, Dalbeth N. An Observational Study of Gout Prevalence and Quality of Care in a National Australian General Practice Population. J Rheumatol 2015; 42(9): 1702-7.
27. Lonardo A, Mantovani A, Lugari S, Targher G. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. Ann Hepatol 2020; 19(4): 359-66.
28. Samouda H, Ruiz-Castell M, Karimi M, et al. Metabolically healthy and unhealthy weight statuses, health issues and related costs: Findings from the 2013-2015 European Health Examination Survey in Luxembourg. Diabetes Metab 2019; 45(2): 140-51.
29. Schulze MB. Metabolic health in normal-weight and obese individuals. Diabetologia 2019; 62(4): 558-66.
30. Buscemi S, Chiarello P, Buscemi C, et al. Characterization of Metabolically Healthy Obese People and Metabolically Unhealthy Normal-Weight People in a General Population Cohort of the ABCD Study. J Diabetes Res 2017; 2017: 9294038.
31. Borghi C, Agabiti-Rosei E, Johnson RJ, et al. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. Eur J Intern Med 2020; 80: 1-11.
32. Bove M, Cicero AF, Veronesi M, Borghi C. An evidence-based review on urate-lowering treatments: implications for optimal treatment of chronic hyperuricemia. Vasc Health Risk Manag 2017; 13: 23-28.
33. Caliceti C, Calabria D, Roda A, Cicero AFG. Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: A Critical Review. Nutrients 2017; 9(4).

Table 1. Clinical characteristics of the study population

Variables	Male		P value	Female		P value
	Without hyperuricemia (n =1967)	With hyperuricemia (n =382)		Without hyperuricemia (n =3226)	With hyperuricemia (n =156)	
Age (year)	46.5(46.0-47.1)	44.5(43.3-45.7)	0.004	43.4(43.0-43.8)	46.6(44.3-49.0)	0.009
WC (cm)	81.3(81.1-81.5)	83.1(82.6-83.6)	<0.001	74.0(73.8-74.2)	76.6(75.5-77.7)	<0.001
BMI (kg/m^2)	21.87(21.80-21.94)	22.33(22.19-22.47)	<0.001	20.94(20.88-21.00)	21.64(21.36-21.92)	<0.001
SBP (mmHg)	122.8(122.1-123.5)	124.1(122.4-125.8)	0.159	115.0(114.4-115.6)	122.2(119.0-125.4)	<0.001
DBP (mmHg)	75.6(75.1-76.1)	77.2(76.1-78.3)	0.009	69.2(68.8-69.6)	73.9(72.1-75.7)	<0.001
ALT (U/L)	21.4(20.6-22.3)	26.5(24.7-28.4)	<0.001	15.2(14.9-15.6)	23.2(18.4-28.0)	0.001
AST (U/L)	20.6(20.1-21.0)	22.5(21.6-23.5)	0.001	18.4(18.1-18.6)	23.1(20.5-25.7)	0.001
GGT (U/L)	30.1(29.1-32.9)	41.6(37.7-45.6)	<0.001	16.8(16.2-17.5)	22.9(19.5-26.3)	<0.001
Creatinine (μmol/L)	81.2(80.6-81.8)	86.5(84.6-88.4)	<0.001	59.5(59.2-59.8)	63.8(62.2-65.4)	<0.001
BUN (mmol/L)	5.12(5.07-5.17)	5.37(5.21-5.53)	0.003	4.55(4.51-4.59)	5.07(4.84-5.30)	<0.001
eGFR	101.1(100.4-101.8)	95.3(93.5-97.1)	<0.001	188.7(188.0-189.4)	109(105.4-112.6)	<0.001
TG (mmol/L)	1.38(1.34-1.42)	1.88(1.76-2.00)	<0.001	1.05(1.03-1.07)	1.60(1.28-1.92)	0.001
TC (mmol/L)	4.49(4.45-4.53)	4.71(4.62-4.80)	<0.001	4.52(4.49-4.55)	4.76(4.62-4.90)	0.001
HDL-C (mmol/L)	1.21(1.20-1.22)	1.14(1.11-1.17)	<0.001	1.44(1.43-1.45)	1.36(1.30-1.42)	0.003
LDL-C (mmol/L)	2.62(2.59-2.65)	2.72(2.65-2.79)	0.012	2.53(2.51-2.55)	2.65(2.53-2.77)	0.026
VLDL-C (mmol/L)	0.65(0.64-0.66)	0.84(0.80-0.88)	<0.001	0.55(0.54-0.56)	0.73(0.65-0.81)	<0.001
FBS (mmol/L)	5.02(4.97-5.07)	5.01(4.93-5.09)	0.815	4.81(4.79-4.83)	5.07(4.93-5.21)	<0.001
Excessive drinking (%)	14.0%(12.5%-15.5%)	19.4%(15.4%-23.4%)	0.007	1.4%(1.0%-1.8%)	3.8%(0.8%-6.8%)	0.016
Smoking history (%)	39.0%(36.8%-41.2%)	42.9%(37.9%-47.9%)	0.15	1.4%(1.0%-1.8%)	1.3%(0%-3.1%)	0.906
SUA (μmol/L)	333.8(331.6-336.0)	467.9(463.2-472.6)	<0.001	260.0(258.5-261.5)	397.1(390.8-403.4)	<0.001

Data are expressed as the mean (95% CI)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate;FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SUA: serum uric acid; TG: triglycerides; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; WC: waist circumference.

Table 2. Prevalence of metabolic disease according to hyperuricemia

	Male			Female		
	Without hyperuricemia	With hyperuricemia	*P*-value	Without hyperuricemia	With hyperuricemia	*P*-value
Metabolic syndrome	5.4%	10.2%	<0.001	4%	16%	<0.001
Metabolic syndrome components						
Waist circumference (> 102 cm in men, >88 cm in women)	0%	0%	/	1.4%	3.2%	0.06
Fasting blood glucose (≥ 6.1 mmol/L)	6.4%	6.5%	0.890	2%	10.9%	<0.001
Triglyceride (≥1.7mmol/L)	21.9%	45%	<0.001	10.8%	26.3%	<0.001
HDL-C (<1.04 mmol/L in men, <1.30 mmol/L in women)	28.9%	37.7%	0.001	35.2%	48.1%	0.001
Blood pressure (≥130/85 mmHg)	33.7%	38%	0.105	19.3%	35.9%	<0.001
Diabetes mellitus	3.4%	2.9%	0.599	1%	2.6%	0.062
NAFLD	13.8%	30.4%	<0.001	6.4%	20.5%	<0.001

HDL-C: high-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease;

Table 3. Multivariable analysis for factors associated with hyperuricemia

Variables	Male		Female	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (year)	0.961(0.950-0.972)	<0.001	0.958 (0.939-0.977)	<0.001
WC (cm)	1.057 (1.030-1.084)	<0.001	1.038 (1.006-1.071)	0.020
DBP (mmHg)	/		1.033(1.016-1.050)	<0.001
ALT (U/L)	/		1.023 (1.013-1.033)	<0.001
AST (U/L)	1.014 (1.004-1.024)	0.005	/	
eGFR (μmol/L)	0.973 (0.965-0.980)	<0.001	0.976 (0.966-0.985)	<0.001
BUN (mmol/L)	1.114 (1.014-1.223)	0.025	1.308 (1.137-1.505)	<0.001
TG (mmol/L)	/		1.423 (1.199-1.690)	<0.001
TC (mmol/L)	2.717 (1.921-3.843)	<0.001	/	
HDL-C (mmol/L)	0.378 (0.240-0.594)	<0.001	/	
LDL-C (mmol/L)	0.386 (0.256-0.583)	<0.001	/	
Excessive drinking	1.501 (1.097-2.055)	0.011	3.562 (1.408-9.011)	0.007
NAFLD	1.959 (1.472-2.607)	<0.001	1.900 (1.164-3.102)	0.010

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; TG: triglycerides; TC: total cholesterol; WC: waist circumference

Figure Legend

Figure 1. Prevalence of hyperuricemia(A) and Serum uric acid(B) in participants

Data was expressed as mean with 95% confidence interval (error bars)

Figure 2. Prevalence of hyperuricemia (A) and Serum uric acid (B) in metabolically healthy or metabolically unhealthy participants. Data was expressed as mean ± SD. $^{**}p<0.01$, $^{***}p<0.001$.

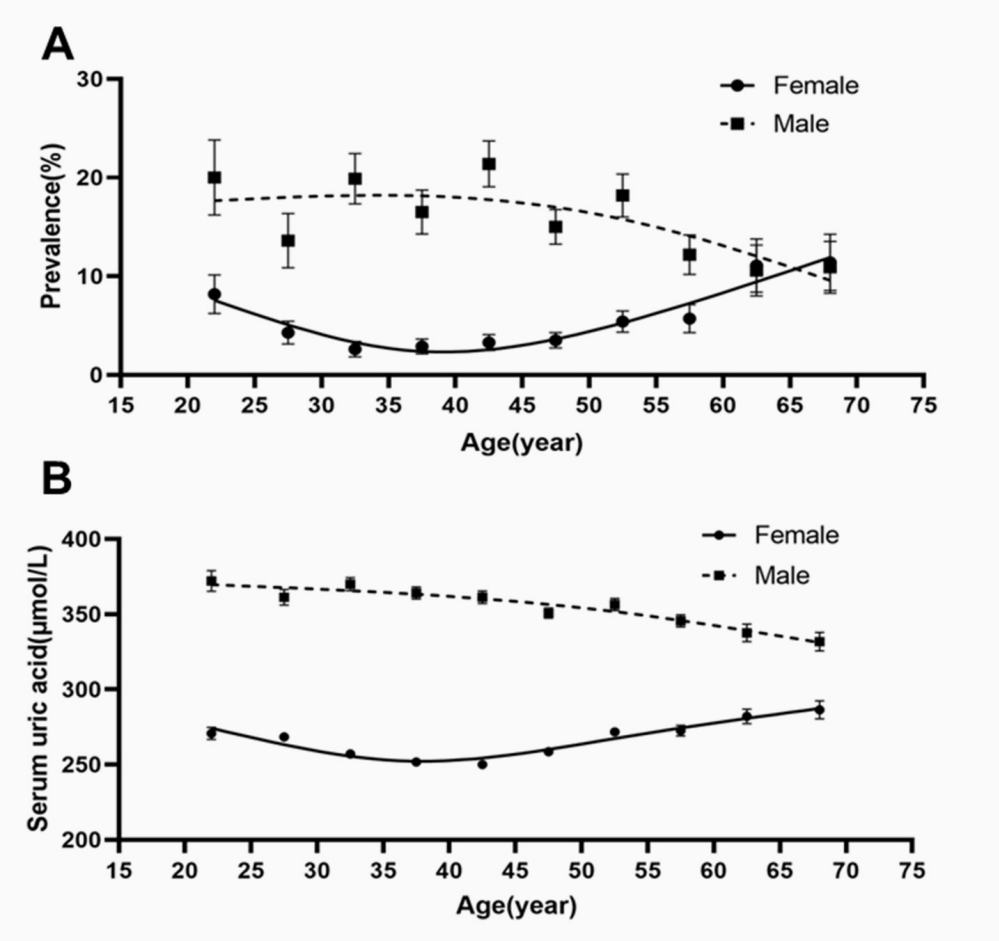

Figure 1

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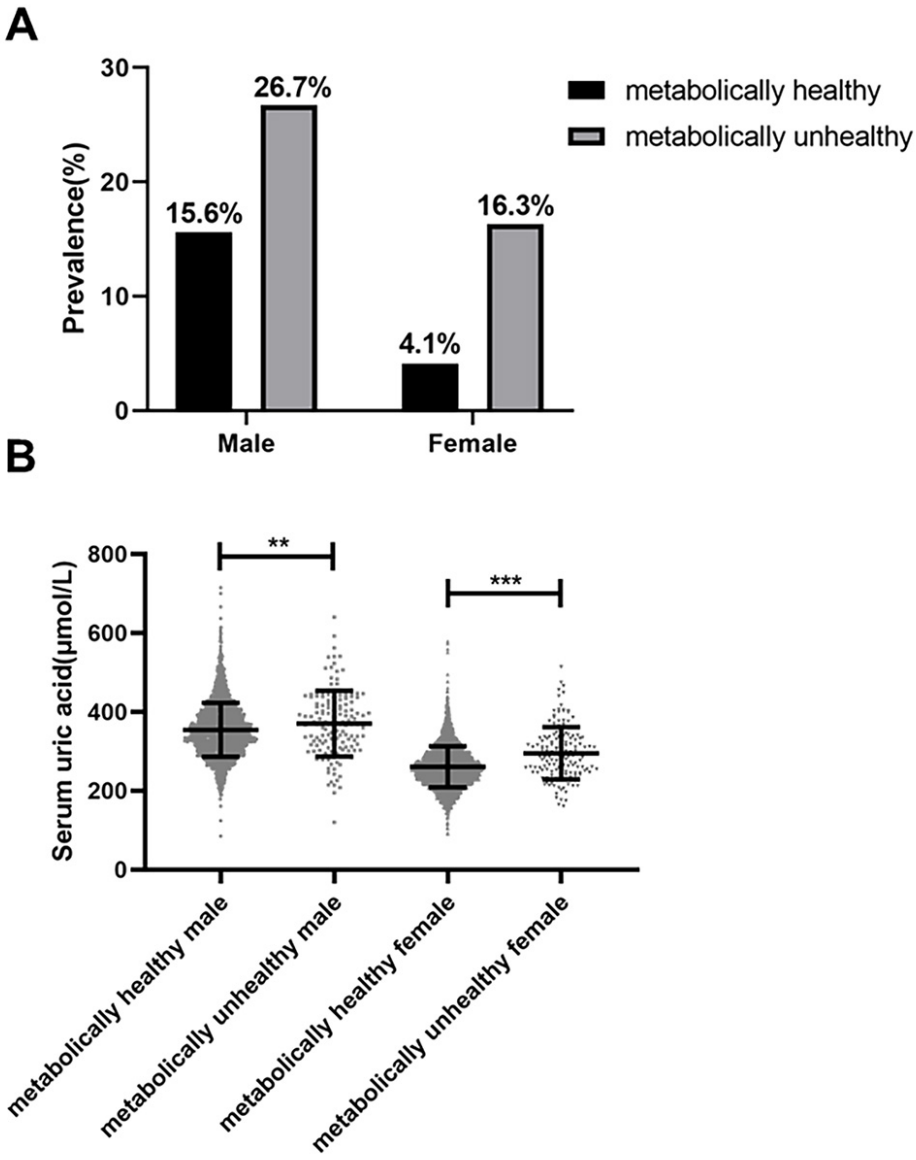

Figure 2

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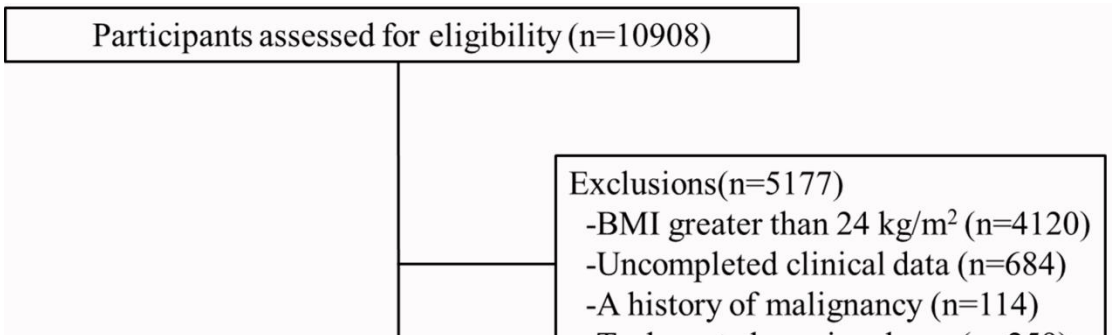

Figure S1. Inclusion and exclusion flow chart of this study

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of hyperuricemia in non-obese Chinese: a single-center cross-sectional study

Jinghua Wang[1,#], Yishu Chen[1,#], Shenghui Chen[1], Xinyu Wang[1], Haoliang Zhai[2,*], Chengfu Xu[1,2,*]

[1] Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

[2] Department of Gastroenterology, Haining Branch of the First Affiliated Hospital, Zhejiang University School of Medicine, Haining 314400, China

***Corresponding author:**

Chengfu Xu, M.D., Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine. 79 Qingchun Road, Hangzhou 310003, China, Tel: 0086-571-87236863, E-mail: xiaofu@zju.edu.cn.

Haoliang Zhai, Department of Gastroenterology, Haining Branch of the First Affiliated Hospital, Zhejiang University School of Medicine. 79 Qingchun Road, Hangzhou 314400, China, Tel: 0086-573-89230531, E-mail: inzaghi1004@sina.com.

# Jinghua Wang and Yishu Chen contributed equally to this work.

Key words: Hyperuricemia; Non-obese; Risk factor; Cross-sectional study; Nonalcoholic fatty liver disease

Abstract

Objectives: Hyperuricemia is closely related to metabolic diseases and is receiving increasing attention from all over the world. This study aimed to investigate the prevalence and factors associated with hyperuricemia in non-obese Chinese population.

Design: Cross-sectional study

Setting: A large general hospital that can provide health checkups in Hangzhou, China.

Participants: A total of 5731 apparently healthy Chinese adults (2349 men and 3382 women) who took their health checkups during the year of 2019. Exclusion criteria: (1) those with BMI $\geqslant$ 24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate-lowering treatment.

Primary and secondary outcome measures: The prevalence and factors associated with hyperuricemia in non-obese Chinese adults.

Results: Of the 5731 non-obese participants enrolled, 538 (9.4%) were diagnosed as hyperuricemia, specifically 16.3% in men and 4.6% in women. The prevalence of hyperuricemia increased greatly in women over 50 years old. The prevalence of hyperuricemia was significantly higher in metabolically unhealthy participants with normal weight than in metabolically healthy participants with normal weight. Hyperuricemic participants showed a higher prevalence of metabolic syndrome and fatty liver disease than normouremic participants. Age, waist circumference, eGFR,

blood urea nitrogen, excessive drinking and fatty liver were associated with hyperuricemia in both genders.

Conclusion: The prevalence of hyperuricemia was 9.4% in non-obese Chinese adults. Non-obese hyperuricemic participants also showed multiple metabolic disorders. We suggest that clinicians pay attention to serum uric acid level in non-obese patients.

Strengths and limitations of this study

This study included a large sample size of participants (more than 5000 adults), which made our findings more convincible.

This is the first study that has evaluated the prevalence of hyperuricemia among non-obese adults in China.

A multivariate logistic model was used to correct selection biases by adjusting for potential confounders.

It is a single-center cross-sectional study, and further multi-center cohort studies are needed.

Patients currently undergoing urate-lowering treatment were excluded, which might cause a selection bias in the prevalence of hyperuricemia in this study.

Introduction

Hyperuricemia, defined as elevated uric acid level in blood, is a metabolic disorder commonly recognized to be closely related to gout and CKD[1]. Over the last decade, more and more studies have found that hyperuricemia is also associated with other metabolic diseases, such as obesity, hypertension, dyslipidemia, and nonalcoholic fatty liver disease (NAFLD)[2-6]. Some studies also suggested hyperuricemia as an independent risk factor for metabolic syndrome and non-alcoholic fatty liver disease[7, 8]. Moreover, the prevalence of hyperuricemia varies across populations and regions. In the United States, approximately 21.4% of adults met the criteria for hyperuricemia in the first decade of the 21st century, which was 3.2% higher than that of NHANES 1988–1994[9]. A recent meta-analysis reported that the pooled prevalence of hyperuricemia was 13.3% in China[10]. A study from Wuhan, China suggested that the prevalence of hyperuricemia in men rose from 26.1% in 2010 to 34.4% in 2019, and the prevalence of hyperuricemia in women rose from 5.8% in 2010 to 10.1% in 2019[11]. The findings above may call for more attention on the health problem of hyperuricemia from a metabolic perspective, yet entailing further verification across populations.

Many metabolism-related indicators are independent risk factors for hyperuricemia. A study from the United States reported that serum levels of triglyceride, total cholesterol, apolipoprotein-B, and low-density lipoprotein cholesterol (LDL-C), and ratio of triglyceride to high-density lipoprotein cholesterol (HDL-C) were strongly positively associated with serum uric acid level, whereas

serum HDL-C level was significantly inversely associated[12]. Juraschek *et al.* found that individuals with uncontrolled blood pressure and additional cardiovascular disease risk factors had a 4-fold or higher prevalence of hyperuricemia[13].

It is generally believed that obesity is closely associated with metabolism-related diseases, and it increases the risk of developing diabetes, NAFLD and hyperuricemia. Recently, more and more studies have shifted their attention to metabolic disorders in the non-obese population. Some studies showed that the non-obese population could also present a high prevalence of NAFLD. For example, as we previously reported, the prevalence of NAFLD in a non-obese Chinese population was 7.3%[14]. A study from Japan warned that more than 60% of Japanese diabetic subjects are non-obese[15]. The findings suggest that it be important to assess metabolic abnormalities in non-obese individuals. So far, there has still been a paucity of studies on hyperuricemia in the non-obese population.

In this study, we conducted a cross-sectional analysis on a non-obese Chinese population to evaluate the prevalence of hyperuricemia and determine its associated factors.

Methods

Study population

We conducted a cross-sectional study on adults who took their health checkups at the First Affiliated Hospital, Zhejiang University School of Medicine from January 1 to December 31, 2019. All participants received medical history collection, anthropometric testing, blood examination, and abdominal ultrasound examination. We excluded the following participants: (1) those with BMI $\geqslant$24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate-lowering treatment. A total of 10908 participants were enrolled in this study, 4120 of whom had BMI greater than 24 kg/m^2, 684 had incomplete data, 114 had a history of malignancy, and 259 took urate-lowering drugs. Finally, a total of 5731 participants (2349 men and 3382 women) were qualified for the cross-sectional study (Figure S1).

Clinical evaluations

We collected standing height, body weight, waist circumference and blood pressure from all participants. Height and weight were measured while participants were wearing light clothes without shoes. BMI (kg/m^2) was calculated as the body weight (kg) divided by the standing height (m) squared. Blood pressure was measured using a standard protocol. Fasting serum samples were obtained for the analysis of biochemical parameters. The values were measured by a Hitachi 7600 clinical analyzer (Hitachi, Tokyo, Japan) using standard methods. Questions about alcohol

intake included frequency of alcohol consumption (per week) and usual amount per day. Questions about smoking history included daily smoking count and years of smoking.

Diagnostic criteria and definitions

BMI was adopted to define obesity. Non-obese was defined as BMI < 24 kg/m^2, and obesity is defined as BMI ≥24 kg/m^2. Excessive drinking was defined as alcohol consumption >210 g/week for men or >70 g/week for women. Hyperuricemia was defined as serum uric acid level >420 μmol/L for men or >360 μmol/L for women[8, 16, 17]. The factor eGFR (estimated glomerular filtration rate) was calculated using the modified MDRD formula[18].

All individuals included in the study underwent abdominal ultrasound examination, which was performed by trained ultrasonographists with a Toshiba Nemio 20 ultrasound system (Toshiba, Tokyo, Japan). The ultrasonographists were blinded to the study design and the clinical data. The criteria for ultrasonic diagnosis of fatty liver were based on those suggested by the Chinese Liver Disease Association[19].

Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III report[20]. Participants diagnosed with metabolic syndrome must have three or more of the following factors: (1) central obesity, defined as waist circumference >102 cm for men or >88 cm for women; (2) raised serum triglyceride level, defined as triglyceride ⩾ 1.7 mmol/L or specific

treatment for this lipid abnormality; (3) reduced HDL cholesterol, defined as HDL cholesterol <1.03 mmol/L for men or <1.29 mmol/L for women; (4) elevated blood pressure, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and (5) raised fasting blood sugar, defined as fasting blood sugar ≥6.1 mmol/L, or previously diagnosed type 2 diabetes. Metabolically unhealthy participants were defined as those who met the criteria of metabolic syndrome.

Statistical analyses

The statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL). Continuous variables were presented as mean and 95% confidence interval (CI) and compared by Student's *t* test or Mann-Whitney *U* test as appropriate. Categorical variables were compared using the χ^2 test. A stepwise logistic regression analysis was performed to examine the relationship between hyperuricemia and anthropometric or biochemical variables (probability to enter = 0.05 and probability to remove = 0.10). A *P* value <0.05 (two-tailed) was considered statistically significant.

Ethics

All participants were verbally informed of the study's aim and procedures, and gave voluntary consent. The subject information was anonymized at collection prior to analysis. All methods were performed in accordance with the approved guidelines.

The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No.2021015).

Patient and public involvement

Patients or the public were not involved in the design, conduct, report, or dissemination of our research.

Results

Prevalence of hyperuricemia in the non-obese population

A total of 5731 non-obese participants (2349 men and 3382 women) with a mean age of 44.6±12.0 years were included in this study. The overall prevalence of hyperuricemia was 9.4% (16.3% in males and 4.6% in females). In non-obese males, the prevalence of hyperuricemia was stable before the age of 50, and gradually decreased after 50. Conversely, in non-obese females, the prevalence of hyperuricemia decreased with age before the age of 50, and gradually increased after 50. An interesting finding was that the prevalence of hyperuricemia in females was even higher than that in males after the age of 65 (Figure 1).

We compared the clinical characteristics of participants with or without hyperuricemia in both genders (Table 1). We found that hyperuricemic participants showed greater BMI (22.33 (22.19—22.47) versus 21.87 (21.80—21.94) kg/m^2, p<0.001 in males; 21.64 (21.36–21.92) versus 20.94 (20.88–21.00) kg/m^2, p<0.001 in females) and waist circumference (83.1 (82.6–83.6) versus 81.3 (81.1–81.5) cm, p<0.001 in males; 76.6 (75.5–77.7) versus 74.0 (73.8–74.2) cm, p<0.001 in females), higher diastolic blood pressure (77.2 (76.1–78.3) versus 75.6 (75.1–76.1) mmHg, p=0.006 in males; 73.9 (72.1–75.7) versus 69.2 (68.8–69.6) mmHg, p<0.001 in females), and worse lipid profiles than those without hyperuricemia. Hyperuricemic participants also had higher serum levels of alanine aminotransferase (ALT) (26.5 (24.7–28.4) versus 21.4 (20.6 - 22.3) U/L, p<0.001 in males; 23.2 (18.4 - 28.0) versus 15.2 (14.9 - 15.6) U/L, p=0.001 in females), aspartate aminotransferase (AST)

(22.5 (21.6 – 23.5) versus 20.6 (20.1 – 21.0) U/L, p=0.001 in males; 23.1 (20.5 – 25.7) versus 18.4 (18.1 – 18.6) U/L, p=0.001 in females), gamma–glutamyl transpeptidase (GGT) (41.6 (37.7 – 45.6) versus 30.1 (29.1 – 32.9) U/L, p<0.001 in males; 22.9 (19.5 – 26.3) versus 16.8 (16.2 – 17.5) U/L, p<0.001 in females), blood urea nitrogen (BUN) (5.37 (5.21 – 5.53) versus 5.12 (5.07 – 5.17) mmol/L, p=0.003 in males; 5.07 (4.84 – 5.30) versus 4.55 (4.51 – 4.59) mmol/L, p<0.001 in females), and creatinine (86.5 (84.6 – 88.4) versus 81.2 (80.6 – 81.8) μmol/L, p<0.001 in males; 63.8 (62.2 – 65.4) versus 59.5 (59.2 – 59.8) μmol/L, p<0.001 in females) than normouremic participants.

Association of hyperuricemia with metabolic disorders in the non-obese population

We classified all the non-obese participants into metabolically healthy normal weight (MHNW) group and metabolically unhealthy normal weight (MUHNW) group, according to their metabolic status. We found that MUHNW participants had a significantly higher prevalence of hyperuricemia than MHNW participants. In detail, the prevalence of hyperuricemia increased from 15.6% in MHNW participants to 26.7% in MUHNW participants in males (p<0.001). Similarly, the prevalence of hyperuricemia increased from 4.1% in MHNW participants to 16.3% in MUHNW participants in females (p<0.001) (Figure 2).

We also analyzed the prevalence of metabolic disorders in non-obese individuals with or without hyperuricemia. We found that the prevalence of metabolic syndrome

were significantly higher in hyperuricemic participants (male 10.2%, female 16%) than in normouremic participants (male 5.4%, female 4%; $p<0.001$ in both genders). We also found that the prevalence of fatty liver disease were significantly higher in hyperuricemic participants (male 30.4%, female 20.5%) than in normouremic participants (male 13.8%, female 6.4%; $p<0.001$ in both genders). Male hyperuricemic participants had a higher prevalence of raised triglyceride level and reduced HDL-C than normouremic participants. Female hyperuricemic participants had a higher prevalence of raised triglyceride level, reduced HDL-C, elevated blood pressure, and raised fasting blood sugar than normouremic participants (Table 2). However, the prevalence of diabetes was not different between the two groups (Table 2).

Factors associated with hyperuricemia among the non-obese population

We analyzed the factors associated with hyperuricemia by stepwise logistic regression analysis. The multivariable model showed that greater waist circumference values (1.057 (1.030–1.084) (the data was expressed as OR (95%CI) , the same below) in males and 1.038 (1.006–1.071) in females), elevated BUN levels (1.114 (1.014–1.223) in males and 1.308 (1.137–1.505) in females), excessive drinking (1.501 (1.097–2.055) in males and 3.562 (1.408–9.011) in females) and presence of fatty liver (1.959 (1.472–2.607) in males and 1.900 (1.164–3.102) in females) were associated with an increased prevalence of hyperuricemia in both genders. Greater age (0.961 (0.950–0.972) in males and 0.958 (0.939–0.977) in females) and elevated

eGFR levels (0.973 (0.965–0.980) in males and 0.976 (0.966–0.985) in females) were associated with a decreased prevalence of hyperuricemia in both genders. Elevated serum levels of AST (1.014 (1.004–1.024)) and total cholesterol (2.717 (1.921–3.843)) were associated with an increased prevalence of hyperuricemia in males. Elevated serum levels of HDL-C (0.378 (0.240–0.594)) and LDL-C (0.386 (0.256–0.583)) were associated with a decreased prevalence of hyperuricemia in males. Elevated diastolic blood pressure (1.033 (1.016–1.050)), higher ALT (1.023 (1.013–1.033)) and triglyceride (1.423 (1.199–1.690)) levels were associated with an increased prevalence of hyperuricemia in females (Table 3).

Discussion

This study investigated the prevalence and factors associated with hyperuricemia in a non-obese Chinese population. We found that the prevalence of hyperuricemia was 9.4% in the non-obese adults, with 16.3% in men and 4.6% in women. Age, waist circumference, eGFR, BUN, excessive drinking and presence of fatty liver were associated with hyperuricemia in both genders.

The prevalence of hyperuricemia in non-obese individuals was 9.4%, lower than the value previously reported in the general population in East Asia [10, 21], which included both non-obese and obese individuals as a whole, not separately. We found that in the non-obese individuals, the overall prevalence of hyperuricemia was higher in men than in women. However, the prevalence of hyperuricemia increased greatly in women older than 50, which could be corroborated by other studies[22, 23]. This is primarily attributable to the sex hormone effects on renal urate transport. It has been reported that estrogen affects serum uric acid level through renal clearance, secretion and reabsorption. Young adult women have a lower serum urate level than young adult men, while the onset of menopause is associated with an increased serum urate level[24].

At the same time, we found that the prevalence of hyperuricemia gradually decreased with age in male non-obese patients, which was inconsistent with previous studies[25, 26]. One possible reason was that we have excluded patients undergoing urate-lowering treatment in our study. Nowadays, as the prevalence of gout increases

significantly with age, the number of patients taking urate-lowering treatment is also on the rise as age grows, which may lead to a selection bias in our research[27, 28].

Some studies have reported the interaction between hyperuricemia and NAFLD. We previously reported that hyperuricemia is independently associated with the risk of NAFLD[6]. Our previous prospective study also found that NAFLD was strongly associated with an increased risk of incident hyperuricemia[8]. In this study, we identified fatty liver as a factor associated with hyperuricemia in the non-obese population. Our results suggested that the interaction between hyperuricemia and metabolic disorders should also be paid attention to in the non-obese population, to prevent further progression to deteriorated metabolic status.

MUHNW, generally defined as normal weight with metabolic syndrome, has raised considerable scientific interest[29]. Individuals with a metabolically unhealthy profile were associated with several health issues and higher healthcare and loss-of-productivity costs[30]. The risk of CVD in MUHNW individuals was 1.5–3-fold higher than that in MHNW individuals, and higher than the relative risk in those with metabolically healthy obesity (MHO) [31]. It is not rare to find that MUHNW individuals have a worse prognosis of diabetes than MHO individuals[32]. In this study, we found that the prevalence of hyperuricemia increased significantly in MUHNW participants compared with that in MHNW participants. This phenomenon was more obvious in women, which implied that we could pay more attention to serum uric acid level in MUHNW individuals. As they are more likely to suffer from hyperuricemia, early intervention in uric acid level may benefit these patients by protecting them

from developing further metabolic disorders[33].

We next assessed the comorbidity of other metabolic disorders in non-obese hyperuricemic patients. We found that the prevalence of metabolic syndrome and of fatty liver disease in non-obese hyperuricemic participants were higher than those in normouremic controls. This indicated that hyperuricemia in the non-obese population could also be accompanied by multiple metabolic disorders. Studies have reported hyperuricemia as a cause of metabolic syndrome[7]. Our previous studies also found that hyperuricemia could promote the occurrence and development of NAFLD, and urate-lowering treatment could alleviate NAFLD[8]. Therefore, non-obese hyperuricemic individuals may also need active intervention in uric acid level to reduce the risk of comorbid metabolic disorders[34].

Several limitations are acknowledged in this study. First, it is a single-center cross-sectional study. Our sample size may be insufficient to represent the entire Chinese adult population, and further multi-center cohort studies are needed. Second, in our study, patients currently undergoing urate-lowering treatment were excluded, which might cause a selection bias in the prevalence of hyperuricemia. In our research, some factors related to uric acid were not included, such as gout, renal disease, and treatment with diuretics, etc. Third, dietary information was not collected, though dietary intake could be a cofactor associated with hyperuricemia. Some studies have shown that fructose-enriched food and drink could increase serum UA levels[35]. Meanwhile, this study defined the non-obese participants by BMI without including waist circumference or waist-to-hip ratio. Some central obese

patients could be mixed in the non-obese participants.

In conclusion, our cross-sectional study showed that the prevalence of hyperuricemia was 9.4% in the non-obese Chinese population. The prevalence of hyperuricemia increased significantly in MUHNW participants compared with MHNW participants. Hyperuricemia in non-obese people could also be accompanied by multiple metabolic disorders. Therefore, we suggest that clinicians pay attention to serum uric acid level in non-obese patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Author Contributions:

Conceived and designed the experiment: X.C.F. and Z.H.L. Collected the clinical information: W.J.H, C.Y.S. and C.S.H. Analyzed the data: W.J.H, W.X.Y. and Z.H.L. Wrote the paper: W.J.H. and C.Y.S. All authors reviewed the manuscript.

Data Availability Statement

Data are available upon reasonable request.

References

1. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology (Oxford) 2019; 58(12): 2177-80.
2. Zheng R, Chen C, Yang T, Chen Q, Lu R, Mao Y. Serum Uric Acid Levels and the Risk of Obesity: a Longitudinal Population-Based Epidemiological Study. Clin Lab 2017; 63(10): 1581-87.
3. Son M, Seo J, Yang S. Association between dyslipidemia and serum uric acid levels in Korean adults: Korea National Health and Nutrition Examination Survey 2016-2017. PLoS One 2020; 15(2): e0228684.
4. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol 2013; 25(2): 210-6.
5. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, Hypertension, and Chronic Kidney Disease: an Emerging Association. Curr Hypertens Rep 2016; 18(10): 74.
6. Li Y, Xu C, Yu C, Xu L, Miao M. Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. J Hepatol 2009; 50(5): 1029-34.
7. King C, Lanaspa MA, Jensen T, Tolan DR, Sanchez-Lozada LG, Johnson RJ. Uric Acid as a Cause of the Metabolic Syndrome. Contrib Nephrol 2018; 192: 88-102.
8. Xu C, Wan X, Xu L, et al. Xanthine oxidase in non-alcoholic fatty liver disease and hyperuricemia: One stone hits two birds. J Hepatol 2015; 62(6): 1412-9.
9. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011; 63(10): 3136-41.
10. Liu R, Han C, Wu D, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. Biomed Res Int 2015; 2015: 762820.
11. Wan Z, Song L, Hu L, Lei X, Huang Y, Lv Y. Temporal trends in hyperuricaemia among adults in Wuhan city, China, from 2010 to 2019: a cross-sectional study. BMJ Open 2021; 11(3): e043917.
12. Peng TC, Wang CC, Kao TW, et al. Relationship between hyperuricemia and lipid profiles in US adults. Biomed Res Int 2015; 2015: 127596.
13. Juraschek SP, Kovell LC, Miller ER, Gelber AC. Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. PLoS One 2013; 8(2): e56546.
14. Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 2013; 108(8): 1299-304.
15. Kashima S, Inoue K, Matsumoto M, Akimoto K. Prevalence and characteristics of non-obese diabetes in Japanese men and women: the Yuport Medical Checkup Center Study. J Diabetes 2015; 7(4): 523-30.
16. Huang YF, Yang KH, Chen SH, et al. [Practice guideline for patients with hyperuricemia/gout]. Zhonghua Nei Ke Za Zhi 2020; 59(7): 519-27.
17. Zhang Y, Nie FQ, Huang XB, et al. High prevalence and low awareness of hyperuricemia in hypertensive patients among adults aged 50-79 years in Southwest China. BMC Cardiovasc Disord 2022; 22(1): 2.
18. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006; 17(10): 2937-44.

19. Fan JG, Wei L, Zhuang H, National Workshop on Fatty L, Alcoholic Liver Disease CSOHCMA, Fatty Liver Disease Expert Committee CMDA. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis 2019; 20(4): 163-73.
20. Expert Panel on Detection E, Treatment of High Blood Cholesterol In A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-97.
21. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018; 37(9): 2529-38.
22. Gaffo AL, Jacobs DR, Jr., Lewis CE, Mikuls TR, Saag KG. Association between being African-American, serum urate levels and the risk of developing hyperuricemia: findings from the Coronary Artery Risk Development in Young Adults cohort. Arthritis Res Ther 2012; 14(1): R4.
23. Mcadams-Demarco MA, Law A, Maynard JW, Coresh J, Baer AN. Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. BMC Musculoskelet Disord 2013; 14: 347.
24. Koga M, Saito H, Mukai M, Kasayama S, Yamamoto T. Factors contributing to increased serum urate in postmenopausal Japanese females. Climacteric 2009; 12(2): 146-52.
25. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. Sci Rep 2018; 8(1): 4314.
26. Cui L, Meng L, Wang G, et al. Prevalence and risk factors of hyperuricemia: results of the Kailuan cohort study. Mod Rheumatol 2017; 27(6): 1066-71.
27. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020; 16(7): 380-90.
28. Robinson PC, Taylor WJ, Dalbeth N. An Observational Study of Gout Prevalence and Quality of Care in a National Australian General Practice Population. J Rheumatol 2015; 42(9): 1702-7.
29. Lonardo A, Mantovani A, Lugari S, Targher G. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. Ann Hepatol 2020; 19(4): 359-66.
30. Samouda H, Ruiz-Castell M, Karimi M, et al. Metabolically healthy and unhealthy weight statuses, health issues and related costs: Findings from the 2013-2015 European Health Examination Survey in Luxembourg. Diabetes Metab 2019; 45(2): 140-51.
31. Schulze MB. Metabolic health in normal-weight and obese individuals. Diabetologia 2019; 62(4): 558-66.
32. Buscemi S, Chiarello P, Buscemi C, et al. Characterization of Metabolically Healthy Obese People and Metabolically Unhealthy Normal-Weight People in a General Population Cohort of the ABCD Study. J Diabetes Res 2017; 2017: 9294038.
33. Borghi C, Agabiti-Rosei E, Johnson RJ, et al. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. Eur J Intern Med 2020; 80: 1-11.
34. Bove M, Cicero AF, Veronesi M, Borghi C. An evidence-based review on urate-lowering treatments: implications for optimal treatment of chronic hyperuricemia. Vasc Health Risk Manag 2017; 13: 23-28.
35. Caliceti C, Calabria D, Roda A, Cicero AFG. Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: A Critical Review. Nutrients 2017; 9(4).

Table 1. Clinical characteristics of the study population

Variables	Male		P value	Female		P value
	Without hyperuricemia (n =1967)	With hyperuricemia (n =382)		Without hyperuricemia (n =3226)	With hyperuricemia (n =156)	
Age (year)	46.5(46.0-47.1)	44.5(43.3-45.7)	0.004	43.4(43.0-43.8)	46.6(44.3-49.0)	0.009
WC (cm)	81.3(81.1-81.5)	83.1(82.6-83.6)	<0.001	74.0(73.8-74.2)	76.6(75.5-77.7)	<0.001
BMI (kg/m^2)	21.87(21.80-21.94)	22.33(22.19-22.47)	<0.001	20.94(20.88-21.00)	21.64(21.36-21.92)	<0.001
SBP (mmHg)	122.8(122.1-123.5)	124.1(122.4-125.8)	0.159	115.0(114.4-115.6)	122.2(119.0-125.4)	<0.001
DBP (mmHg)	75.6(75.1-76.1)	77.2(76.1-78.3)	0.009	69.2(68.8-69.6)	73.9(72.1-75.7)	<0.001
ALT (U/L)	21.4(20.6-22.3)	26.5(24.7-28.4)	<0.001	15.2(14.9-15.6)	23.2(18.4-28.0)	0.001
AST (U/L)	20.6(20.1-21.0)	22.5(21.6-23.5)	0.001	18.4(18.1-18.6)	23.1(20.5-25.7)	0.001
GGT (U/L)	30.1(29.1-32.9)	41.6(37.7-45.6)	<0.001	16.8(16.2-17.5)	22.9(19.5-26.3)	<0.001
Creatinine (μmol/L)	81.2(80.6-81.8)	86.5(84.6-88.4)	<0.001	59.5(59.2-59.8)	63.8(62.2-65.4)	<0.001
BUN (mmol/L)	5.12(5.07-5.17)	5.37(5.21-5.53)	0.003	4.55(4.51-4.59)	5.07(4.84-5.30)	<0.001
eGFR	101.1(100.4-101.8)	95.3(93.5-97.1)	<0.001	188.7(188.0-189.4)	109(105.4-112.6)	<0.001
TG (mmol/L)	1.38(1.34-1.42)	1.88(1.76-2.00)	<0.001	1.05(1.03-1.07)	1.60(1.28-1.92)	0.001
TC (mmol/L)	4.49(4.45-4.53)	4.71(4.62-4.80)	<0.001	4.52(4.49-4.55)	4.76(4.62-4.90)	0.001
HDL-C (mmol/L)	1.21(1.20-1.22)	1.14(1.11-1.17)	<0.001	1.44(1.43-1.45)	1.36(1.30-1.42)	0.003
LDL-C (mmol/L)	2.62(2.59-2.65)	2.72(2.65-2.79)	0.012	2.53(2.51-2.55)	2.65(2.53-2.77)	0.026
VLDL-C (mmol/L)	0.65(0.64-0.66)	0.84(0.80-0.88)	<0.001	0.55(0.54-0.56)	0.73(0.65-0.81)	<0.001
FBS (mmol/L)	5.02(4.97-5.07)	5.01(4.93-5.09)	0.815	4.81(4.79-4.83)	5.07(4.93-5.21)	<0.001
Excessive drinking (%)	14.0%(12.5%-15.5%)	19.4%(15.4%-23.4%)	0.007	1.4%(1.0%-1.8%)	3.8%(0.8%-6.8%)	0.016
Smoking history (%)	39.0%(36.8%-41.2%)	42.9%(37.9%-47.9%)	0.15	1.4%(1.0%-1.8%)	1.3%(0%-3.1%)	0.906
SUA (μmol/L)	333.8(331.6-336.0)	467.9(463.2-472.6)	<0.001	260.0(258.5-261.5)	397.1(390.8-403.4)	<0.001

Data are expressed as the mean (95% CI)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SUA: serum uric acid; TG: triglyceride; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; WC: waist circumference.

Table 2. Prevalence of metabolic disease according to hyperuricemia

	Male			Female		
	Without hyperuricemia	With hyperuricemia	*P*-value	Without hyperuricemia	With hyperuricemia	*P*-value
Metabolic syndrome	5.4%	10.2%	<0.001	4%	16%	<0.001
Metabolic syndrome components						
Waist circumference (> 102 cm in men, >88 cm in women)	0%	0%	/	1.4%	3.2%	0.06
Fasting blood glucose (≥ 6.1 mmol/L)	6.4%	6.5%	0.890	2%	10.9%	<0.001
Triglyceride (≥1.7mmol/L)	21.9%	45%	<0.001	10.8%	26.3%	<0.001
HDL-C (<1.04 mmol/L in men, <1.30 mmol/L in women)	28.9%	37.7%	0.001	35.2%	48.1%	0.001
Blood pressure (≥130/85 mmHg)	33.7%	38%	0.105	19.3%	35.9%	<0.001
Diabetes mellitus	3.4%	2.9%	0.599	1%	2.6%	0.062
NAFLD	13.8%	30.4%	<0.001	6.4%	20.5%	<0.001

HDL-C: high-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease;

Table 3. Multivariable analysis for factors associated with hyperuricemia

Variables	Male		Female	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (year)	0.961(0.950-0.972)	<0.001	0.958 (0.939-0.977)	<0.001
WC (cm)	1.057 (1.030-1.084)	<0.001	1.038 (1.006-1.071)	0.020
DBP (mmHg)	/		1.033(1.016-1.050)	<0.001
ALT (U/L)	/		1.023 (1.013-1.033)	<0.001
AST (U/L)	1.014 (1.004-1.024)	0.005	/	
eGFR (μmol/L)	0.973 (0.965-0.980)	<0.001	0.976 (0.966-0.985)	<0.001
BUN (mmol/L)	1.114 (1.014-1.223)	0.025	1.308 (1.137-1.505)	<0.001
TG (mmol/L)	/		1.423 (1.199-1.690)	<0.001
TC (mmol/L)	2.717 (1.921-3.843)	<0.001	/	
HDL-C (mmol/L)	0.378 (0.240-0.594)	<0.001	/	
LDL-C (mmol/L)	0.386 (0.256-0.583)	<0.001	/	
Excessive drinking	1.501 (1.097-2.055)	0.011	3.562 (1.408-9.011)	0.007
NAFLD	1.959 (1.472-2.607)	<0.001	1.900 (1.164-3.102)	0.010

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; TG: triglyceride; TC: total cholesterol; WC: waist circumference

Figure Legend

Figure 1. Prevalence of hyperuricemia(A) and Serum uric acid(B) in participants

Data was expressed as mean with 95% confidence interval (error bars)

Figure 2. Prevalence of hyperuricemia (A) and Serum uric acid (B) in metabolically healthy or metabolically unhealthy participants. Data was expressed as mean ± SD. $^{**}p<0.01$, $^{***}p<0.001$.

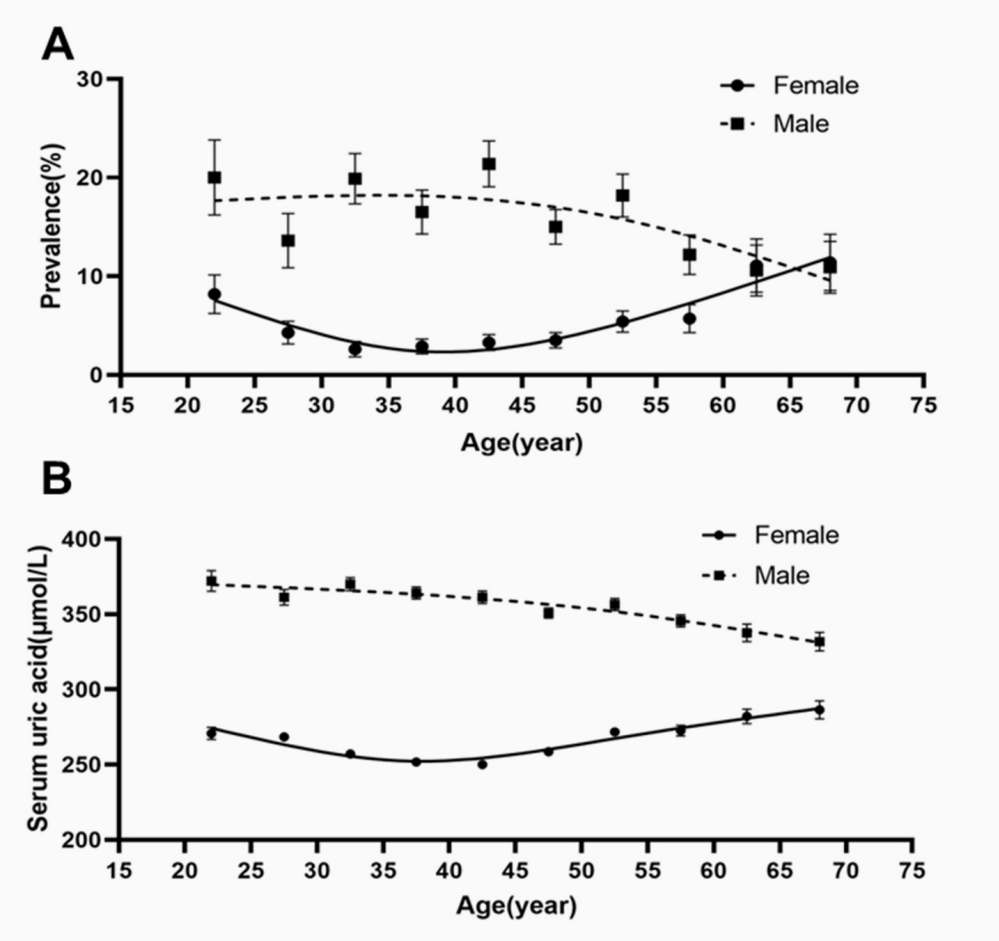

Figure 1

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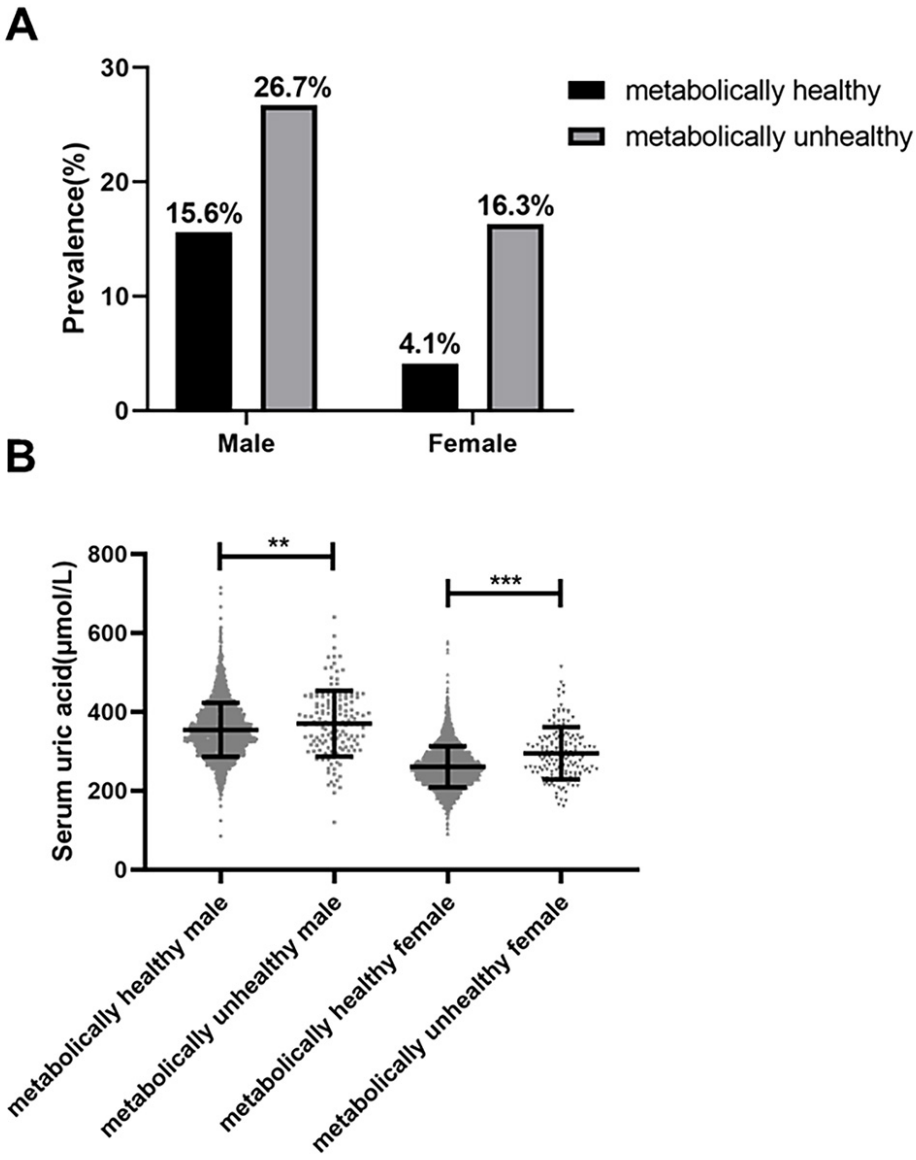

Figure 2

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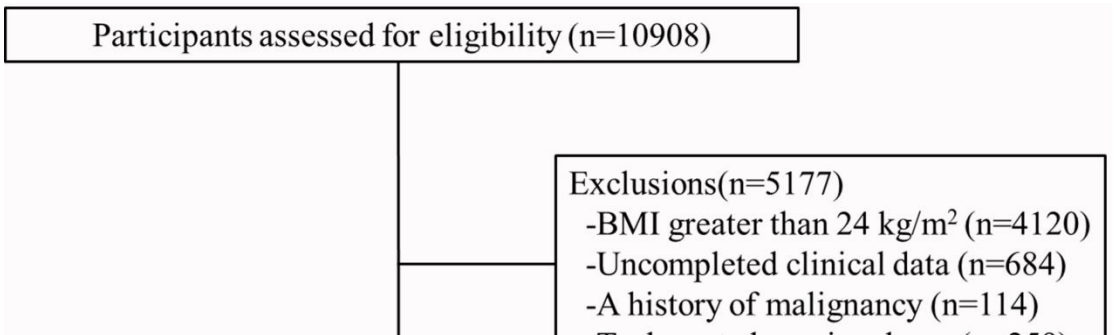

Figure S1. Inclusion and exclusion flow chart of this study

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of hyperuricemia in non-obese Chinese: a single-center cross-sectional study

Jinghua Wang[1,#], Yishu Chen[1,#], Shenghui Chen[1], Xinyu Wang[1], Haoliang Zhai[2,*], Chengfu Xu[1,2,*]

[1] Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

[2] Department of Gastroenterology, Haining Branch of the First Affiliated Hospital, Zhejiang University School of Medicine, Haining 314400, China

***Corresponding author:**

Chengfu Xu, M.D., Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine. 79 Qingchun Road, Hangzhou 310003, China, Tel: 0086-571-87236863, E-mail: xiaofu@zju.edu.cn.

Haoliang Zhai, Department of Gastroenterology, Haining Branch of the First Affiliated Hospital, Zhejiang University School of Medicine. 79 Qingchun Road, Hangzhou 314400, China, Tel: 0086-573-89230531, E-mail: inzaghi1004@sina.com.

# Jinghua Wang and Yishu Chen contributed equally to this work.

Key words: Hyperuricemia; Non-obese; Risk factor; Cross-sectional study; Nonalcoholic fatty liver disease

Abstract

Objectives: Hyperuricemia is closely related to metabolic diseases and is receiving increasing attention from all over the world. This study aimed to investigate the prevalence and factors associated with hyperuricemia in non-obese Chinese population.

Design: Cross-sectional study

Setting: A large general hospital that can provide health checkups in Hangzhou, China.

Participants: A total of 5731 apparently healthy Chinese adults (2349 men and 3382 women) who took their health checkups during the year of 2019. Exclusion criteria: (1) those with BMI $\geqslant$ 24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate-lowering treatment.

Primary and secondary outcome measures: The prevalence and factors associated with hyperuricemia in non-obese Chinese adults.

Results: Of the 5731 non-obese participants enrolled, 538 (9.4%) were diagnosed as hyperuricemia, specifically 16.3% in men and 4.6% in women. The prevalence of hyperuricemia increased greatly in women over 50 years old. The prevalence of hyperuricemia was significantly higher in metabolically unhealthy participants with normal weight than in metabolically healthy participants with normal weight. Hyperuricemic participants showed a higher prevalence of metabolic syndrome and fatty liver disease than normouremic participants. Age, waist circumference, eGFR,

blood urea nitrogen, excessive drinking and fatty liver were associated with hyperuricemia in both genders.

Conclusion: The prevalence of hyperuricemia was 9.4% in non-obese Chinese adults. Non-obese hyperuricemic participants also showed multiple metabolic disorders. We suggest that clinicians pay attention to serum uric acid level in non-obese patients.

Strengths and limitations of this study

This study included a large sample size of participants (more than 5000 adults), which made our findings more convincible.

This is the first study that has evaluated the prevalence of hyperuricemia among non-obese adults in China.

A multivariate logistic model was used to correct selection biases by adjusting for potential confounders.

It is a single-center cross-sectional study, and further multi-center cohort studies are needed.

Patients currently undergoing urate-lowering treatment were excluded, which might cause a selection bias in the prevalence of hyperuricemia in this study.

Introduction

Hyperuricemia, defined as elevated uric acid level in blood, is a metabolic disorder commonly recognized to be closely related to gout and CKD[1]. Over the last decade, more and more studies have found that hyperuricemia is also associated with other metabolic diseases, such as obesity, hypertension, dyslipidemia, and nonalcoholic fatty liver disease (NAFLD)[2-6]. Some studies also suggested hyperuricemia as an independent risk factor for metabolic syndrome and non-alcoholic fatty liver disease[7, 8]. Moreover, the prevalence of hyperuricemia varies across populations and regions. In the United States, approximately 21.4% of adults met the criteria for hyperuricemia in the first decade of the 21st century, which was 3.2% higher than that of NHANES 1988–1994[9]. A recent meta-analysis reported that the pooled prevalence of hyperuricemia was 13.3% in China[10]. A study from Wuhan, China suggested that the prevalence of hyperuricemia in men rose from 26.1% in 2010 to 34.4% in 2019, and the prevalence of hyperuricemia in women rose from 5.8% in 2010 to 10.1% in 2019[11]. The findings above may call for more attention on the health problem of hyperuricemia from a metabolic perspective, yet entailing further verification across populations.

Many metabolism-related indicators are independent risk factors for hyperuricemia. A study from the United States reported that serum levels of triglyceride, total cholesterol, apolipoprotein-B, and low-density lipoprotein cholesterol (LDL-C), and ratio of triglyceride to high-density lipoprotein cholesterol (HDL-C) were strongly positively associated with serum uric acid level, whereas

serum HDL-C level was significantly inversely associated[12]. Juraschek *et al.* found that individuals with uncontrolled blood pressure and additional cardiovascular disease risk factors had a 4-fold or higher prevalence of hyperuricemia[13].

It is generally believed that obesity is closely associated with metabolism-related diseases, and it increases the risk of developing diabetes, NAFLD and hyperuricemia. Recently, more and more studies have shifted their attention to metabolic disorders in the non-obese population. Some studies showed that the non-obese population could also present a high prevalence of NAFLD. For example, as we previously reported, the prevalence of NAFLD in a non-obese Chinese population was 7.3%[14]. A study from Japan warned that more than 60% of Japanese diabetic subjects are non-obese[15]. The findings suggest that it be important to assess metabolic abnormalities in non-obese individuals. So far, there has still been a paucity of studies on hyperuricemia in the non-obese population.

In this study, we conducted a cross-sectional analysis on a non-obese Chinese population to evaluate the prevalence of hyperuricemia and determine its associated factors.

Methods

Study population

We conducted a cross-sectional study on adults who took their health checkups at the First Affiliated Hospital, Zhejiang University School of Medicine from January 1 to December 31, 2019. All participants received medical history collection, anthropometric testing, blood examination, and abdominal ultrasound examination. We excluded the following participants: (1) those with BMI $\geqslant$24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate-lowering treatment. A total of 10908 participants were enrolled in this study, 4120 of whom had BMI greater than 24 kg/m^2, 684 had incomplete data, 114 had a history of malignancy, and 259 took urate-lowering drugs. Finally, a total of 5731 participants (2349 men and 3382 women) were qualified for the cross-sectional study (Figure S1).

Clinical evaluations

We collected standing height, body weight, waist circumference and blood pressure from all participants. Height and weight were measured while participants were wearing light clothes without shoes. BMI (kg/m^2) was calculated as the body weight (kg) divided by the standing height (m) squared. Blood pressure was measured using a standard protocol. Fasting serum samples were obtained for the analysis of biochemical parameters. The values were measured by a Hitachi 7600 clinical analyzer (Hitachi, Tokyo, Japan) using standard methods. Questions about alcohol

intake included frequency of alcohol consumption (per week) and usual amount per day. Questions about smoking history included daily smoking count and years of smoking.

Diagnostic criteria and definitions

BMI was adopted to define obesity. Non-obese was defined as BMI < 24 kg/m^2, and obesity is defined as BMI ≥24 kg/m^2. Excessive drinking was defined as alcohol consumption >210 g/week for men or >70 g/week for women. Hyperuricemia was defined as serum uric acid level >420 μmol/L for men or >360 μmol/L for women[8, 16, 17]. The factor eGFR (estimated glomerular filtration rate) was calculated using the modified MDRD formula[18].

All individuals included in the study underwent abdominal ultrasound examination, which was performed by trained ultrasonographists with a Toshiba Nemio 20 ultrasound system (Toshiba, Tokyo, Japan). The ultrasonographists were blinded to the study design and the clinical data. The criteria for ultrasonic diagnosis of fatty liver were based on those suggested by the Chinese Liver Disease Association[19].

Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III report[20]. Participants diagnosed with metabolic syndrome must have three or more of the following factors: (1) central obesity, defined as waist circumference >102 cm for men or >88 cm for women; (2) raised serum triglyceride level, defined as triglyceride ⩾ 1.7 mmol/L or specific

treatment for this lipid abnormality; (3) reduced HDL cholesterol, defined as HDL cholesterol <1.03 mmol/L for men or <1.29 mmol/L for women; (4) elevated blood pressure, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and (5) raised fasting blood sugar, defined as fasting blood sugar ≥6.1 mmol/L, or previously diagnosed type 2 diabetes. Metabolically unhealthy participants were defined as those who met the criteria of metabolic syndrome.

Statistical analyses

The statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL). Continuous variables were presented as mean and 95% confidence interval (CI) and compared by Student's *t* test or Mann-Whitney *U* test as appropriate. Categorical variables were compared using the χ^2 test. A stepwise logistic regression analysis was performed to examine the relationship between hyperuricemia and anthropometric or biochemical variables (probability to enter = 0.05 and probability to remove = 0.10). A *P* value <0.05 (two-tailed) was considered statistically significant.

Ethics

All participants were verbally informed of the study's aim and procedures, and gave voluntary consent. The subject information was anonymized at collection prior to analysis. All methods were performed in accordance with the approved guidelines.

The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No.2021015).

Patient and public involvement

Patients or the public were not involved in the design, conduct, report, or dissemination of our research.

Results

Prevalence of hyperuricemia in the non-obese population

A total of 5731 non-obese participants (2349 men and 3382 women) with a mean age of 44.6±12.0 years were included in this study. The overall prevalence of hyperuricemia was 9.4% (16.3% in males and 4.6% in females). In non-obese males, the prevalence of hyperuricemia was stable before the age of 50, and gradually decreased after 50. Conversely, in non-obese females, the prevalence of hyperuricemia decreased with age before the age of 50, and gradually increased after 50. An interesting finding was that the prevalence of hyperuricemia in females was even higher than that in males after the age of 65 (Figure 1).

We compared the clinical characteristics of participants with or without hyperuricemia in both genders (Table 1). We found that hyperuricemic participants showed greater BMI (22.33 (22.19—22.47) versus 21.87 (21.80—21.94) kg/m^2, p<0.001 in males; 21.64 (21.36–21.92) versus 20.94 (20.88–21.00) kg/m^2, p<0.001 in females) and waist circumference (83.1 (82.6–83.6) versus 81.3 (81.1–81.5) cm, p<0.001 in males; 76.6 (75.5–77.7) versus 74.0 (73.8–74.2) cm, p<0.001 in females), higher diastolic blood pressure (77.2 (76.1–78.3) versus 75.6 (75.1–76.1) mmHg, p=0.006 in males; 73.9 (72.1–75.7) versus 69.2 (68.8–69.6) mmHg, p<0.001 in females), and worse lipid profiles than those without hyperuricemia. Hyperuricemic participants also had higher serum levels of alanine aminotransferase (ALT) (26.5 (24.7–28.4) versus 21.4 (20.6 - 22.3) U/L, p<0.001 in males; 23.2 (18.4 - 28.0) versus 15.2 (14.9 - 15.6) U/L, p=0.001 in females), aspartate aminotransferase (AST)

(22.5 (21.6 – 23.5) versus 20.6 (20.1 – 21.0) U/L, p=0.001 in males; 23.1 (20.5 – 25.7) versus 18.4 (18.1 – 18.6) U/L, p=0.001 in females), gamma–glutamyl transpeptidase (GGT) (41.6 (37.7 – 45.6) versus 30.1 (29.1 – 32.9) U/L, p<0.001 in males; 22.9 (19.5 – 26.3) versus 16.8 (16.2 – 17.5) U/L, p<0.001 in females), blood urea nitrogen (BUN) (5.37 (5.21 – 5.53) versus 5.12 (5.07 – 5.17) mmol/L, p=0.003 in males; 5.07 (4.84 – 5.30) versus 4.55 (4.51 – 4.59) mmol/L, p<0.001 in females), and creatinine (86.5 (84.6 – 88.4) versus 81.2 (80.6 – 81.8) μmol/L, p<0.001 in males; 63.8 (62.2 – 65.4) versus 59.5 (59.2 – 59.8) μmol/L, p<0.001 in females) than normouremic participants.

Association of hyperuricemia with metabolic disorders in the non-obese population

We classified all the non-obese participants into metabolically healthy normal weight (MHNW) group and metabolically unhealthy normal weight (MUHNW) group, according to their metabolic status. We found that MUHNW participants had a significantly higher prevalence of hyperuricemia than MHNW participants. In detail, the prevalence of hyperuricemia increased from 15.6% in MHNW participants to 26.7% in MUHNW participants in males (p<0.001). Similarly, the prevalence of hyperuricemia increased from 4.1% in MHNW participants to 16.3% in MUHNW participants in females (p<0.001) (Figure 2).

We also analyzed the prevalence of metabolic disorders in non-obese individuals with or without hyperuricemia. We found that the prevalence of metabolic syndrome

were significantly higher in hyperuricemic participants (male 10.2%, female 16%) than in normouremic participants (male 5.4%, female 4%; $p<0.001$ in both genders). We also found that the prevalence of fatty liver disease were significantly higher in hyperuricemic participants (male 30.4%, female 20.5%) than in normouremic participants (male 13.8%, female 6.4%; $p<0.001$ in both genders). Male hyperuricemic participants had a higher prevalence of raised triglyceride level and reduced HDL-C than normouremic participants. Female hyperuricemic participants had a higher prevalence of raised triglyceride level, reduced HDL-C, elevated blood pressure, and raised fasting blood sugar than normouremic participants (Table 2). However, the prevalence of diabetes was not different between the two groups (Table 2).

Factors associated with hyperuricemia among the non-obese population

We analyzed the factors associated with hyperuricemia by stepwise logistic regression analysis. The multivariable model showed that greater waist circumference values (1.057 (1.030–1.084) (the data was expressed as OR (95%CI) , the same below) in males and 1.038 (1.006–1.071) in females), elevated BUN levels (1.114 (1.014–1.223) in males and 1.308 (1.137–1.505) in females), excessive drinking (1.501 (1.097–2.055) in males and 3.562 (1.408–9.011) in females) and presence of fatty liver (1.959 (1.472–2.607) in males and 1.900 (1.164–3.102) in females) were associated with an increased prevalence of hyperuricemia in both genders. Greater age (0.961 (0.950–0.972) in males and 0.958 (0.939–0.977) in females) and elevated

eGFR levels (0.973 (0.965–0.980) in males and 0.976 (0.966–0.985) in females) were associated with a decreased prevalence of hyperuricemia in both genders. Elevated serum levels of AST (1.014 (1.004–1.024)) and total cholesterol (2.717 (1.921–3.843)) were associated with an increased prevalence of hyperuricemia in males. Elevated serum levels of HDL-C (0.378 (0.240–0.594)) and LDL-C (0.386 (0.256–0.583)) were associated with a decreased prevalence of hyperuricemia in males. Elevated diastolic blood pressure (1.033 (1.016–1.050)), higher ALT (1.023 (1.013–1.033)) and triglyceride (1.423 (1.199–1.690)) levels were associated with an increased prevalence of hyperuricemia in females (Table 3).

Discussion

This study investigated the prevalence and factors associated with hyperuricemia in a non-obese Chinese population. We found that the prevalence of hyperuricemia was 9.4% in the non-obese adults, with 16.3% in men and 4.6% in women. Age, waist circumference, eGFR, BUN, excessive drinking and presence of fatty liver were associated with hyperuricemia in both genders.

The prevalence of hyperuricemia in non-obese individuals was 9.4%, lower than the value previously reported in the general population in East Asia [10, 21], which included both non-obese and obese individuals as a whole, not separately. We found that in the non-obese individuals, the overall prevalence of hyperuricemia was higher in men than in women. However, the prevalence of hyperuricemia increased greatly in women older than 50, which could be corroborated by other studies[22, 23]. This is primarily attributable to the sex hormone effects on renal urate transport. It has been reported that estrogen affects serum uric acid level through renal clearance, secretion and reabsorption. Young adult women have a lower serum urate level than young adult men, while the onset of menopause is associated with an increased serum urate level[24].

At the same time, we found that the prevalence of hyperuricemia gradually decreased with age in male non-obese patients, which was inconsistent with previous studies[25, 26]. One possible reason was that we have excluded patients undergoing urate-lowering treatment in our study. Nowadays, as the prevalence of gout increases

significantly with age, the number of patients taking urate-lowering treatment is also on the rise as age grows, which may lead to a selection bias in our research[27, 28].

Some studies have reported the interaction between hyperuricemia and NAFLD. We previously reported that hyperuricemia is independently associated with the risk of NAFLD[6]. Our previous prospective study also found that NAFLD was strongly associated with an increased risk of incident hyperuricemia[8]. In this study, we identified fatty liver as a factor associated with hyperuricemia in the non-obese population. Our results suggested that the interaction between hyperuricemia and metabolic disorders should also be paid attention to in the non-obese population, to prevent further progression to deteriorated metabolic status.

MUHNW, generally defined as normal weight with metabolic syndrome, has raised considerable scientific interest[29]. Individuals with a metabolically unhealthy profile were associated with several health issues and higher healthcare and loss-of-productivity costs[30]. The risk of CVD in MUHNW individuals was 1.5–3-fold higher than that in MHNW individuals, and higher than the relative risk in those with metabolically healthy obesity (MHO) [31]. It is not rare to find that MUHNW individuals have a worse prognosis of diabetes than MHO individuals[32]. In this study, we found that the prevalence of hyperuricemia increased significantly in MUHNW participants compared with that in MHNW participants. This phenomenon was more obvious in women, which implied that we could pay more attention to serum uric acid level in MUHNW individuals. As they are more likely to suffer from hyperuricemia, early intervention in uric acid level may benefit these patients by protecting them

from developing further metabolic disorders[33].

We next assessed the comorbidity of other metabolic disorders in non-obese hyperuricemic patients. We found that the prevalence of metabolic syndrome and of fatty liver disease in non-obese hyperuricemic participants were higher than those in normouremic controls. This indicated that hyperuricemia in the non-obese population could also be accompanied by multiple metabolic disorders. Studies have reported hyperuricemia as a cause of metabolic syndrome[7]. Our previous studies also found that hyperuricemia could promote the occurrence and development of NAFLD, and urate-lowering treatment could alleviate NAFLD[8]. Therefore, non-obese hyperuricemic individuals may also need active intervention in uric acid level to reduce the risk of comorbid metabolic disorders[34].

Several limitations are acknowledged in this study. First, it is a single-center cross-sectional study. Our sample size may be insufficient to represent the entire Chinese adult population, and further multi-center cohort studies are needed. Second, in our study, patients currently undergoing urate-lowering treatment were excluded, which might cause a selection bias in the prevalence of hyperuricemia. In our research, some factors related to uric acid were not included, such as gout, renal disease, and treatment with diuretics, etc. Third, dietary information was not collected, though dietary intake could be a cofactor associated with hyperuricemia. Some studies have shown that fructose-enriched food and drink could increase serum UA levels[35]. Meanwhile, this study defined the non-obese participants by BMI without including waist circumference or waist-to-hip ratio. Some central obese

patients could be mixed in the non-obese participants.

In conclusion, our cross-sectional study showed that the prevalence of hyperuricemia was 9.4% in the non-obese Chinese population. The prevalence of hyperuricemia increased significantly in MUHNW participants compared with MHNW participants. Hyperuricemia in non-obese people could also be accompanied by multiple metabolic disorders. Therefore, we suggest that clinicians pay attention to serum uric acid level in non-obese patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Author Contributions:

Conceived and designed the experiment: X.C.F. and Z.H.L. Collected the clinical information: W.J.H, C.Y.S. and C.S.H. Analyzed the data: W.J.H, W.X.Y. and Z.H.L. Wrote the paper: W.J.H. and C.Y.S. All authors reviewed the manuscript.

Data Availability Statement

Data are available upon reasonable request.

References

1. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology (Oxford) 2019; 58(12): 2177-80.
2. Zheng R, Chen C, Yang T, Chen Q, Lu R, Mao Y. Serum Uric Acid Levels and the Risk of Obesity: a Longitudinal Population-Based Epidemiological Study. Clin Lab 2017; 63(10): 1581-87.
3. Son M, Seo J, Yang S. Association between dyslipidemia and serum uric acid levels in Korean adults: Korea National Health and Nutrition Examination Survey 2016-2017. PLoS One 2020; 15(2): e0228684.
4. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol 2013; 25(2): 210-6.
5. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, Hypertension, and Chronic Kidney Disease: an Emerging Association. Curr Hypertens Rep 2016; 18(10): 74.
6. Li Y, Xu C, Yu C, Xu L, Miao M. Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. J Hepatol 2009; 50(5): 1029-34.
7. King C, Lanaspa MA, Jensen T, Tolan DR, Sanchez-Lozada LG, Johnson RJ. Uric Acid as a Cause of the Metabolic Syndrome. Contrib Nephrol 2018; 192: 88-102.
8. Xu C, Wan X, Xu L, et al. Xanthine oxidase in non-alcoholic fatty liver disease and hyperuricemia: One stone hits two birds. J Hepatol 2015; 62(6): 1412-9.
9. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011; 63(10): 3136-41.
10. Liu R, Han C, Wu D, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. Biomed Res Int 2015; 2015: 762820.
11. Wan Z, Song L, Hu L, Lei X, Huang Y, Lv Y. Temporal trends in hyperuricaemia among adults in Wuhan city, China, from 2010 to 2019: a cross-sectional study. BMJ Open 2021; 11(3): e043917.
12. Peng TC, Wang CC, Kao TW, et al. Relationship between hyperuricemia and lipid profiles in US adults. Biomed Res Int 2015; 2015: 127596.
13. Juraschek SP, Kovell LC, Miller ER, Gelber AC. Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. PLoS One 2013; 8(2): e56546.
14. Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 2013; 108(8): 1299-304.
15. Kashima S, Inoue K, Matsumoto M, Akimoto K. Prevalence and characteristics of non-obese diabetes in Japanese men and women: the Yuport Medical Checkup Center Study. J Diabetes 2015; 7(4): 523-30.
16. Huang YF, Yang KH, Chen SH, et al. [Practice guideline for patients with hyperuricemia/gout]. Zhonghua Nei Ke Za Zhi 2020; 59(7): 519-27.
17. Zhang Y, Nie FQ, Huang XB, et al. High prevalence and low awareness of hyperuricemia in hypertensive patients among adults aged 50-79 years in Southwest China. BMC Cardiovasc Disord 2022; 22(1): 2.
18. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006; 17(10): 2937-44.

19. Fan JG, Wei L, Zhuang H, National Workshop on Fatty L, Alcoholic Liver Disease CSOHCMA, Fatty Liver Disease Expert Committee CMDA. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis 2019; 20(4): 163-73.
20. Expert Panel on Detection E, Treatment of High Blood Cholesterol In A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-97.
21. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018; 37(9): 2529-38.
22. Gaffo AL, Jacobs DR, Jr., Lewis CE, Mikuls TR, Saag KG. Association between being African-American, serum urate levels and the risk of developing hyperuricemia: findings from the Coronary Artery Risk Development in Young Adults cohort. Arthritis Res Ther 2012; 14(1): R4.
23. Mcadams-Demarco MA, Law A, Maynard JW, Coresh J, Baer AN. Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. BMC Musculoskelet Disord 2013; 14: 347.
24. Koga M, Saito H, Mukai M, Kasayama S, Yamamoto T. Factors contributing to increased serum urate in postmenopausal Japanese females. Climacteric 2009; 12(2): 146-52.
25. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. Sci Rep 2018; 8(1): 4314.
26. Cui L, Meng L, Wang G, et al. Prevalence and risk factors of hyperuricemia: results of the Kailuan cohort study. Mod Rheumatol 2017; 27(6): 1066-71.
27. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020; 16(7): 380-90.
28. Robinson PC, Taylor WJ, Dalbeth N. An Observational Study of Gout Prevalence and Quality of Care in a National Australian General Practice Population. J Rheumatol 2015; 42(9): 1702-7.
29. Lonardo A, Mantovani A, Lugari S, Targher G. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. Ann Hepatol 2020; 19(4): 359-66.
30. Samouda H, Ruiz-Castell M, Karimi M, et al. Metabolically healthy and unhealthy weight statuses, health issues and related costs: Findings from the 2013-2015 European Health Examination Survey in Luxembourg. Diabetes Metab 2019; 45(2): 140-51.
31. Schulze MB. Metabolic health in normal-weight and obese individuals. Diabetologia 2019; 62(4): 558-66.
32. Buscemi S, Chiarello P, Buscemi C, et al. Characterization of Metabolically Healthy Obese People and Metabolically Unhealthy Normal-Weight People in a General Population Cohort of the ABCD Study. J Diabetes Res 2017; 2017: 9294038.
33. Borghi C, Agabiti-Rosei E, Johnson RJ, et al. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. Eur J Intern Med 2020; 80: 1-11.
34. Bove M, Cicero AF, Veronesi M, Borghi C. An evidence-based review on urate-lowering treatments: implications for optimal treatment of chronic hyperuricemia. Vasc Health Risk Manag 2017; 13: 23-28.
35. Caliceti C, Calabria D, Roda A, Cicero AFG. Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: A Critical Review. Nutrients 2017; 9(4).

Table 1. Clinical characteristics of the study population

Variables	Male		P value	Female		P value
	Without hyperuricemia (n =1967)	With hyperuricemia (n =382)		Without hyperuricemia (n =3226)	With hyperuricemia (n =156)	
Age (year)	46.5(46.0-47.1)	44.5(43.3-45.7)	0.004	43.4(43.0-43.8)	46.6(44.3-49.0)	0.009
WC (cm)	81.3(81.1-81.5)	83.1(82.6-83.6)	<0.001	74.0(73.8-74.2)	76.6(75.5-77.7)	<0.001
BMI (kg/m^2)	21.87(21.80-21.94)	22.33(22.19-22.47)	<0.001	20.94(20.88-21.00)	21.64(21.36-21.92)	<0.001
SBP (mmHg)	122.8(122.1-123.5)	124.1(122.4-125.8)	0.159	115.0(114.4-115.6)	122.2(119.0-125.4)	<0.001
DBP (mmHg)	75.6(75.1-76.1)	77.2(76.1-78.3)	0.009	69.2(68.8-69.6)	73.9(72.1-75.7)	<0.001
ALT (U/L)	21.4(20.6-22.3)	26.5(24.7-28.4)	<0.001	15.2(14.9-15.6)	23.2(18.4-28.0)	0.001
AST (U/L)	20.6(20.1-21.0)	22.5(21.6-23.5)	0.001	18.4(18.1-18.6)	23.1(20.5-25.7)	0.001
GGT (U/L)	30.1(29.1-32.9)	41.6(37.7-45.6)	<0.001	16.8(16.2-17.5)	22.9(19.5-26.3)	<0.001
Creatinine (μmol/L)	81.2(80.6-81.8)	86.5(84.6-88.4)	<0.001	59.5(59.2-59.8)	63.8(62.2-65.4)	<0.001
BUN (mmol/L)	5.12(5.07-5.17)	5.37(5.21-5.53)	0.003	4.55(4.51-4.59)	5.07(4.84-5.30)	<0.001
eGFR	101.1(100.4-101.8)	95.3(93.5-97.1)	<0.001	188.7(188.0-189.4)	109(105.4-112.6)	<0.001
TG (mmol/L)	1.38(1.34-1.42)	1.88(1.76-2.00)	<0.001	1.05(1.03-1.07)	1.60(1.28-1.92)	0.001
TC (mmol/L)	4.49(4.45-4.53)	4.71(4.62-4.80)	<0.001	4.52(4.49-4.55)	4.76(4.62-4.90)	0.001
HDL-C (mmol/L)	1.21(1.20-1.22)	1.14(1.11-1.17)	<0.001	1.44(1.43-1.45)	1.36(1.30-1.42)	0.003
LDL-C (mmol/L)	2.62(2.59-2.65)	2.72(2.65-2.79)	0.012	2.53(2.51-2.55)	2.65(2.53-2.77)	0.026
VLDL-C (mmol/L)	0.65(0.64-0.66)	0.84(0.80-0.88)	<0.001	0.55(0.54-0.56)	0.73(0.65-0.81)	<0.001
FBS (mmol/L)	5.02(4.97-5.07)	5.01(4.93-5.09)	0.815	4.81(4.79-4.83)	5.07(4.93-5.21)	<0.001
Excessive drinking (%)	14.0%(12.5%-15.5%)	19.4%(15.4%-23.4%)	0.007	1.4%(1.0%-1.8%)	3.8%(0.8%-6.8%)	0.016
Smoking history (%)	39.0%(36.8%-41.2%)	42.9%(37.9%-47.9%)	0.15	1.4%(1.0%-1.8%)	1.3%(0%-3.1%)	0.906
SUA (μmol/L)	333.8(331.6-336.0)	467.9(463.2-472.6)	<0.001	260.0(258.5-261.5)	397.1(390.8-403.4)	<0.001

Data are expressed as the mean (95% CI)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SUA: serum uric acid; TG: triglyceride; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; WC: waist circumference.

Table 2. Prevalence of metabolic disease according to hyperuricemia

	Male			Female		
	Without hyperuricemia	With hyperuricemia	*P*-value	Without hyperuricemia	With hyperuricemia	*P*-value
Metabolic syndrome	5.4%	10.2%	<0.001	4%	16%	<0.001
Metabolic syndrome components						
Waist circumference (> 102 cm in men, >88 cm in women)	0%	0%	/	1.4%	3.2%	0.06
Fasting blood glucose (≥ 6.1 mmol/L)	6.4%	6.5%	0.890	2%	10.9%	<0.001
Triglyceride (≥1.7mmol/L)	21.9%	45%	<0.001	10.8%	26.3%	<0.001
HDL-C (<1.04 mmol/L in men, <1.30 mmol/L in women)	28.9%	37.7%	0.001	35.2%	48.1%	0.001
Blood pressure (≥130/85 mmHg)	33.7%	38%	0.105	19.3%	35.9%	<0.001
Diabetes mellitus	3.4%	2.9%	0.599	1%	2.6%	0.062
NAFLD	13.8%	30.4%	<0.001	6.4%	20.5%	<0.001

HDL-C: high-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease;

Table 3. Multivariable analysis for factors associated with hyperuricemia

Variables	Male		Female	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (year)	0.961(0.950-0.972)	<0.001	0.958 (0.939-0.977)	<0.001
WC (cm)	1.057 (1.030-1.084)	<0.001	1.038 (1.006-1.071)	0.020
DBP (mmHg)	/		1.033(1.016-1.050)	<0.001
ALT (U/L)	/		1.023 (1.013-1.033)	<0.001
AST (U/L)	1.014 (1.004-1.024)	0.005	/	
eGFR (μmol/L)	0.973 (0.965-0.980)	<0.001	0.976 (0.966-0.985)	<0.001
BUN (mmol/L)	1.114 (1.014-1.223)	0.025	1.308 (1.137-1.505)	<0.001
TG (mmol/L)	/		1.423 (1.199-1.690)	<0.001
TC (mmol/L)	2.717 (1.921-3.843)	<0.001	/	
HDL-C (mmol/L)	0.378 (0.240-0.594)	<0.001	/	
LDL-C (mmol/L)	0.386 (0.256-0.583)	<0.001	/	
Excessive drinking	1.501 (1.097-2.055)	0.011	3.562 (1.408-9.011)	0.007
NAFLD	1.959 (1.472-2.607)	<0.001	1.900 (1.164-3.102)	0.010

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; TG: triglyceride; TC: total cholesterol; WC: waist circumference

Figure Legend

Figure 1. Prevalence of hyperuricemia(A) and Serum uric acid(B) in participants

Data was expressed as mean with 95% confidence interval (error bars)

Figure 2. Prevalence of hyperuricemia (A) and Serum uric acid (B) in metabolically healthy or metabolically unhealthy participants. Data was expressed as mean ± SD. $^{**}p<0.01$, $^{***}p<0.001$.

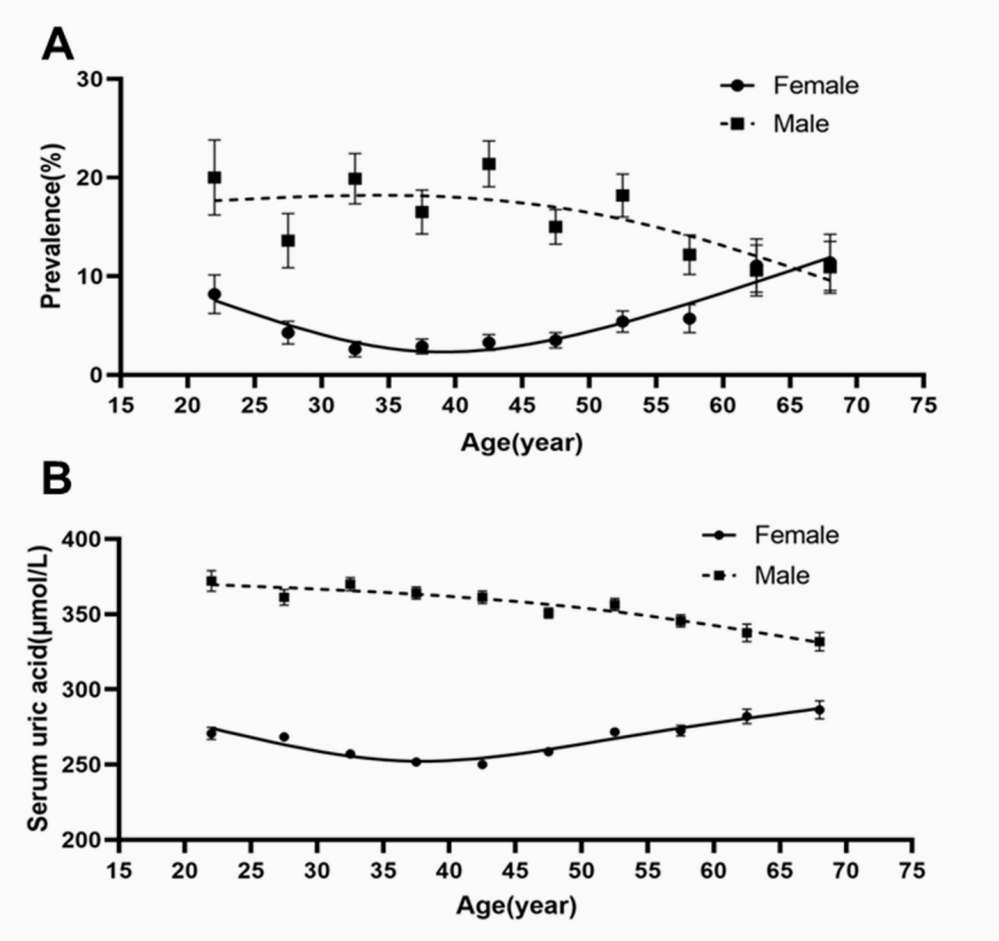

Figure 1

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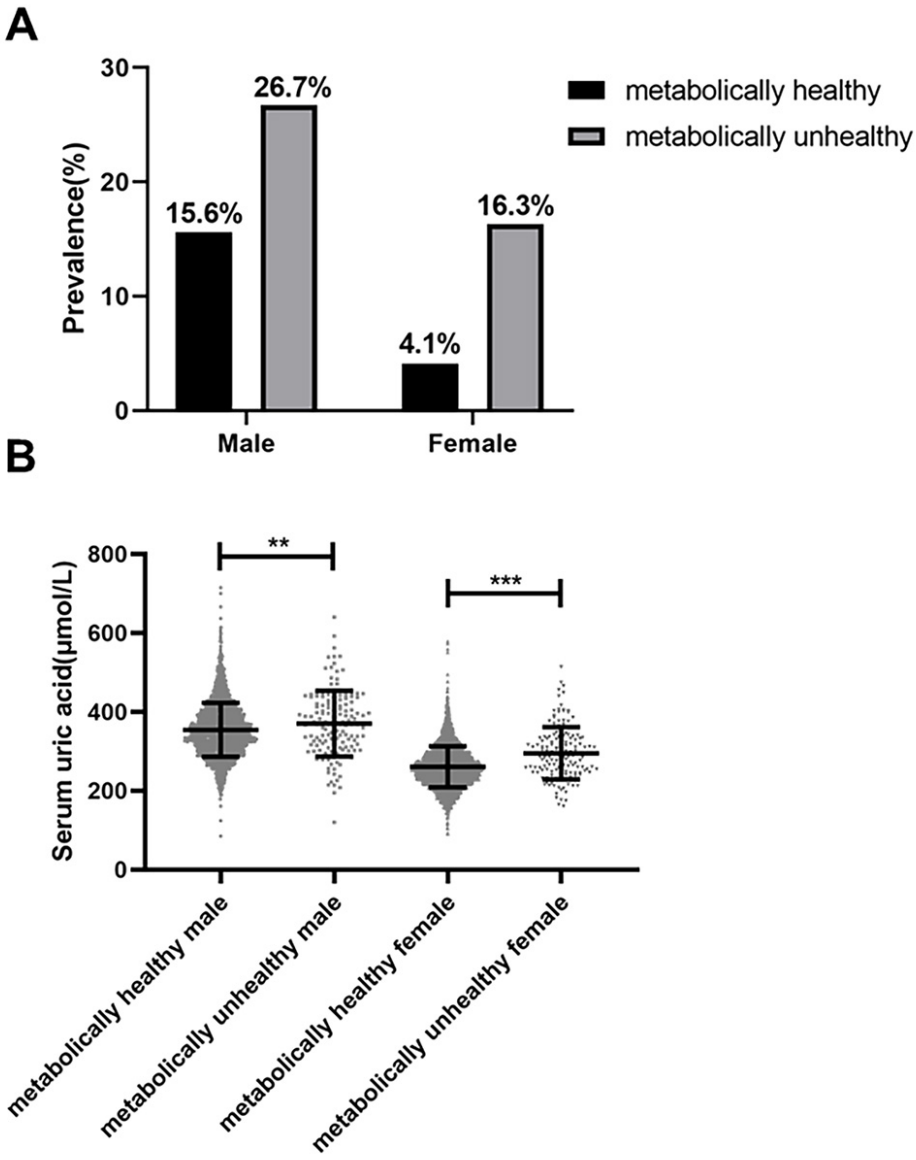

Figure 2

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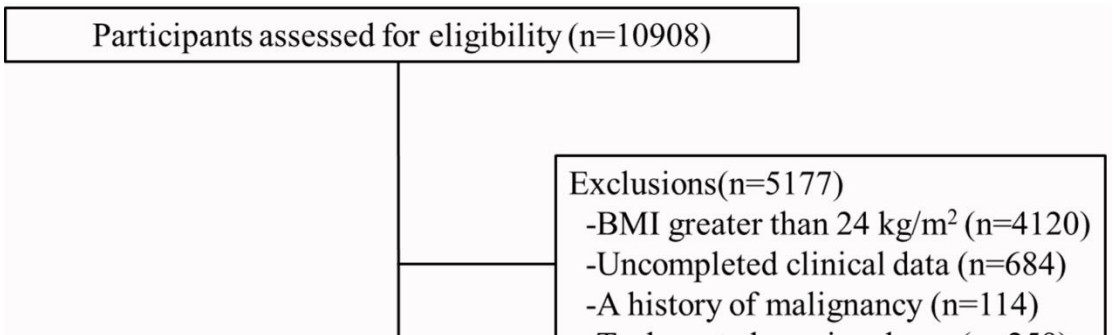

Figure S1. Inclusion and exclusion flow chart of this study

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of hyperuricemia in non-obese Chinese: a single-center cross-sectional study

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Prevalence and risk factors of hyperuricemia in non-obese Chinese: a single-center cross-sectional study

Jinghua Wang[1,#], Yishu Chen[1,#], Shenghui Chen[1], Xinyu Wang[1], Haoliang Zhai[2,*], Chengfu Xu[1,2,*]

[1] Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

[2] Department of Gastroenterology, Haining Branch of the First Affiliated Hospital, Zhejiang University School of Medicine, Haining 314400, China

***Corresponding author:**

Chengfu Xu, M.D., Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine. 79 Qingchun Road, Hangzhou 310003, China, Tel: 0086-571-87236863, E-mail: xiaofu@zju.edu.cn.

Haoliang Zhai, Department of Gastroenterology, Haining Branch of the First Affiliated Hospital, Zhejiang University School of Medicine. 79 Qingchun Road, Hangzhou 314400, China, Tel: 0086-573-89230531, E-mail: inzaghi1004@sina.com.

# Jinghua Wang and Yishu Chen contributed equally to this work.

Key words: Hyperuricemia; Non-obese; Risk factor; Cross-sectional study; Nonalcoholic fatty liver disease

Abstract

Objectives: Hyperuricemia is closely related to metabolic diseases and is receiving increasing attention from all over the world. This study aimed to investigate the prevalence and factors associated with hyperuricemia in non-obese Chinese population.

Design: Retrospective cross-sectional study

Setting: A large general hospital that can provide health checkups in Hangzhou, China.

Participants: A total of 5731 apparently healthy Chinese adults (2349 men and 3382 women) who took their health checkups during the year of 2019. Exclusion criteria: (1) those with BMI $\geqslant$ 24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate-lowering treatment.

Primary and secondary outcome measures: The prevalence and factors associated with hyperuricemia in non-obese Chinese adults.

Results: Of the 5731 non-obese participants enrolled, 538 (9.4%) were diagnosed as hyperuricemia, specifically 16.3% in men and 4.6% in women. The prevalence of hyperuricemia increased greatly in women over 50 years old. The prevalence of hyperuricemia was significantly higher in metabolically unhealthy participants with normal weight than in metabolically healthy participants with normal weight. Hyperuricemic participants showed a higher prevalence of metabolic syndrome and fatty liver disease than normouremic participants. Age, waist circumference, eGFR,

blood urea nitrogen, excessive drinking and fatty liver were associated with hyperuricemia in both genders.

Conclusion: The prevalence of hyperuricemia was 9.4% in non-obese Chinese adults. Non-obese hyperuricemic participants also showed multiple metabolic disorders. We suggest that clinicians pay attention to serum uric acid level in non-obese patients.

Strengths and limitations of this study

This study included a large sample size of participants (more than 5000 adults), which made our findings more convincible.

This is the first study that has evaluated the prevalence of hyperuricemia among non-obese adults in China.

A multivariate logistic model was used to correct selection biases by adjusting for potential confounders.

It is a single-center cross-sectional study, and further multi-center cohort studies are needed.

Patients currently undergoing urate-lowering treatment were excluded, which might cause a selection bias in the prevalence of hyperuricemia in this study.

Introduction

Hyperuricemia, defined as elevated uric acid level in blood, is a metabolic disorder commonly recognized to be closely related to gout and CKD[1]. Over the last decade, more and more studies have found that hyperuricemia is also associated with other metabolic diseases, such as obesity, hypertension, dyslipidemia, and nonalcoholic fatty liver disease (NAFLD)[2-6]. Some studies also suggested hyperuricemia as an independent risk factor for metabolic syndrome and non-alcoholic fatty liver disease[7, 8]. Moreover, the prevalence of hyperuricemia varies across populations and regions. In the United States, approximately 21.4% of adults met the criteria for hyperuricemia in the first decade of the 21st century, which was 3.2% higher than that of NHANES 1988–1994[9]. A recent meta-analysis reported that the pooled prevalence of hyperuricemia was 13.3% in China[10]. A study from Wuhan, China suggested that the prevalence of hyperuricemia in men rose from 26.1% in 2010 to 34.4% in 2019, and the prevalence of hyperuricemia in women rose from 5.8% in 2010 to 10.1% in 2019[11]. The findings above may call for more attention on the health problem of hyperuricemia from a metabolic perspective, yet entailing further verification across populations.

Many metabolism-related indicators are independent risk factors for hyperuricemia. A study from the United States reported that serum levels of triglyceride, total cholesterol, apolipoprotein-B, and low-density lipoprotein cholesterol (LDL-C), and ratio of triglyceride to high-density lipoprotein cholesterol (HDL-C) were strongly positively associated with serum uric acid level, whereas

serum HDL-C level was significantly inversely associated[12]. Juraschek *et al.* found that individuals with uncontrolled blood pressure and additional cardiovascular disease risk factors had a 4-fold or higher prevalence of hyperuricemia[13].

It is generally believed that obesity is closely associated with metabolism-related diseases, and it increases the risk of developing diabetes, NAFLD and hyperuricemia. Recently, more and more studies have shifted their attention to metabolic disorders in the non-obese population. Some studies showed that the non-obese population could also present a high prevalence of NAFLD. For example, as we previously reported, the prevalence of NAFLD in a non-obese Chinese population was 7.3%[14]. A study from Japan warned that more than 60% of Japanese diabetic subjects are non-obese[15]. The findings suggest that it be important to assess metabolic abnormalities in non-obese individuals. So far, there has still been a paucity of studies on hyperuricemia in the non-obese population.

In this study, we conducted a retrospective cross-sectional analysis on a non-obese Chinese population to evaluate the prevalence of hyperuricemia and determine its associated factors.

Methods

Study population

The study population of this cross-sectional study was adults who took their health checkups at the First Affiliated Hospital, Zhejiang University School of Medicine from January 1 to December 31, 2019. All participants received medical history collection, anthropometric testing, blood examination, and abdominal ultrasound examination. The exclusion criteria of the study were as follows: (1) those with BMI $\geqslant$24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate-lowering treatment. A total of 10908 participants were enrolled in this study, 4120 of whom had a BMI greater than 24 kg/m^2, 684 had incomplete data, 114 had a history of malignancy, and 259 took urate-lowering drugs. Finally, a total of 5731 participants (2349 men and 3382 women) were qualified for the cross-sectional study (Figure S1).

Clinical evaluations

Standing height, body weight, waist circumference and blood pressure were collected from all participants. Height and weight were measured while participants were wearing light clothes without shoes. BMI (kg/m^2) was calculated as the body weight (kg) divided by the standing height (m) squared. Blood pressure was measured using a standard protocol. Fasting serum samples were obtained for the analysis of biochemical parameters. The values were measured by a Hitachi 7600 clinical analyzer (Hitachi, Tokyo, Japan) using standard methods. Questions about alcohol

intake included frequency of alcohol consumption (per week) and usual amount per day. Questions about smoking history included daily smoking count and years of smoking.

Diagnostic criteria and definitions

BMI was adopted to define obesity. Non-obese was defined as BMI < 24 kg/m^2, and obesity is defined as BMI ≥24 kg/m^2. Excessive drinking was defined as alcohol consumption >210 g/week for men or >70 g/week for women. Hyperuricemia was defined as serum uric acid level >420 μmol/L for men or >360 μmol/L for women[8, 16, 17]. The factor eGFR (estimated glomerular filtration rate) was calculated using the modified MDRD formula[18].

All individuals included in the study underwent abdominal ultrasound examination, which was performed by trained ultrasonographists with a Toshiba Nemio 20 ultrasound system (Toshiba, Tokyo, Japan). The ultrasonographists were blinded to clinical assessments and laboratory results. The criteria for ultrasonic diagnosis of fatty liver were based on those suggested by the Chinese Liver Disease Association[19].

Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III report[20]. Participants diagnosed with metabolic syndrome must have three or more of the following factors: (1) central obesity, defined as waist circumference >102 cm for men or >88 cm for women; (2) raised serum triglyceride level, defined as triglyceride ⩾ 1.7 mmol/L or specific

treatment for this lipid abnormality; (3) reduced HDL cholesterol, defined as HDL cholesterol <1.03 mmol/L for men or <1.29 mmol/L for women; (4) elevated blood pressure, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and (5) raised fasting blood sugar, defined as fasting blood sugar ≥6.1 mmol/L, or previously diagnosed type 2 diabetes. Metabolically unhealthy participants were defined as those who met the criteria of metabolic syndrome.

Statistical analyses

The statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL). Continuous variables were presented as mean and 95% confidence interval (CI) and compared by Student's *t* test or Mann-Whitney *U* test as appropriate. Categorical variables were compared using the χ^2 test. A stepwise logistic regression analysis was performed to examine the relationship between hyperuricemia and anthropometric or biochemical variables (probability to enter = 0.05 and probability to remove = 0.10). A *P* value <0.05 (two-tailed) was considered statistically significant.

Ethics

During the health checkup, the participants were informed of the potential use of their checkups data for future research and that the subject information would be anonymized at collection prior to analysis. All methods were performed in accordance with the approved guidelines. The study was approved by the Clinical Research

Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No.2021015). Written consent was not required because of the retrospective observational design of the study.

Patient and public involvement

Patients or the public were not involved in the design, conduct, report, or dissemination of our research.

Results

Prevalence of hyperuricemia in the non-obese population

A total of 5731 non-obese participants (2349 men and 3382 women) with a mean age of 44.6±12.0 years were included in this study. The overall prevalence of hyperuricemia was 9.4% (16.3% in males and 4.6% in females). In non-obese males, the prevalence of hyperuricemia was stable before the age of 50, and gradually decreased after 50. Conversely, in non-obese females, the prevalence of hyperuricemia decreased with age before the age of 50, and gradually increased after 50. An interesting finding was that the prevalence of hyperuricemia in females was even higher than that in males after the age of 65 (Figure 1).

We compared the clinical characteristics of participants with or without hyperuricemia in both genders (Table 1). We found that hyperuricemic participants showed greater BMI (22.33 (22.19—22.47) versus 21.87 (21.80—21.94) kg/m^2, p<0.001 in males; 21.64 (21.36–21.92) versus 20.94 (20.88–21.00) kg/m^2, p<0.001 in females) and waist circumference (83.1 (82.6–83.6) versus 81.3 (81.1–81.5) cm, p<0.001 in males; 76.6 (75.5–77.7) versus 74.0 (73.8–74.2) cm, p<0.001 in females), higher diastolic blood pressure (77.2 (76.1–78.3) versus 75.6 (75.1–76.1) mmHg, p=0.006 in males; 73.9 (72.1–75.7) versus 69.2 (68.8–69.6) mmHg, p<0.001 in females), and worse lipid profiles than those without hyperuricemia. Hyperuricemic participants also had higher serum levels of alanine aminotransferase (ALT) (26.5 (24.7–28.4) versus 21.4 (20.6 - 22.3) U/L, p<0.001 in males; 23.2 (18.4 - 28.0) versus 15.2 (14.9 - 15.6) U/L, p=0.001 in females), aspartate aminotransferase (AST)

(22.5 (21.6 – 23.5) versus 20.6 (20.1 – 21.0) U/L, p=0.001 in males; 23.1 (20.5 – 25.7) versus 18.4 (18.1 – 18.6) U/L, p=0.001 in females), gamma–glutamyl transpeptidase (GGT) (41.6 (37.7 – 45.6) versus 30.1 (29.1 – 32.9) U/L, p<0.001 in males; 22.9 (19.5 – 26.3) versus 16.8 (16.2 – 17.5) U/L, p<0.001 in females), blood urea nitrogen (BUN) (5.37 (5.21 – 5.53) versus 5.12 (5.07 – 5.17) mmol/L, p=0.003 in males; 5.07 (4.84 – 5.30) versus 4.55 (4.51 – 4.59) mmol/L, p<0.001 in females), and creatinine (86.5 (84.6 – 88.4) versus 81.2 (80.6 – 81.8) μmol/L, p<0.001 in males; 63.8 (62.2 – 65.4) versus 59.5 (59.2 – 59.8) μmol/L, p<0.001 in females) than normouremic participants.

Association of hyperuricemia with metabolic disorders in the non-obese population

We classified all the non-obese participants into metabolically healthy normal weight (MHNW) group and metabolically unhealthy normal weight (MUHNW) group, according to their metabolic status. We found that MUHNW participants had a significantly higher prevalence of hyperuricemia than MHNW participants. In detail, the prevalence of hyperuricemia increased from 15.6% in MHNW participants to 26.7% in MUHNW participants in males (p<0.001). Similarly, the prevalence of hyperuricemia increased from 4.1% in MHNW participants to 16.3% in MUHNW participants in females (p<0.001) (Figure 2).

We also analyzed the prevalence of metabolic disorders in non-obese individuals with or without hyperuricemia. We found that the prevalence of metabolic syndrome

were significantly higher in hyperuricemic participants (male 10.2%, female 16%) than in normouremic participants (male 5.4%, female 4%; $p<0.001$ in both genders). We also found that the prevalence of fatty liver disease were significantly higher in hyperuricemic participants (male 30.4%, female 20.5%) than in normouremic participants (male 13.8%, female 6.4%; $p<0.001$ in both genders). Male hyperuricemic participants had a higher prevalence of raised triglyceride level and reduced HDL-C than normouremic participants. Female hyperuricemic participants had a higher prevalence of raised triglyceride level, reduced HDL-C, elevated blood pressure, and raised fasting blood sugar than normouremic participants (Table 2). However, the prevalence of diabetes was not different between the two groups (Table 2).

Factors associated with hyperuricemia among the non-obese population

We analyzed the factors associated with hyperuricemia by stepwise logistic regression analysis. The multivariable model showed that greater waist circumference values (1.057 (1.030–1.084) (the data was expressed as OR (95%CI) , the same below) in males and 1.038 (1.006–1.071) in females), elevated BUN levels (1.114 (1.014–1.223) in males and 1.308 (1.137–1.505) in females), excessive drinking (1.501 (1.097–2.055) in males and 3.562 (1.408–9.011) in females) and presence of fatty liver (1.959 (1.472–2.607) in males and 1.900 (1.164–3.102) in females) were associated with an increased prevalence of hyperuricemia in both genders. Greater age (0.961 (0.950–0.972) in males and 0.958 (0.939–0.977) in females) and elevated

eGFR levels (0.973 (0.965–0.980) in males and 0.976 (0.966–0.985) in females) were associated with a decreased prevalence of hyperuricemia in both genders. Elevated serum levels of AST (1.014 (1.004–1.024)) and total cholesterol (2.717 (1.921–3.843)) were associated with an increased prevalence of hyperuricemia in males. Elevated serum levels of HDL-C (0.378 (0.240–0.594)) and LDL-C (0.386 (0.256–0.583)) were associated with a decreased prevalence of hyperuricemia in males. Elevated diastolic blood pressure (1.033 (1.016–1.050)), higher ALT (1.023 (1.013–1.033)) and triglyceride (1.423 (1.199–1.690)) levels were associated with an increased prevalence of hyperuricemia in females (Table 3).

Discussion

This study investigated the prevalence and factors associated with hyperuricemia in a non-obese Chinese population. We found that the prevalence of hyperuricemia was 9.4% in the non-obese adults, with 16.3% in men and 4.6% in women. Age, waist circumference, eGFR, BUN, excessive drinking and presence of fatty liver were associated with hyperuricemia in both genders.

The prevalence of hyperuricemia in non-obese individuals was 9.4%, lower than the value previously reported in the general population in East Asia [10, 21], which included both non-obese and obese individuals as a whole, not separately. We found that in the non-obese individuals, the overall prevalence of hyperuricemia was higher in men than in women. However, the prevalence of hyperuricemia increased greatly in women older than 50, which could be corroborated by other studies[22, 23]. This is primarily attributable to the sex hormone effects on renal urate transport. It has been reported that estrogen affects serum uric acid level through renal clearance, secretion and reabsorption. Young adult women have a lower serum urate level than young adult men, while the onset of menopause is associated with an increased serum urate level[24].

At the same time, we found that the prevalence of hyperuricemia gradually decreased with age in male non-obese patients, which was inconsistent with previous studies[25, 26]. One possible reason was that we have excluded patients undergoing urate-lowering treatment in our study. Nowadays, as the prevalence of gout increases

significantly with age, the number of patients taking urate-lowering treatment is also on the rise as age grows, which may lead to a selection bias in our research[27, 28].

Some studies have reported the interaction between hyperuricemia and NAFLD. We previously reported that hyperuricemia is independently associated with the risk of NAFLD[6]. Our previous prospective study also found that NAFLD was strongly associated with an increased risk of incident hyperuricemia[8]. In this study, we identified fatty liver as a factor associated with hyperuricemia in the non-obese population. Our results suggested that the interaction between hyperuricemia and metabolic disorders should also be paid attention to in the non-obese population, to prevent further progression to deteriorated metabolic status.

MUHNW, generally defined as normal weight with metabolic syndrome, has raised considerable scientific interest[29]. Individuals with a metabolically unhealthy profile were associated with several health issues and higher healthcare and loss-of-productivity costs[30]. The risk of CVD in MUHNW individuals was 1.5–3-fold higher than that in MHNW individuals, and higher than the relative risk in those with metabolically healthy obesity (MHO) [31]. It is not rare to find that MUHNW individuals have a worse prognosis of diabetes than MHO individuals[32]. In this study, we found that the prevalence of hyperuricemia increased significantly in MUHNW participants compared with that in MHNW participants. This phenomenon was more obvious in women, which implied that we could pay more attention to serum uric acid level in MUHNW individuals. As they are more likely to suffer from hyperuricemia, early intervention in uric acid level may benefit these patients by protecting them

from developing further metabolic disorders[33].

We next assessed the comorbidity of other metabolic disorders in non-obese hyperuricemic patients. We found that the prevalence of metabolic syndrome and of fatty liver disease in non-obese hyperuricemic participants were higher than those in normouremic controls. This indicated that hyperuricemia in the non-obese population could also be accompanied by multiple metabolic disorders. Studies have reported hyperuricemia as a cause of metabolic syndrome[7]. Our previous studies also found that hyperuricemia could promote the occurrence and development of NAFLD, and urate-lowering treatment could alleviate NAFLD[8]. Therefore, non-obese hyperuricemic individuals may also need active intervention in uric acid level to reduce the risk of comorbid metabolic disorders[34].

Several limitations are acknowledged in this study. First, it is a single-center cross-sectional study. Our sample size may be insufficient to represent the entire Chinese adult population, and further multi-center cohort studies are needed. Second, in our study, patients currently undergoing urate-lowering treatment were excluded, which might cause a selection bias in the prevalence of hyperuricemia. In our research, some factors related to uric acid were not included, such as gout, renal disease, and treatment with diuretics, etc. Third, dietary information was not collected, though dietary intake could be a cofactor associated with hyperuricemia. Some studies have shown that fructose-enriched food and drink could increase serum UA levels[35]. Meanwhile, this study defined the non-obese participants by BMI without including waist circumference or waist-to-hip ratio. Some central obese

patients could be mixed in the non-obese participants.

In conclusion, our retrospective cross-sectional study showed that the prevalence of hyperuricemia was 9.4% in the non-obese Chinese population. The prevalence of hyperuricemia increased significantly in MUHNW participants compared with MHNW participants. Hyperuricemia in non-obese people could also be accompanied by multiple metabolic disorders. Therefore, we suggest that clinicians pay attention to serum uric acid level in non-obese patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Author Contributions:

Conceived and designed the experiment: X.C.F. and Z.H.L. Collected the clinical information: W.J.H, C.Y.S. and C.S.H. Analyzed the data: W.J.H, W.X.Y. and Z.H.L. Wrote the paper: W.J.H. and C.Y.S. All authors reviewed the manuscript.

Data Availability Statement

Data are available upon reasonable request.

References

1. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology (Oxford) 2019; 58(12): 2177-80.
2. Zheng R, Chen C, Yang T, Chen Q, Lu R, Mao Y. Serum Uric Acid Levels and the Risk of Obesity: a Longitudinal Population-Based Epidemiological Study. Clin Lab 2017; 63(10): 1581-87.
3. Son M, Seo J, Yang S. Association between dyslipidemia and serum uric acid levels in Korean adults: Korea National Health and Nutrition Examination Survey 2016-2017. PLoS One 2020; 15(2): e0228684.
4. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol 2013; 25(2): 210-6.
5. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, Hypertension, and Chronic Kidney Disease: an Emerging Association. Curr Hypertens Rep 2016; 18(10): 74.
6. Li Y, Xu C, Yu C, Xu L, Miao M. Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. J Hepatol 2009; 50(5): 1029-34.
7. King C, Lanaspa MA, Jensen T, Tolan DR, Sanchez-Lozada LG, Johnson RJ. Uric Acid as a Cause of the Metabolic Syndrome. Contrib Nephrol 2018; 192: 88-102.
8. Xu C, Wan X, Xu L, et al. Xanthine oxidase in non-alcoholic fatty liver disease and hyperuricemia: One stone hits two birds. J Hepatol 2015; 62(6): 1412-9.
9. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011; 63(10): 3136-41.
10. Liu R, Han C, Wu D, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. Biomed Res Int 2015; 2015: 762820.
11. Wan Z, Song L, Hu L, Lei X, Huang Y, Lv Y. Temporal trends in hyperuricaemia among adults in Wuhan city, China, from 2010 to 2019: a cross-sectional study. BMJ Open 2021; 11(3): e043917.
12. Peng TC, Wang CC, Kao TW, et al. Relationship between hyperuricemia and lipid profiles in US adults. Biomed Res Int 2015; 2015: 127596.
13. Juraschek SP, Kovell LC, Miller ER, Gelber AC. Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. PLoS One 2013; 8(2): e56546.
14. Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 2013; 108(8): 1299-304.
15. Kashima S, Inoue K, Matsumoto M, Akimoto K. Prevalence and characteristics of non-obese diabetes in Japanese men and women: the Yuport Medical Checkup Center Study. J Diabetes 2015; 7(4): 523-30.
16. Huang YF, Yang KH, Chen SH, et al. [Practice guideline for patients with hyperuricemia/gout]. Zhonghua Nei Ke Za Zhi 2020; 59(7): 519-27.
17. Zhang Y, Nie FQ, Huang XB, et al. High prevalence and low awareness of hyperuricemia in hypertensive patients among adults aged 50-79 years in Southwest China. BMC Cardiovasc Disord 2022; 22(1): 2.
18. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006; 17(10): 2937-44.

19. Fan JG, Wei L, Zhuang H, National Workshop on Fatty L, Alcoholic Liver Disease CSOHCMA, Fatty Liver Disease Expert Committee CMDA. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis 2019; 20(4): 163-73.
20. Expert Panel on Detection E, Treatment of High Blood Cholesterol In A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-97.
21. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018; 37(9): 2529-38.
22. Gaffo AL, Jacobs DR, Jr., Lewis CE, Mikuls TR, Saag KG. Association between being African-American, serum urate levels and the risk of developing hyperuricemia: findings from the Coronary Artery Risk Development in Young Adults cohort. Arthritis Res Ther 2012; 14(1): R4.
23. Mcadams-Demarco MA, Law A, Maynard JW, Coresh J, Baer AN. Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. BMC Musculoskelet Disord 2013; 14: 347.
24. Koga M, Saito H, Mukai M, Kasayama S, Yamamoto T. Factors contributing to increased serum urate in postmenopausal Japanese females. Climacteric 2009; 12(2): 146-52.
25. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. Sci Rep 2018; 8(1): 4314.
26. Cui L, Meng L, Wang G, et al. Prevalence and risk factors of hyperuricemia: results of the Kailuan cohort study. Mod Rheumatol 2017; 27(6): 1066-71.
27. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020; 16(7): 380-90.
28. Robinson PC, Taylor WJ, Dalbeth N. An Observational Study of Gout Prevalence and Quality of Care in a National Australian General Practice Population. J Rheumatol 2015; 42(9): 1702-7.
29. Lonardo A, Mantovani A, Lugari S, Targher G. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. Ann Hepatol 2020; 19(4): 359-66.
30. Samouda H, Ruiz-Castell M, Karimi M, et al. Metabolically healthy and unhealthy weight statuses, health issues and related costs: Findings from the 2013-2015 European Health Examination Survey in Luxembourg. Diabetes Metab 2019; 45(2): 140-51.
31. Schulze MB. Metabolic health in normal-weight and obese individuals. Diabetologia 2019; 62(4): 558-66.
32. Buscemi S, Chiarello P, Buscemi C, et al. Characterization of Metabolically Healthy Obese People and Metabolically Unhealthy Normal-Weight People in a General Population Cohort of the ABCD Study. J Diabetes Res 2017; 2017: 9294038.
33. Borghi C, Agabiti-Rosei E, Johnson RJ, et al. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. Eur J Intern Med 2020; 80: 1-11.
34. Bove M, Cicero AF, Veronesi M, Borghi C. An evidence-based review on urate-lowering treatments: implications for optimal treatment of chronic hyperuricemia. Vasc Health Risk Manag 2017; 13: 23-28.
35. Caliceti C, Calabria D, Roda A, Cicero AFG. Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: A Critical Review. Nutrients 2017; 9(4).

Table 1. Clinical characteristics of the study population

Variables	Male		P value	Female		P value
	Without hyperuricemia (n =1967)	With hyperuricemia (n =382)		Without hyperuricemia (n =3226)	With hyperuricemia (n =156)	
Age (year)	46.5(46.0-47.1)	44.5(43.3-45.7)	0.004	43.4(43.0-43.8)	46.6(44.3-49.0)	0.009
WC (cm)	81.3(81.1-81.5)	83.1(82.6-83.6)	<0.001	74.0(73.8-74.2)	76.6(75.5-77.7)	<0.001
BMI (kg/m^2)	21.87(21.80-21.94)	22.33(22.19-22.47)	<0.001	20.94(20.88-21.00)	21.64(21.36-21.92)	<0.001
SBP (mmHg)	122.8(122.1-123.5)	124.1(122.4-125.8)	0.159	115.0(114.4-115.6)	122.2(119.0-125.4)	<0.001
DBP (mmHg)	75.6(75.1-76.1)	77.2(76.1-78.3)	0.009	69.2(68.8-69.6)	73.9(72.1-75.7)	<0.001
ALT (U/L)	21.4(20.6-22.3)	26.5(24.7-28.4)	<0.001	15.2(14.9-15.6)	23.2(18.4-28.0)	0.001
AST (U/L)	20.6(20.1-21.0)	22.5(21.6-23.5)	0.001	18.4(18.1-18.6)	23.1(20.5-25.7)	0.001
GGT (U/L)	30.1(29.1-32.9)	41.6(37.7-45.6)	<0.001	16.8(16.2-17.5)	22.9(19.5-26.3)	<0.001
Creatinine (μmol/L)	81.2(80.6-81.8)	86.5(84.6-88.4)	<0.001	59.5(59.2-59.8)	63.8(62.2-65.4)	<0.001
BUN (mmol/L)	5.12(5.07-5.17)	5.37(5.21-5.53)	0.003	4.55(4.51-4.59)	5.07(4.84-5.30)	<0.001
eGFR	101.1(100.4-101.8)	95.3(93.5-97.1)	<0.001	188.7(188.0-189.4)	109(105.4-112.6)	<0.001
TG (mmol/L)	1.38(1.34-1.42)	1.88(1.76-2.00)	<0.001	1.05(1.03-1.07)	1.60(1.28-1.92)	0.001
TC (mmol/L)	4.49(4.45-4.53)	4.71(4.62-4.80)	<0.001	4.52(4.49-4.55)	4.76(4.62-4.90)	0.001
HDL-C (mmol/L)	1.21(1.20-1.22)	1.14(1.11-1.17)	<0.001	1.44(1.43-1.45)	1.36(1.30-1.42)	0.003
LDL-C (mmol/L)	2.62(2.59-2.65)	2.72(2.65-2.79)	0.012	2.53(2.51-2.55)	2.65(2.53-2.77)	0.026
VLDL-C (mmol/L)	0.65(0.64-0.66)	0.84(0.80-0.88)	<0.001	0.55(0.54-0.56)	0.73(0.65-0.81)	<0.001
FBS (mmol/L)	5.02(4.97-5.07)	5.01(4.93-5.09)	0.815	4.81(4.79-4.83)	5.07(4.93-5.21)	<0.001
Excessive drinking (%)	14.0%(12.5%-15.5%)	19.4%(15.4%-23.4%)	0.007	1.4%(1.0%-1.8%)	3.8%(0.8%-6.8%)	0.016
Smoking history (%)	39.0%(36.8%-41.2%)	42.9%(37.9%-47.9%)	0.15	1.4%(1.0%-1.8%)	1.3%(0%-3.1%)	0.906
SUA (μmol/L)	333.8(331.6-336.0)	467.9(463.2-472.6)	<0.001	260.0(258.5-261.5)	397.1(390.8-403.4)	<0.001

Data are expressed as the mean (95% CI)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SUA: serum uric acid; TG: triglyceride; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; WC: waist circumference.

Table 2. Prevalence of metabolic disease according to hyperuricemia

	Male			Female		
	Without hyperuricemia	With hyperuricemia	*P*-value	Without hyperuricemia	With hyperuricemia	*P*-value
Metabolic syndrome	5.4%	10.2%	<0.001	4%	16%	<0.001
Metabolic syndrome components						
Waist circumference (> 102 cm in men, >88 cm in women)	0%	0%	/	1.4%	3.2%	0.06
Fasting blood glucose (≥ 6.1 mmol/L)	6.4%	6.5%	0.890	2%	10.9%	<0.001
Triglyceride (≥1.7mmol/L)	21.9%	45%	<0.001	10.8%	26.3%	<0.001
HDL-C (<1.04 mmol/L in men, <1.30 mmol/L in women)	28.9%	37.7%	0.001	35.2%	48.1%	0.001
Blood pressure (≥130/85 mmHg)	33.7%	38%	0.105	19.3%	35.9%	<0.001
Diabetes mellitus	3.4%	2.9%	0.599	1%	2.6%	0.062
NAFLD	13.8%	30.4%	<0.001	6.4%	20.5%	<0.001

HDL-C: high-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease;

Table 3. Multivariable analysis for factors associated with hyperuricemia

Variables	Male		Female	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (year)	0.961(0.950-0.972)	<0.001	0.958 (0.939-0.977)	<0.001
WC (cm)	1.057 (1.030-1.084)	<0.001	1.038 (1.006-1.071)	0.020
DBP (mmHg)	/		1.033(1.016-1.050)	<0.001
ALT (U/L)	/		1.023 (1.013-1.033)	<0.001
AST (U/L)	1.014 (1.004-1.024)	0.005	/	
eGFR (μmol/L)	0.973 (0.965-0.980)	<0.001	0.976 (0.966-0.985)	<0.001
BUN (mmol/L)	1.114 (1.014-1.223)	0.025	1.308 (1.137-1.505)	<0.001
TG (mmol/L)	/		1.423 (1.199-1.690)	<0.001
TC (mmol/L)	2.717 (1.921-3.843)	<0.001	/	
HDL-C (mmol/L)	0.378 (0.240-0.594)	<0.001	/	
LDL-C (mmol/L)	0.386 (0.256-0.583)	<0.001	/	
Excessive drinking	1.501 (1.097-2.055)	0.011	3.562 (1.408-9.011)	0.007
NAFLD	1.959 (1.472-2.607)	<0.001	1.900 (1.164-3.102)	0.010

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; TG: triglyceride; TC: total cholesterol; WC: waist circumference

Figure Legend

Figure 1. Prevalence of hyperuricemia(A) and Serum uric acid(B) in participants

Data was expressed as mean with 95% confidence interval (error bars)

Figure 2. Prevalence of hyperuricemia (A) and Serum uric acid (B) in metabolically healthy or metabolically unhealthy participants. Data was expressed as mean ± SD. $^{**}p<0.01$, $^{***}p<0.001$.

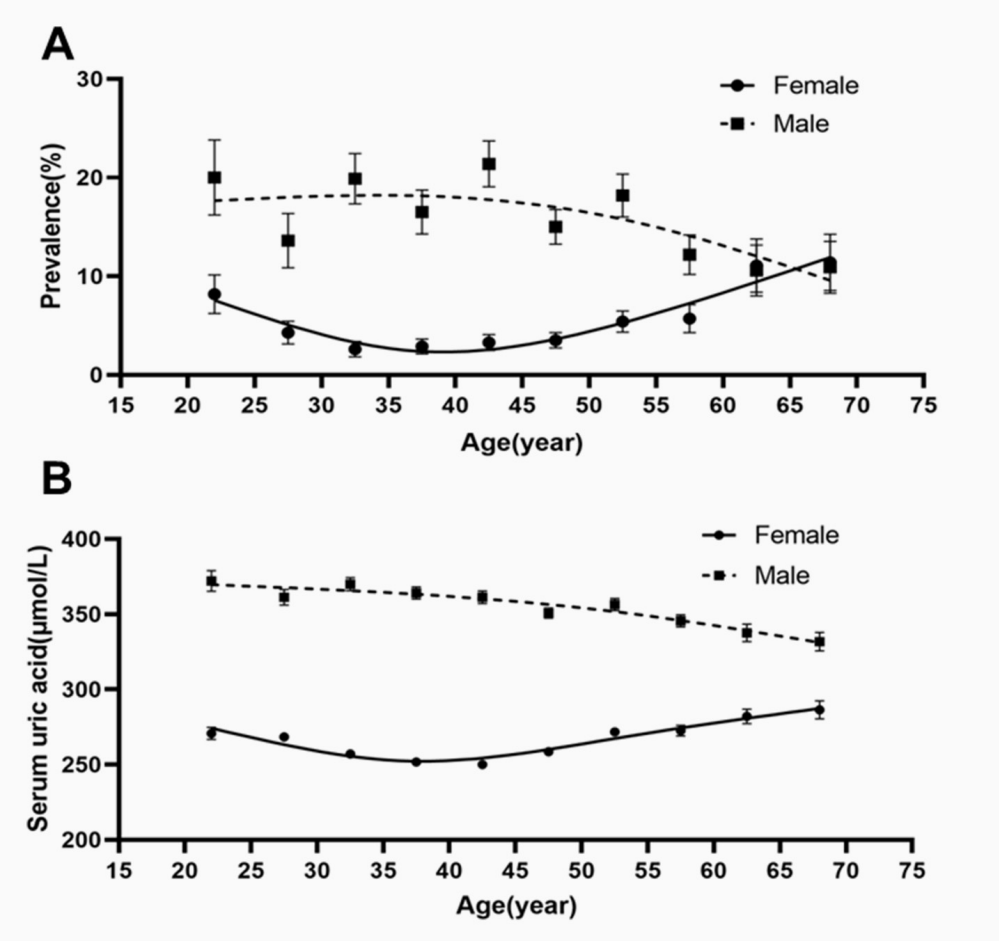

Figure 1

121x114mm (300 x 300 DPI)

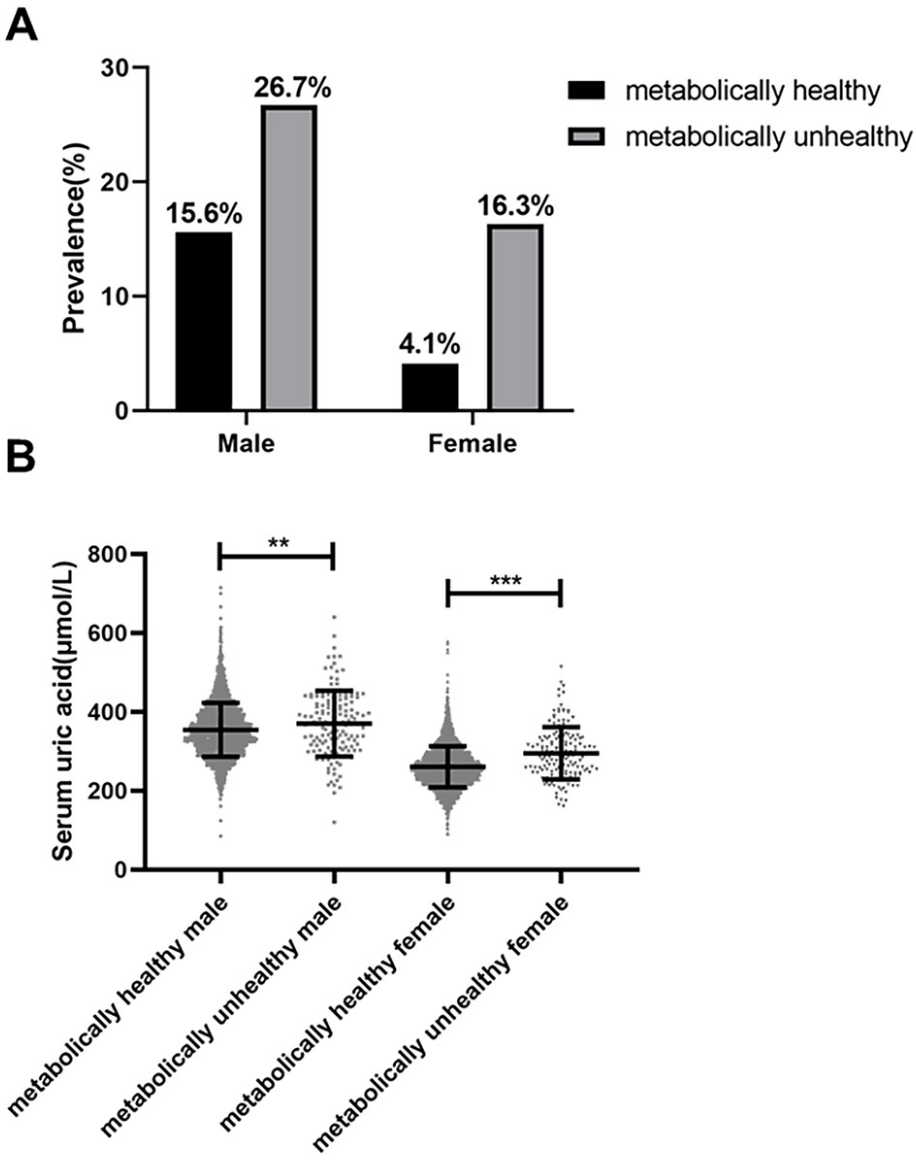

Figure 2

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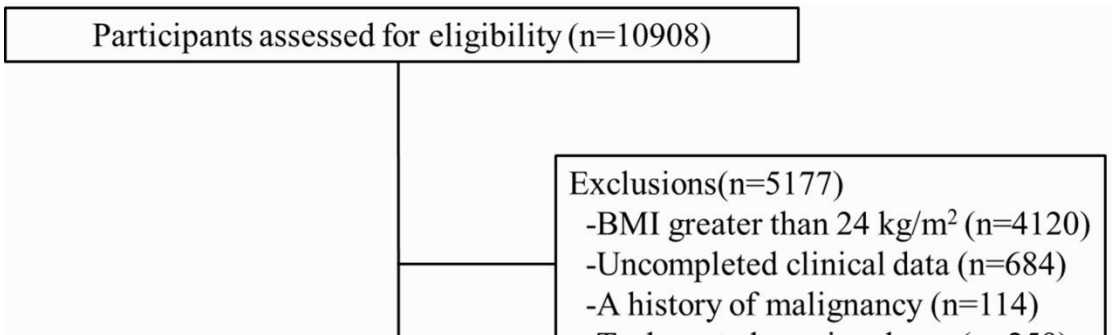

Figure S1. Inclusion and exclusion flow chart of this study

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence and risk factors of hyperuricemia in non-obese Chinese: a single-center cross-sectional study

Jinghua Wang[1,#], Yishu Chen[1,#], Shenghui Chen[1], Xinyu Wang[1], Haoliang Zhai[2,*], Chengfu Xu[1,2,*]

[1] Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

[2] Department of Gastroenterology, Haining Branch of the First Affiliated Hospital, Zhejiang University School of Medicine, Haining 314400, China

***Corresponding author:**

Chengfu Xu, M.D., Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine. 79 Qingchun Road, Hangzhou 310003, China, Tel: 0086-571-87236863, E-mail: xiaofu@zju.edu.cn.

Haoliang Zhai, Department of Gastroenterology, Haining Branch of the First Affiliated Hospital, Zhejiang University School of Medicine. 79 Qingchun Road, Hangzhou 314400, China, Tel: 0086-573-89230531, E-mail: inzaghi1004@sina.com.

# Jinghua Wang and Yishu Chen contributed equally to this work.

Key words: Hyperuricemia; Non-obese; Risk factor; Cross-sectional study; Nonalcoholic fatty liver disease

Abstract

Objectives: Hyperuricemia is closely related to metabolic diseases and is receiving increasing attention from all over the world. This study aimed to investigate the prevalence and factors associated with hyperuricemia in non-obese Chinese population.

Design: Retrospective cross-sectional study

Setting: A large general hospital that can provide health checkups in Hangzhou, China.

Participants: A total of 5731 apparently healthy Chinese adults (2349 men and 3382 women) who took their health checkups during the year of 2019. Exclusion criteria: (1) those with BMI $\geqslant$ 24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate-lowering treatment.

Primary and secondary outcome measures: The prevalence and factors associated with hyperuricemia in non-obese Chinese adults.

Results: Of the 5731 non-obese subjects enrolled, 538 (9.4%) were identified as hyperuricemia, specifically 16.3% in men and 4.6% in women. The prevalence of hyperuricemia markedly increased in females aged above 50. The prevalence of hyperuricemia was significantly higher in metabolically unhealthy participants with normal weight than in metabolically healthy participants with normal weight. Hyperuricemic participants showed a higher prevalence of metabolic syndrome and fatty liver disease than normouremic participants. Age, waist circumference, eGFR,

blood urea nitrogen, excessive drinking and fatty liver were associated with hyperuricemia in both genders.

Conclusion: The prevalence of hyperuricemia was 9.4% in non-obese Chinese adults. Non-obese hyperuricemic participants also showed multiple metabolic disorders. We suggest that clinicians pay attention to serum uric acid level in non-obese patients.

Strengths and limitations of this study

This study included a large sample size of participants (more than 5000 adults), which made our findings more convincible.

This is the first study that has evaluated the prevalence of hyperuricemia among non-obese adults in China.

A multivariate logistic model was used to correct selection biases by adjusting for potential confounders.

It is a single-center cross-sectional study, and further multi-center cohort studies are needed.

Patients currently undergoing urate-lowering treatment were excluded, which might cause a selection bias in the prevalence of hyperuricemia in this study.

Introduction

Hyperuricemia, defined as elevated uric acid level in blood, is a metabolic disorder commonly recognized to be closely related to gout and CKD[1]. Over the last decade, more and more studies have found that hyperuricemia is also associated with other metabolic diseases, such as obesity, hypertension, dyslipidemia, and nonalcoholic fatty liver disease (NAFLD)[2-6]. Some studies also suggested hyperuricemia as an independent risk factor for metabolic syndrome and non-alcoholic fatty liver disease[7, 8]. Moreover, the prevalence of hyperuricemia varies across populations and regions. In the United States, approximately 21.4% of adults met the criteria for hyperuricemia in the first decade of the 21st century, which was 3.2% higher than the proportion reported by NHANES 1988–1994[9]. According to a recent meta-analysis, the pooled prevalence of hyperuricemia was 13.3% in China[10]. A study from Wuhan, China suggested that the prevalence of hyperuricemia in men rose from 26.1% in 2010 to 34.4% in 2019, and the prevalence of hyperuricemia in women rose from 5.8% in 2010 to 10.1% in 2019[11]. It is reported that the prevalence of hyperuricemia was 18.4% and the incidence of hyperuricemia was 68.58 cases per 1000 person-year of follow-up in Eastern China[12]. The findings above may call for more attention on the health problem of hyperuricemia from a metabolic perspective, yet entailing further verification across populations.

Many metabolism-related indicators are independent risk factors for hyperuricemia. Serum levels of triglyceride, total cholesterol, apolipoprotein-B, and low-density lipoprotein cholesterol (LDL-C), and the ratio of triglyceride to

high-density lipoprotein cholesterol (HDL-C) have been reported to be positively correlated with the serum uric acid level, while the serum HDL-C level inversely[13]. Juraschek *et al.* found a 4-fold or higher prevalence of hyperuricemia in individuals who had blood pressure uncontrolled and were exposed to other risk factors of cardiovascular diseases [14].

It is generally believed that obesity is closely associated with metabolism-related diseases, and it increases the risk of developing diabetes, NAFLD and hyperuricemia. Recently, more and more studies have shifted their attention to metabolic disorders in the non-obese population. Some studies showed that the non-obese population could also present a high prevalence of NAFLD. For example, as we previously reported, the prevalence of NAFLD in a non-obese Chinese population was 7.3%[15]. A study from Japan warned that more than 60% of Japanese diabetic subjects are non-obese[16]. The findings suggest that it be important to assess metabolic abnormalities in non-obese individuals. So far, there has still been a paucity of studies on hyperuricemia in the non-obese population.

In this study, we conducted a retrospective cross-sectional analysis on a non-obese Chinese population to evaluate the prevalence of hyperuricemia and determine its associated factors.

Methods

Study population

The study population of this cross-sectional study was adults who took their health checkups at the First Affiliated Hospital, Zhejiang University School of Medicine from January 1 to December 31, 2019. Following the hospital's standard health checkup protocol, all participants received medical history collection, anthropometric measurement, blood examination, and abdominal ultrasound examination. For research purpose, we collected these data from their checkup reports and excluded participants meeting the following criteria: (1) those with BMI $\geqslant$24 kg/m^2; (2) those with incomplete anthropometric and biochemical data; (3) those with a history of malignancy; and (4) those under urate-lowering treatment. A total of 10908 participants were enrolled in this study, 4120 of whom had a BMI greater than 24 kg/m^2, 684 had incomplete data, 114 had a history of malignancy, and 259 took urate-lowering drugs. Finally, this study qualified 5731 participants (including 2349 men and 3382 women)(Figure S1).

Clinical evaluations

For all the participants undergoing the health checkup, anthropometric parameters including standing height, body weight, and waist circumference were measured. Blood pressure was gauged following a standard protocol. For height and weight, participants should be in light clothes with shoes taken off. BMI (kg/m^2) was calculated as the body weight (kg) divided by the standing height (m) squared. Fasting

serum samples were obtained for biochemical analysis with a Hitachi 7600 clinical analyzer (Hitachi, Tokyo, Japan) in accordance with standard methods. Questions about alcohol intake included frequency of alcohol consumption (per week) and usual amount per day. Questions about smoking history included daily smoking count and years of smoking.

Diagnostic criteria and definitions

BMI was adopted to define obesity. Non-obese was defined as BMI < 24 kg/m^2, and obesity is defined as BMI ≥24 kg/m^2. Excessive drinking was defined as alcohol consumption >210 g/week for men or >70 g/week for women. Hyperuricemia could be diagnosed with the serum uric acid level >420 μmol/L for men or >360 μmol/L for women[8, 17, 18]. The factor eGFR (estimated glomerular filtration rate) was calculated using the modified MDRD formula[19].

In the health checkup, all individuals underwent abdominal ultrasound examination, which was performed by trained ultrasonographists with a Toshiba Nemio 20 ultrasound system (Toshiba, Tokyo, Japan). The criteria for ultrasonic diagnosis of fatty liver were based on those suggested by the Chinese Liver Disease Association[20].

Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III report[21]. Participants diagnosed with metabolic syndrome must have three or more of the following factors: (1) central obesity, defined as waist circumference >102 cm for men or >88 cm for women; (2)

raised serum triglyceride level, defined as triglyceride ⩾ 1.7 mmol/L or specific treatment for this lipid abnormality; (3) reduced HDL cholesterol, defined as HDL cholesterol <1.03 mmol/L for men or <1.29 mmol/L for women; (4) elevated blood pressure, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and (5) raised fasting blood sugar, defined as fasting blood sugar ≥6.1 mmol/L, or previously diagnosed type 2 diabetes. Metabolically unhealthy participants were defined as those who met the criteria of metabolic syndrome.

Statistical analyses

The statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL). Continuous variables were presented as mean and 95% confidence interval (CI) and compared by Student's *t* test or Mann-Whitney *U* test as appropriate. Categorical variables were compared using the χ^2 test. A stepwise logistic regression approach was introduced to explore the association of hyperuricemia with anthropometric or biochemical parameters (probability to enter = 0.05 and probability to remove = 0.10). It was considered that P <0.05 (two-tailed test) was statistically significant.

Ethics

During the health checkup, all participants were informed of the potential use of their checkup data for future research and that subject information would be anonymized at collection prior to research analysis. All methods were performed in accordance with

the approved guidelines. The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No.2021015). Written consent was not required because of the retrospective observational design of the study.

Patient and public involvement

Patients or the public were not involved in the design, conduct, report, or dissemination of our research.

Results

Prevalence of hyperuricemia in the non-obese population

A total of 5731 non-obese participants (2349 men and 3382 women) with a mean age of 44.6±12.0 years were included in this study. The overall prevalence of hyperuricemia was 9.4% (16.3% in males and 4.6% in females). In non-obese males, the prevalence of hyperuricemia was stable before the age of 50, and gradually decreased after 50. Conversely, in non-obese females, the prevalence of hyperuricemia decreased with age before the age of 50, and gradually increased after 50. An interesting finding was that the prevalence of hyperuricemia in females was even higher than that in males after the age of 65 (Figure 1).

We compared the clinical characteristics of participants with or without hyperuricemia in both genders (Table 1). We found that hyperuricemic participants showed greater BMI (22.33 (22.19—22.47) versus 21.87 (21.80—21.94) kg/m^2, p<0.001 in males; 21.64 (21.36–21.92) versus 20.94 (20.88–21.00) kg/m^2, p<0.001 in females) and waist circumference (83.1 (82.6–83.6) versus 81.3 (81.1–81.5) cm, p<0.001 in males; 76.6 (75.5–77.7) versus 74.0 (73.8–74.2) cm, p<0.001 in females), higher diastolic blood pressure (77.2 (76.1–78.3) versus 75.6 (75.1–76.1) mmHg, p=0.006 in males; 73.9 (72.1–75.7) versus 69.2 (68.8–69.6) mmHg, p<0.001 in females), and worse lipid profiles than those without hyperuricemia. Hyperuricemic participants also had higher serum levels of alanine aminotransferase (ALT) (26.5 (24.7–28.4) versus 21.4 (20.6 - 22.3) U/L, p<0.001 in males; 23.2 (18.4 - 28.0) versus 15.2 (14.9 - 15.6) U/L, p=0.001 in females), aspartate aminotransferase (AST)

(22.5 (21.6 – 23.5) versus 20.6 (20.1 – 21.0) U/L, p=0.001 in males; 23.1 (20.5 – 25.7) versus 18.4 (18.1 – 18.6) U/L, p=0.001 in females), gamma–glutamyl transpeptidase (GGT) (41.6 (37.7 – 45.6) versus 30.1 (29.1 – 32.9) U/L, p<0.001 in males; 22.9 (19.5 – 26.3) versus 16.8 (16.2 – 17.5) U/L, p<0.001 in females), blood urea nitrogen (BUN) (5.37 (5.21 – 5.53) versus 5.12 (5.07 – 5.17) mmol/L, p=0.003 in males; 5.07 (4.84 – 5.30) versus 4.55 (4.51 – 4.59) mmol/L, p<0.001 in females), and creatinine (86.5 (84.6 – 88.4) versus 81.2 (80.6 – 81.8) μmol/L, p<0.001 in males; 63.8 (62.2 – 65.4) versus 59.5 (59.2 – 59.8) μmol/L, p<0.001 in females) than normouremic participants.

Association of hyperuricemia with metabolic disorders in the non-obese population

We classified all the non-obese participants into metabolically healthy normal weight (MHNW) group and metabolically unhealthy normal weight (MUHNW) group, according to their metabolic status. We found that MUHNW participants had a significantly higher prevalence of hyperuricemia than MHNW participants. In detail, the prevalence of hyperuricemia increased from 15.6% in MHNW participants to 26.7% in MUHNW participants in males (p<0.001). Similarly, the prevalence of hyperuricemia increased from 4.1% in MHNW participants to 16.3% in MUHNW participants in females (p<0.001) (Figure 2).

We also analyzed the prevalence of metabolic disorders in non-obese individuals with or without hyperuricemia. We found that the prevalence of metabolic syndrome

were significantly higher in hyperuricemic participants (male 10.2%, female 16%) than in normouremic participants (male 5.4%, female 4%; $p<0.001$ in both genders). We also found that the prevalence of fatty liver disease were significantly higher in hyperuricemic participants (male 30.4%, female 20.5%) than in normouremic participants (male 13.8%, female 6.4%; $p<0.001$ in both genders). Male hyperuricemic participants had a higher prevalence of raised triglyceride level and reduced HDL-C than normouremic participants. Female hyperuricemic participants had a higher prevalence of raised triglyceride level, reduced HDL-C, elevated blood pressure, and raised fasting blood sugar than normouremic participants (Table 2). However, the prevalence of diabetes was not different between the two groups (Table 2).

Factors associated with hyperuricemia among the non-obese population

We adopted a stepwise logistic regression approach to analyze the factors associated with hyperuricemia. The multivariable model showed that greater waist circumference values (1.057 (1.030–1.084) (the data was expressed as OR (95%CI) , the same below) in males and 1.038 (1.006–1.071) in females), elevated BUN levels (1.114 (1.014–1.223) in males and 1.308 (1.137–1.505) in females), excessive drinking (1.501 (1.097–2.055) in males and 3.562 (1.408–9.011) in females) and presence of fatty liver (1.959 (1.472–2.607) in males and 1.900 (1.164–3.102) in females) were associated with an increased prevalence of hyperuricemia in both genders. Greater age (0.961 (0.950–0.972) in males and 0.958 (0.939–0.977) in

females) and elevated eGFR levels (0.973 (0.965–0.980) in males and 0.976 (0.966–0.985) in females) were associated with a decreased prevalence of hyperuricemia in both genders. Elevated serum levels of AST (1.014 (1.004–1.024)) and total cholesterol (2.717 (1.921–3.843)) were associated with an increased prevalence of hyperuricemia in males. Elevated serum levels of HDL-C (0.378 (0.240–0.594)) and LDL-C (0.386 (0.256–0.583)) were associated with a decreased prevalence of hyperuricemia in males. Elevated diastolic blood pressure (1.033 (1.016–1.050)), higher ALT (1.023 (1.013–1.033)) and triglyceride (1.423 (1.199–1.690)) levels were associated with an increased prevalence of hyperuricemia in females (Table 3).

Discussion

This study investigated the prevalence and factors associated with hyperuricemia in a non-obese Chinese population. We found that the prevalence of hyperuricemia was 9.4% in the non-obese adults, with 16.3% in men and 4.6% in women. Age, waist circumference, eGFR, BUN, excessive drinking and presence of fatty liver were associated with hyperuricemia in both genders.

The prevalence of hyperuricemia in non-obese individuals was 9.4%, lower than that previously reported in the general population in East Asia [10, 22], which included both non-obese and obese individuals as a whole, rather than separately. We found that in the non-obese individuals, the overall prevalence of hyperuricemia was higher in men than in women. However, the prevalence of hyperuricemia increased greatly in women older than 50, which could be corroborated by other studies[23, 24]. A possible explanation could be the effects of sex hormones on renal urate transport. Estrogen affects serum uric acid level through renal clearance, secretion and reabsorption. Serum urate level is generally lower in young adult women than in their male counterparts, while the onset of menopause has been reported to correlate with an increased serum urate level[25].

At the same time, we found that the prevalence of hyperuricemia gradually decreased with age in male non-obese patients, which was inconsistent with previous studies[26, 27]. One possible reason was that we have excluded patients undergoing urate-lowering treatment in our study. Nowadays, as the prevalence of gout increases

significantly with age, the number of patients taking urate-lowering treatment is also on the rise as age grows, which may lead to a selection bias in our research[28, 29].

Some studies have reported the interaction between hyperuricemia and NAFLD. We previously reported that hyperuricemia is independently associated with the risk of NAFLD[6]. Our previous prospective study also found that NAFLD was strongly associated with an increased risk of incident hyperuricemia[8]. In this study, we identified fatty liver as a factor associated with hyperuricemia in the non-obese population. Our results suggested that the interaction between hyperuricemia and metabolic disorders should also be paid attention to in the non-obese population, to prevent further progression to deteriorated metabolic status.

MUHNW, generally defined as normal weight with metabolic syndrome, has raised considerable scientific interest[30]. Individuals with a metabolically unhealthy profile were associated with several health issues and higher healthcare and loss-of-productivity costs[31]. The risk of CVD in MUHNW individuals was 1.5–3-fold higher than that in MHNW individuals, and higher than the relative risk in those with metabolically healthy obesity (MHO) [32]. It is not rare to find that MUHNW individuals have a worse prognosis of diabetes than MHO individuals[33]. In this study, we found that the prevalence of hyperuricemia increased significantly in MUHNW participants compared with that in MHNW participants. This phenomenon was more obvious in women, which implied that we could pay more attention to serum uric acid level in MUHNW individuals. As they are more likely to suffer from hyperuricemia, early intervention in uric acid level may benefit these patients by protecting them

from developing further metabolic disorders[34].

We next assessed the comorbidity of other metabolic disorders in non-obese hyperuricemic patients. We found that the prevalence of metabolic syndrome and of fatty liver disease in non-obese hyperuricemic participants were higher than those in normouremic controls. This indicated that hyperuricemia in the non-obese population could also be accompanied by multiple metabolic disorders. Studies have reported hyperuricemia as a cause of metabolic syndrome[7]. Our previous studies also found that hyperuricemia could promote the occurrence and development of NAFLD, and urate-lowering treatment could alleviate NAFLD[8]. Therefore, non-obese hyperuricemic individuals may also need active intervention in uric acid level to reduce the risk of comorbid metabolic disorders[35].

Several limitations are acknowledged for this study. First, due to the single-center design and the limited sample size, the results of this study may not apply to the entire Chinese adult population. Further multi-center cohort studies are needed. Second, in our study, patients currently undergoing urate-lowering treatment were excluded, which might cause a selection bias in the prevalence of hyperuricemia. In our research, some factors related to uric acid were not included, such as gout, renal disease, and treatment with diuretics, etc. Third, several studies have demonstrated that fructose-enriched foods and drinks lead to increased serum UA levels[36], indicating the role of dietary intake in the development of hyperuricemia. Dietary information, however, was not unavailable in the checkup reports and thus was not discussed in this study. Meanwhile, this study defined the non-obese participants by

BMI without including waist circumference or waist-to-hip ratio. Some central obese patients could be mixed in the non-obese participants.

In conclusion, our retrospective cross-sectional study showed that the prevalence of hyperuricemia was 9.4% in the non-obese Chinese population. The prevalence of hyperuricemia increased significantly in MUHNW participants compared with MHNW participants. Hyperuricemia in non-obese people could also be accompanied by multiple metabolic disorders. Therefore, we suggest that clinicians pay attention to serum uric acid level in non-obese patients.

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Conflicts of interest

The authors declare no conflicts of interest.

Author Contributions:

Conceived and designed the experiment: X.C.F. and Z.H.L. Collected the clinical information: W.J.H, C.Y.S. and C.S.H. Analyzed the data: W.J.H, W.X.Y. and Z.H.L. Wrote the paper: W.J.H. and C.Y.S. All authors reviewed the manuscript.

Data Availability Statement

Data are available upon reasonable request.

References

1. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology (Oxford) 2019; 58(12): 2177-80.
2. Zheng R, Chen C, Yang T, Chen Q, Lu R, Mao Y. Serum Uric Acid Levels and the Risk of Obesity: a Longitudinal Population-Based Epidemiological Study. Clin Lab 2017; 63(10): 1581-87.
3. Son M, Seo J, Yang S. Association between dyslipidemia and serum uric acid levels in Korean adults: Korea National Health and Nutrition Examination Survey 2016-2017. PLoS One 2020; 15(2): e0228684.
4. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol 2013; 25(2): 210-6.
5. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, Hypertension, and Chronic Kidney Disease: an Emerging Association. Curr Hypertens Rep 2016; 18(10): 74.
6. Li Y, Xu C, Yu C, Xu L, Miao M. Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. J Hepatol 2009; 50(5): 1029-34.
7. King C, Lanaspa MA, Jensen T, Tolan DR, Sanchez-Lozada LG, Johnson RJ. Uric Acid as a Cause of the Metabolic Syndrome. Contrib Nephrol 2018; 192: 88-102.
8. Xu C, Wan X, Xu L, et al. Xanthine oxidase in non-alcoholic fatty liver disease and hyperuricemia: One stone hits two birds. J Hepatol 2015; 62(6): 1412-9.
9. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011; 63(10): 3136-41.
10. Liu R, Han C, Wu D, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. Biomed Res Int 2015; 2015: 762820.
11. Wan Z, Song L, Hu L, Lei X, Huang Y, Lv Y. Temporal trends in hyperuricaemia among adults in Wuhan city, China, from 2010 to 2019: a cross-sectional study. BMJ Open 2021; 11(3): e043917.
12. Ni Q, Lu X, Chen C, Du H, Zhang R. Risk factors for the development of hyperuricemia A STROBE-compliant cross-sectional and longitudinal study. Medicine 2019; 98: 42.
13. Peng TC, Wang CC, Kao TW, et al. Relationship between hyperuricemia and lipid profiles in US adults. Biomed Res Int 2015; 2015: 127596.
14. Juraschek SP, Kovell LC, Miller ER, Gelber AC. Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. PLoS One 2013; 8(2): e56546.
15. Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 2013; 108(8): 1299-304.
16. Kashima S, Inoue K, Matsumoto M, Akimoto K. Prevalence and characteristics of non-obese diabetes in Japanese men and women: the Yuport Medical Checkup Center Study. J Diabetes 2015; 7(4): 523-30.
17. Huang YF, Yang KH, Chen SH, et al. [Practice guideline for patients with hyperuricemia/gout]. Zhonghua Nei Ke Za Zhi 2020; 59(7): 519-27.
18. Zhang Y, Nie FQ, Huang XB, et al. High prevalence and low awareness of hyperuricemia in hypertensive patients among adults aged 50-79 years in Southwest China. BMC Cardiovasc Disord 2022; 22(1): 2.

19. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006; 17(10): 2937-44.
20. Fan JG, Wei L, Zhuang H, National Workshop on Fatty L, Alcoholic Liver Disease CSOHCMA, Fatty Liver Disease Expert Committee CMDA. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). J Dig Dis 2019; 20(4): 163-73.
21. Expert Panel on Detection E, Treatment of High Blood Cholesterol In A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-97.
22. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018; 37(9): 2529-38.
23. Gaffo AL, Jacobs DR, Jr., Lewis CE, Mikuls TR, Saag KG. Association between being African-American, serum urate levels and the risk of developing hyperuricemia: findings from the Coronary Artery Risk Development in Young Adults cohort. Arthritis Res Ther 2012; 14(1): R4.
24. Mcadams-Demarco MA, Law A, Maynard JW, Coresh J, Baer AN. Risk factors for incident hyperuricemia during mid-adulthood in African American and white men and women enrolled in the ARIC cohort study. BMC Musculoskelet Disord 2013; 14: 347.
25. Koga M, Saito H, Mukai M, Kasayama S, Yamamoto T. Factors contributing to increased serum urate in postmenopausal Japanese females. Climacteric 2009; 12(2): 146-52.
26. Song P, Wang H, Xia W, Chang X, Wang M, An L. Prevalence and correlates of hyperuricemia in the middle-aged and older adults in China. Sci Rep 2018; 8(1): 4314.
27. Cui L, Meng L, Wang G, et al. Prevalence and risk factors of hyperuricemia: results of the Kailuan cohort study. Mod Rheumatol 2017; 27(6): 1066-71.
28. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020; 16(7): 380-90.
29. Robinson PC, Taylor WJ, Dalbeth N. An Observational Study of Gout Prevalence and Quality of Care in a National Australian General Practice Population. J Rheumatol 2015; 42(9): 1702-7.
30. Lonardo A, Mantovani A, Lugari S, Targher G. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. Ann Hepatol 2020; 19(4): 359-66.
31. Samouda H, Ruiz-Castell M, Karimi M, et al. Metabolically healthy and unhealthy weight statuses, health issues and related costs: Findings from the 2013-2015 European Health Examination Survey in Luxembourg. Diabetes Metab 2019; 45(2): 140-51.
32. Schulze MB. Metabolic health in normal-weight and obese individuals. Diabetologia 2019; 62(4): 558-66.
33. Buscemi S, Chiarello P, Buscemi C, et al. Characterization of Metabolically Healthy Obese People and Metabolically Unhealthy Normal-Weight People in a General Population Cohort of the ABCD Study. J Diabetes Res 2017; 2017: 9294038.
34. Borghi C, Agabiti-Rosei E, Johnson RJ, et al. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. Eur J Intern Med 2020; 80: 1-11.
35. Bove M, Cicero AF, Veronesi M, Borghi C. An evidence-based review on urate-lowering treatments: implications for optimal treatment of chronic hyperuricemia. Vasc Health Risk Manag 2017; 13: 23-28.

36. Caliceti C, Calabria D, Roda A, Cicero AFG. Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: A Critical Review. Nutrients 2017; 9(4).

Table 1. Clinical characteristics of the study population

Variables	Male		P value	Female		P value
	Without hyperuricemia (n =1967)	With hyperuricemia (n =382)		Without hyperuricemia (n =3226)	With hyperuricemia (n =156)	
Age (year)	46.5(46.0-47.1)	44.5(43.3-45.7)	0.004	43.4(43.0-43.8)	46.6(44.3-49.0)	0.009
WC (cm)	81.3(81.1-81.5)	83.1(82.6-83.6)	<0.001	74.0(73.8-74.2)	76.6(75.5-77.7)	<0.001
BMI (kg/m^2)	21.87(21.80-21.94)	22.33(22.19-22.47)	<0.001	20.94(20.88-21.00)	21.64(21.36-21.92)	<0.001
SBP (mmHg)	122.8(122.1-123.5)	124.1(122.4-125.8)	0.159	115.0(114.4-115.6)	122.2(119.0-125.4)	<0.001
DBP (mmHg)	75.6(75.1-76.1)	77.2(76.1-78.3)	0.009	69.2(68.8-69.6)	73.9(72.1-75.7)	<0.001
ALT (U/L)	21.4(20.6-22.3)	26.5(24.7-28.4)	<0.001	15.2(14.9-15.6)	23.2(18.4-28.0)	0.001
AST (U/L)	20.6(20.1-21.0)	22.5(21.6-23.5)	0.001	18.4(18.1-18.6)	23.1(20.5-25.7)	0.001
GGT (U/L)	30.1(29.1-32.9)	41.6(37.7-45.6)	<0.001	16.8(16.2-17.5)	22.9(19.5-26.3)	<0.001
Creatinine (μmol/L)	81.2(80.6-81.8)	86.5(84.6-88.4)	<0.001	59.5(59.2-59.8)	63.8(62.2-65.4)	<0.001
BUN (mmol/L)	5.12(5.07-5.17)	5.37(5.21-5.53)	0.003	4.55(4.51-4.59)	5.07(4.84-5.30)	<0.001
eGFR	101.1(100.4-101.8)	95.3(93.5-97.1)	<0.001	188.7(188.0-189.4)	109(105.4-112.6)	<0.001
TG (mmol/L)	1.38(1.34-1.42)	1.88(1.76-2.00)	<0.001	1.05(1.03-1.07)	1.60(1.28-1.92)	0.001
TC (mmol/L)	4.49(4.45-4.53)	4.71(4.62-4.80)	<0.001	4.52(4.49-4.55)	4.76(4.62-4.90)	0.001
HDL-C (mmol/L)	1.21(1.20-1.22)	1.14(1.11-1.17)	<0.001	1.44(1.43-1.45)	1.36(1.30-1.42)	0.003
LDL-C (mmol/L)	2.62(2.59-2.65)	2.72(2.65-2.79)	0.012	2.53(2.51-2.55)	2.65(2.53-2.77)	0.026
VLDL-C (mmol/L)	0.65(0.64-0.66)	0.84(0.80-0.88)	<0.001	0.55(0.54-0.56)	0.73(0.65-0.81)	<0.001
FBS (mmol/L)	5.02(4.97-5.07)	5.01(4.93-5.09)	0.815	4.81(4.79-4.83)	5.07(4.93-5.21)	<0.001
Excessive drinking (%)	14.0%(12.5%-15.5%)	19.4%(15.4%-23.4%)	0.007	1.4%(1.0%-1.8%)	3.8%(0.8%-6.8%)	0.016
Smoking history (%)	39.0%(36.8%-41.2%)	42.9%(37.9%-47.9%)	0.15	1.4%(1.0%-1.8%)	1.3%(0%-3.1%)	0.906
SUA (μmol/L)	333.8(331.6-336.0)	467.9(463.2-472.6)	<0.001	260.0(258.5-261.5)	397.1(390.8-403.4)	<0.001

Data are expressed as the mean (95% CI)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SUA: serum uric acid; TG: triglyceride; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; WC: waist circumference.

Table 2. Prevalence of metabolic disease according to hyperuricemia

	Male			Female		
	Without hyperuricemia	With hyperuricemia	*P*-value	Without hyperuricemia	With hyperuricemia	*P*-value
Metabolic syndrome	5.4%	10.2%	<0.001	4%	16%	<0.001
Metabolic syndrome components						
Waist circumference (> 102 cm in men, >88 cm in women)	0%	0%	/	1.4%	3.2%	0.06
Fasting blood glucose (≥ 6.1 mmol/L)	6.4%	6.5%	0.890	2%	10.9%	<0.001
Triglyceride (≥1.7mmol/L)	21.9%	45%	<0.001	10.8%	26.3%	<0.001
HDL-C (<1.04 mmol/L in men, <1.30 mmol/L in women)	28.9%	37.7%	0.001	35.2%	48.1%	0.001
Blood pressure (≥130/85 mmHg)	33.7%	38%	0.105	19.3%	35.9%	<0.001
Diabetes mellitus	3.4%	2.9%	0.599	1%	2.6%	0.062
NAFLD	13.8%	30.4%	<0.001	6.4%	20.5%	<0.001

HDL-C: high-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease;

Table 3. Multivariable analysis for factors associated with hyperuricemia

Variables	Male		Female	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (year)	0.961(0.950-0.972)	<0.001	0.958 (0.939-0.977)	<0.001
WC (cm)	1.057 (1.030-1.084)	<0.001	1.038 (1.006-1.071)	0.020
DBP (mmHg)	/		1.033(1.016-1.050)	<0.001
ALT (U/L)	/		1.023 (1.013-1.033)	<0.001
AST (U/L)	1.014 (1.004-1.024)	0.005	/	
eGFR (μmol/L)	0.973 (0.965-0.980)	<0.001	0.976 (0.966-0.985)	<0.001
BUN (mmol/L)	1.114 (1.014-1.223)	0.025	1.308 (1.137-1.505)	<0.001
TG (mmol/L)	/		1.423 (1.199-1.690)	<0.001
TC (mmol/L)	2.717 (1.921-3.843)	<0.001	/	
HDL-C (mmol/L)	0.378 (0.240-0.594)	<0.001	/	
LDL-C (mmol/L)	0.386 (0.256-0.583)	<0.001	/	
Excessive drinking	1.501 (1.097-2.055)	0.011	3.562 (1.408-9.011)	0.007
NAFLD	1.959 (1.472-2.607)	<0.001	1.900 (1.164-3.102)	0.010

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FBS: fasting blood sugar; GGT: gamma-glutamyl transpeptidase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NAFLD: nonalcoholic fatty liver disease; TG: triglyceride; TC: total cholesterol; WC: waist circumference

Figure Legend

Figure 1. Prevalence of hyperuricemia(A) and Serum uric acid(B) in participants

Data was expressed as mean with 95% confidence interval (error bars)

Figure 2. Prevalence of hyperuricemia (A) and Serum uric acid (B) in metabolically healthy or metabolically unhealthy participants. Data was expressed as mean ± SD. $^{**}p<0.01$, $^{***}p<0.001$.

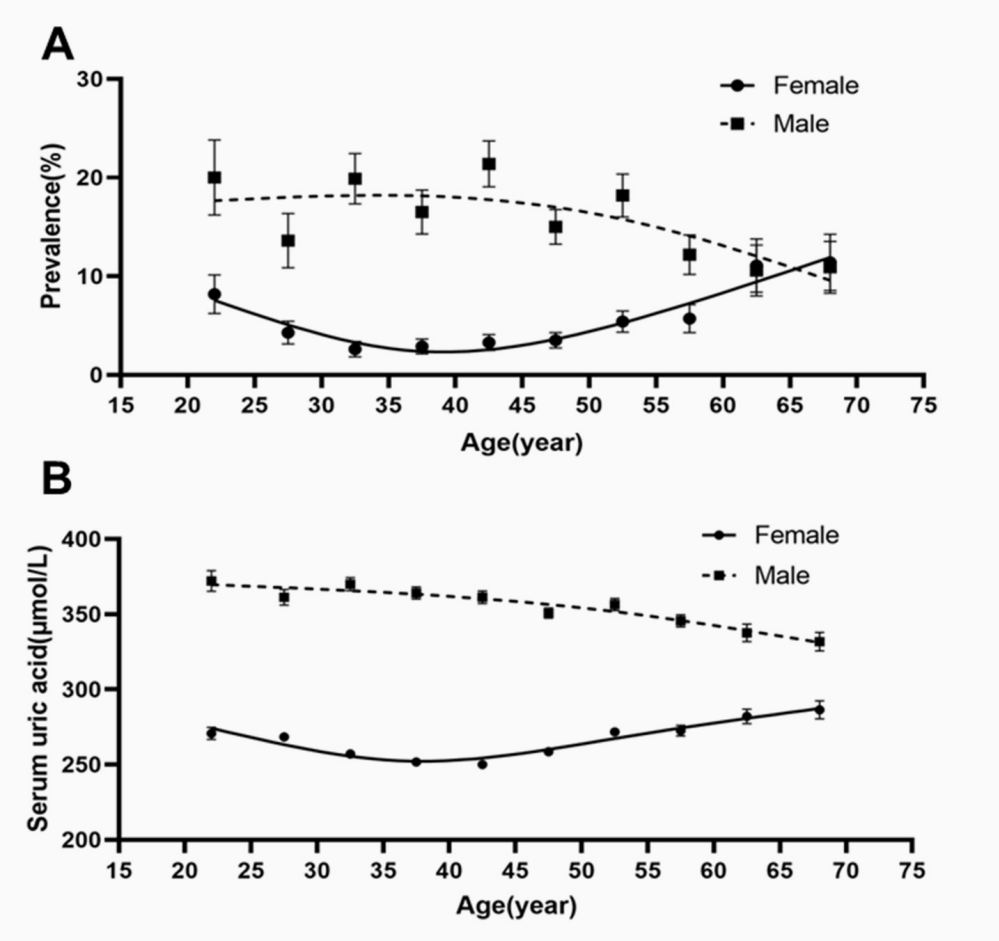

Figure 1

121x114mm (300 x 300 DPI)

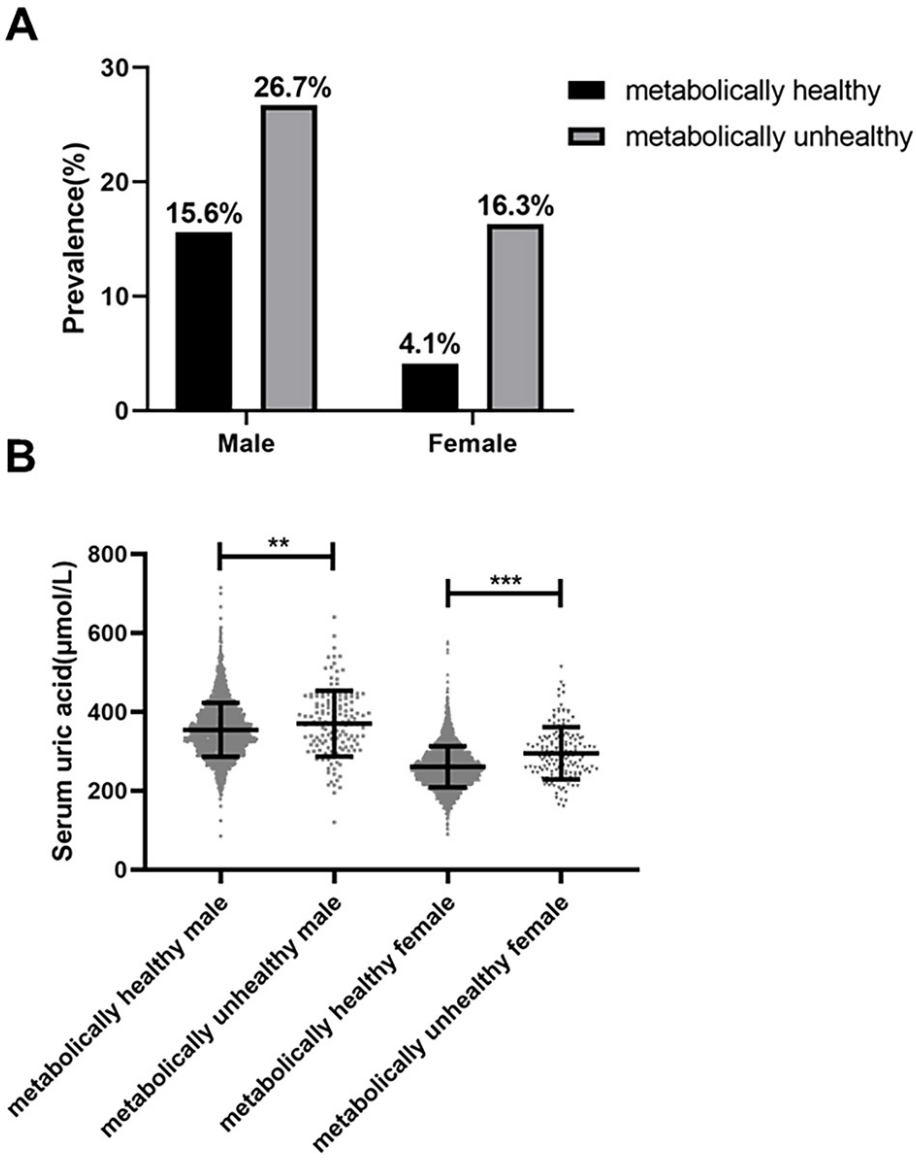

Figure 2

83x104mm (300 x 300 DPI)

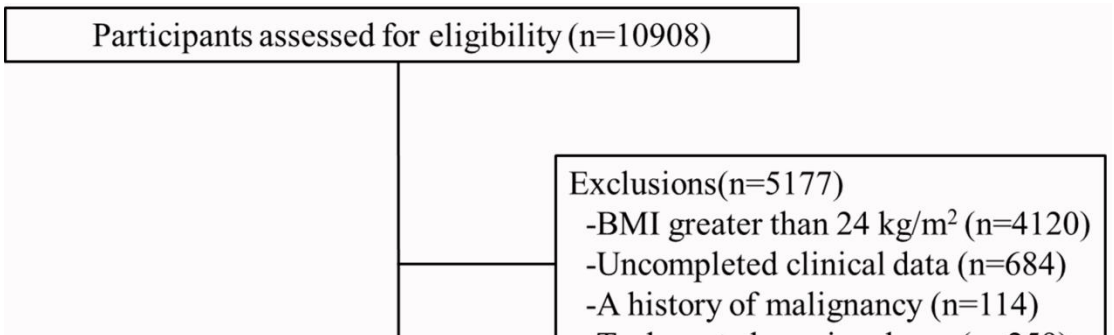

Figure S1. Inclusion and exclusion flow chart of this study

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	*N/A*
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.