Int J Clin Exp Med 2015;8(11):21122-21129
www.ijcem.com /ISSN:1940-5901/IJCEM0014460

Original Article

The association between serum uric acid and metabolic syndrome among adolescents in northeast China

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Received August 13, 2015; Accepted October 10, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: Purpose: Data about the association between serum uric acid and metabolic syndrome in healthy adolescents are sparse. This study examined this association and determined the optimal cutoffs for serum uric acid to predict metabolic syndrome among healthy adolescents. Methods: During 2010-2011, we conducted a cross-sectional study of 927 adolescents (53.0% boys) aged 11-16 years from junior and senior high schools in northeast China. All participants received a physical examination and gave venous blood samples. Results: Serum uric acid was positively associated with abdominal obesity, dyslipidemia and hypertension in boys and with abdominal obesity and dyslipidemia in girls. For those with hyperurecemia, the odds ratios (95% CI) for metabolic syndrome were 7.67 (95% CI, 2.58~22.78) for boys and 4.77 (95% CI, 1.01~22.60) for girls. SUA was a better predictor of metabolic syndrome than fasting glucose, though not as good as waist circumference. Conclusions: Among adolescents in China, serum uric acid level may be a useful predictor of metabolic syndrome.

Keywords: Adolescents, metabolic syndrome, public health, uric acid

Introduction

Recent changes in standards of living, lifestyle, and diet have led to a worldwide increase in the prevalence of chronic diseases such as hyperuricemia and metabolic syndrome. In China in particular, the Chinese prevalence of hyperuricemia has risen substantially over the past decade, increasing from 8.2~19.8% in males and 5.1~7.6% in females in the 1990s [1], to 35.94% in males and 16.32% in females in 2009 [2]. Similarly, the prevalence of metabolic syndrome also shows a rapid growth trend in China, increasing from 8.5% in 2002 to 21.18% in 2009 [3]. Hyperuricemia shows positive associations with metabolic syndrome [4, 5], metabolic syndrome components like hypertension [10, 11], and diabetes mellitus [8, 9]. This suggests that hyperuricemia could be a cause of metabolic syndrome. At the same time, it is difficult to sort out the causal ordering of these associations, and the associations may reflect the hyperuricemia is a consequence, rather than a cause of, metabolic syndrome.

A positive association between serum uric acid and metabolic syndrome in a young population that is mostly free of adult chronic disorders would provide some evidence that hyperurecemia may be a cause rather than a consequence of metabolic syndrome. A few studies of adolescents in the U.S. [14] and Japan [15] have reported a positive association between uric acid and metabolic syndrome, but additional data are needed to clearly establish the nature of this association in young persons in other populations, such as China. Accordingly, we investigated uric acid's association with metabolic syndrome and its components in Chinese adolescents.

Methods

Subjects

From December 2010 to January 2011, we used a stratified cluster sampling method to enroll 936 students (500 boys and 436 girls) aged 11 to 16 years without known metabolic

Table 1. The SUA levels among boys and girls (Mean ± SD)

Age (years)	Boys		Girls	
	SUA (μmol/L)	n.	SUA (μmol/L)	n.
11~	264.4±73.2*	8	260.7±59.0	10
12~	331.9±84.1#	120	268.0±64.9	109
13~	358.8±103.4	119	273.3±74.0	95
14~	357.9±84.5	76	263.5±71.6	61
15~	369.2±84.4	85	255.3±54.1	90
16~	362.7±88.2	83	261.5±53.9	71
Total	353.0±91.1	491	264.7±64.1	436

*P < 0.05 VS boys aged 12~16 years old; #P < 0.05 VS boys aged 13~16 years old.

syndrome from junior and senior high schools in an urban district of Liaoyang, a moderately developed city in northeast China. The study protocol was approved by the hospital ethnics committee and written informed consent was obtained from students and their parents.

Questionnaire and measurement

All participants completed a self-administered questionnaire addressing lifestyle factors. They also received a physical examination which included measurement of height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference (WC), hip circumference, and signs of acanthosis nigricans. Fasting venous blood samples were collected in order to measure serum concentrations of uric acid (SUA), total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), fasting plasma glucose (FPG), hemoglobin (HbA1c), and fasting plasma insulin (FINS).

Height, weight, WC and hip circumference were measured with adolescents lightly clothed and without shoes in a standing position. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, and weight to the nearest 0.1 kg using a standard beam balance scale. WC was measured midway between the tenth rib cage and the top of the iliac crest during minimal respiration, and hip circumference measurement was measured at the largest girth. Both measurements were made using a non-elastic flexible tape without pressure to the body surface, and recorded to the nearest 0.5 cm. SBP and DBP were measured after a 10-min rest while sitting using a mercury-gravity sphygmomanometer, and two measurements at two-minute intervals were recorded and averaged. Blood samples were obtained after an overnight fast of at least 10 hours. Within a half an hour of obtaining the blood sample, a portion of the sample was sent to a laboratory in Liaoyang Diabetes Hospital to measure FPG, TG, TC, HDL-C and SUA using an Olympus AU system (Olympus 400, Olympus Optical Company, Japan). FPG was measured using the glucose oxidase method. TG, TC and HDL-C were measured by the routine enzymatic methods. LDL-C was calculated from Friedwald's equation [16]. For HbA1c, plasma was sent to the central laboratory in Shengjing Hospital of China Medical University within 4 hours of sampling, and measured using high-performance liquid chromatography with a D-10 hemoglobin testing system (Bio-Rad Laboratories, Inc., Hercules, CA). FINS serum samples were stored at -80°C and determined on a separate day by radioimmunoassay (China Institute of Atomic Energy).

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Insulin resistance (IR) was estimated using the homeostasis assessment model of insulin resistance (HOMA-IR) [17], which was calculated as FINS (μU/mL) × FPG (mmol/L)/22.5.

Definition of metabolic syndrome and hyperuricemia

Consensus criteria for metabolic syndrome (MetS) for adolescents are currently unavailable. To define MetS among young participants, we used the 2007 International Diabetes Federation criterion for children and adolescents [18]. To qualify as having MetS, participants had to have abdominal obesity (defined as WC ≥90th percentile in Chinese children and adolescents of the same age and sex [19]. and at least two of the following four criteria: TG ≥1.70 mmol/L; HDL-C < 1.03 mmol/L for individuals 10-15 years and boys aged ≥16 years, or < 1.29 mmol/L for girls aged ≥16 years; SBP ≥130 mmHg and/or DBP ≥85 mmHg; and FPG ≥5.6 mmol/L or Type 2 diabetes mellitus.

Because no universally accepted threshold defines hyperuricemia in children and adolescents, we defined hyperuricemia as SUA > 420 μmol/L for boys and SUA > 340 μmol/L for girls.

Table 2. Baseline Characteristics (Mean ± SD) according to SUA quartiles in boys and girls

	Quartiles of SUA in boys				*P* Value
	Q1	Q2	Q3	Q4	Q1 vs Q4
SUA range (μmol/l)	≤296	297-347	348-412	≥413	
n.	123	123	123	122	
age (years)	13.4±1.5	13.7±1.5	13.8±1.4	14.0±1.4	0.001
BMI (kg/m^2)	20.3±3.5	21.7±4.3	22.8±4.4	24.0±4.7	< 0.001
WC (cm)	68.0±9.4	70.9±9.9	73.6±11.3	76.8±11.6	< 0.001
SBP (mmHg)	112±14	117±13	119±14	120±15	< 0.001
DBP (mmHg)	67±12	69±12	69±11	70±12	> 0.05
TG (mmol/L)	0.98±0.43	0.98±0.44	1.00±0.58	1.22±0.70	0.001
TC (mmol/L)	4.35±0.80	4.29±0.87	4.35±0.71	4.60±7.77	0.016
HDL-C (mmol/L)	1.06±0.28	1.06±0.25	1.06±0.27	1.03±0.26	> 0.05
LDL-C (mmol/L)	3.34±0.14	3.35±0.17	3.36±0.15	3.39±0.18	0.037
FPG (mmol/L)	4.80±0.59	4.79±0.50	4.79±0.48	4.86±0.52	> 0.05
HbA1c (%)	5.44±0.27	5.43±0.30	5.47±0.36	5.46±0.30	> 0.05
FINS[a]	2.69±0.45	2.84±0.54	2.85±0.51	3.01±0.53	< 0.001
HOMA-IR[a]	1.13±0.47	1.29±0.58	1.30±0.52	1.47±0.55	< 0.001
Acanthosis nigricans manifestation (%)	4.07	8.94	13.82	23.77	< 0.001
MetS (%)	7.27	6.76	12.04	14.31	< 0.001
	Quartiles of SUA in girls				*P* Value
	Q1	Q2	Q3	Q4	Q1 vs Q4
SUA range (μmol/l)	≤225	226-259	260-300	≥301	
n.	109	109	108	110	
age (years)	13.8±1.5	13.9±1.5	13.7±1.4	13.6±1.5	> 0.05
BMI (kg/m^2)	19.8±3.2	20.1±3.3	21.0±3.7	22.8±4.3	< 0.001
WC (cm)	65.8±9.4	65.6±8.0	68.5±9.5	70.9±9.4	< 0.001
SBP (mmHg)	109±14	111±13	111±13	114±12	0.005
DBP (mmHg)	70±10	72±11	79±75	72±11	> 0.05
TG (mmol/L)	0.93±0.37	1.00±0.43	1.12±0.51	1.21±0.53	< 0.001
TC (mmol/L)	4.52±0.88	4.51±0.77	4.66±0.78	4.66±0.76	> 0.05
HDL-C (mmol/L)	1.07±0.24	1.10±0.25	1.09±0.26	1.04±0.28	> 0.05
LDL-C (mmol/L)	3.37±0.16	3.35±0.14	3.39±0.19	3.40±0.27	> 0.05
FPG (mmol/L)	4.68±0.47	4.73±0.47	4.71±0.51	4.80±1.06	> 0.05
HbA1c (%)	5.40±0.26	5.41±0.23	5.38±0.24	5.45±0.43	> 0.05
FINS[a]	2.88±0.41	2.83±0.39	2.94±0.44	3.03±0.43	0.010
HOMA-IR[a]	1.31±0.44	1.26±0.41	1.37±0.47	1.47±0.46	0.007
Acanthosis nigricans manifestation (%)	1.83	2.75	3.70	11.11	0.006
MetS (%)	3.07	5.16	5.56	7.94	< 0.001

a: The data was ln-transformed to normality before analysis.

Statistical analysis

Gender-specific quartiles of SUA were used because of a substantial difference in SUA concentrations between boys and girls. Normally distributed continuous variables were presented as means with standard deviations (SD). FINS and HOMA-IR were ln-transformed to normality before analysis. Categorical data were given as a number (percentage). Differences between group means were tested using Student's *t*-test or analysis of variance (ANOVA) and least significant differences (LSD) post-hoc tests. Categorical data were analyzed by the χ^2 test. To examine associations between each component of MetS and concentrations of uric

Table 3. Odds ratios for Mets and its components, according to SUA quartiles: Results of logistic regression models

	Odds ratios (95% CI) in boys			
	Q1	Q2	Q3	Q4
Abdominal obesity	1.00	1.75 (0.87-3.52)	3.52 (1.82-6.82)	5.86 (3.07-11.19)#
Dyslipidemia[a]	1.00	1.41 (0.55-3.64)	1.55 (0.61-3.95)	3.89 (1.69-9.00)#
Hypertension	1.00	1.93 (0.97-3.86)	2.22 (1.12-4.39)	2.67 (1.36-5.23)#
Increased FPG	1.00	0.69 (0.29-1.62)	0.26 (0.08-0.82)	0.62 (0.26-1.49)
MetS	1.00	2.35 (0.70-7.84)	4.77 (1.56-14.63)	7.67 (2.58-22.78)#
	The odds ratios (95% CI) in girls			
	Q1	Q2	Q3	Q4
Abdominal obesity	1.00	1.30 (0.58-2.93)	2.44 (1.15-5.15)	3.62 (1.75-7.45)#
Dyslipidemia[a]	1.00	5.40 (1.16-25.27)	7.32 (1.61-33.28)	6.55 (1.43-30.01)*
Hypertension	1.00	2.35 (1.01-5.45)	1.66 (0.68-4.00)	1.89 (0.80-4.49)
Increased FPG	1.00	3.67 (0.75-18.09)	3.71 (0.75-18.27)	3.64 (0.74-17.91)
MetS	1.00	1.00 (0.14-7.23)	3.71 (0.75-18.27)	4.77 (1.01-22.60)*

*: VS Q1, P < 0.05; #: VS Q1, P < 0.01. a: Because there was no significant change in HDL-C in 4 quartiles of SUA, we categorized these students into dyslipidemia as defined only according to TG.

acid, we ran several logistic regression models. The Receiver Operating Characteristic (ROC) curve was used to determine optimal cut-offs of WC, TG, SBP, FBG and SUA for predicting metabolic syndrome status. The optimal cutoff was identified as the coordinate closest to the y-intercept (0, 1) of the ROC curve when the sum of sensitivity and specificity is maximal. Diagnostic accuracy was assessed by the area under the curve (AUC). All analyses used SPSS for windows v.17.0 (SPSS Inc., Chicago, IL.) and *p*-values < 0.05 were considered statistically significant.

Results

This study had 936 participants aged 11~16 years. MetS status could not be determined for 9 participants, so 927 participants (491 boys and 436 girls) were included in our analytic sample. MetS prevalence was 8.1% in the entire group (11.2% for boys, 5.7% for girls), and hyperuricemia prevalence was 15.1% in the entire group (22.4% boys, 6.9% girls). Both MetS prevalence and hyperuricemia prevalence were significantly higher in boys than girls (P < 0.01).

In the overall group, SUA concentrations ranged from 116~655 μmol/L, with a mean of 312.0±90.5 μmol/L. SUA ranged from 116~598 μmol/L in boys, and 140~655 μmol/L in girls. With the exception of the 16-year-old group, mean SUA was significantly higher in boys than girls in each age group (353.0±91.1 μmol/L for boys vs. 264.7±64.1 μmol/L for girls, P < 0.01). As age increased, SUA increased in boys, while there was no significant trend in boys of 13~16-year-old groups and in girls of each-year-old group (insert **Table 1** here).

Because no universally accepted threshold defines hyperuricemia in children and adolescents, we calculated prevalence using four gender-specific quartiles: for boys, (Q1) ≤296 μmol/L; (Q2) 297~347 μmol/L; (Q3) 348~412 μmol/L; (Q4) ≥413 μmol/L; and for girls (Q1) ≤225 μmol/L; (Q2) 226~259 μmol/L; (Q3) 260~300 μmol/L; (Q4) ≥301 μmol/L. For each SUA quartile, we calculated the mean of each baseline characteristic, the prevalence of acanthosis nigricans manifestation, and the prevalence of MetS for each. Compared to the lowest quartile of SUA (Q1), BMI, WC, SBP, TG, FINS, HOMA-IR and positive acanthosis nigricans manifestation were significantly higher in the highest SUA quartile (Q4) for both sexes. In addition, age, TC, and LDL-C increased significantly in boys. In all subjects, prevalence of MetS was higher in Q4 than Q1. No significant difference was observed between quartiles for SUA, FPG, or HbA1c in either gender (insert **Table 2** here).

In logistic regression models, SUA was significantly associated with the prevalence of

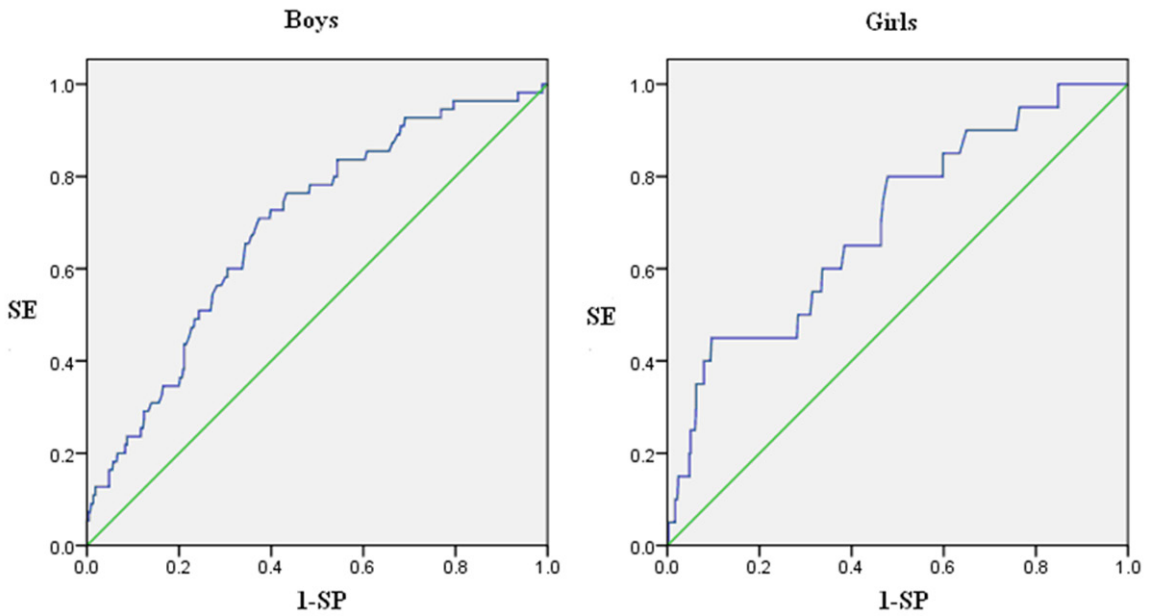

Figure 1. ROC cures of SUA in relation to the presence of MetS in boys and girls.

abdominal obesity, dyslipidemia and hypertension in Q4 in boys, and abdominal obesity and dyslipidemia only in girls. SUA was significantly associated with the prevalence of MetS in both sexes, and the odds ratios (95% confidence interval [CI]) of the highest quartile of SUA for MetS were 7.67 (95% CI, 2.58~22.78) for boys and 4.77 (95% CI, 1.01~22.60) for girls (insert **Table 3** here).

As shown in **Figure 1**, SUA helped discriminate between those with and without MetS in boys (AUC: 0.69, 95% CI: 0.62~0.76, P < 0.01) and girls (AUC: 0.70, 95% CI: 0.58~0.82, P=0.01) on a continuous scale using ROC curves. The optimal SUA cutpoints for SUA for discriminating MetS status were 367.5 μmol/L for boys (sensitivity 70.9%, specificity 62.6%) and 335.5 μmol/L for girls (sensitivity 45.0%, specificity 90.4%).

Among the four MetS components, in boys, MetS were predicted by WC (AUC: 0.92, 95% CI: 0.90~0.95, P < 0.01), TG (AUC: 0.79, 95% CI: 0.72~0.86, P < 0.01) and SBP (AUC: 0.79, 95%CI: 0.72~0.85, P < 0.01) on a continuous scale using ROC curves, but not FBG (AUC: 0.55, 95% CI: 0.46~0.64, P=0.21). In girls, MetS were predicted by WC (AUC: 0.93, 95% CI: 0.90~0.96, P < 0.01), TG (AUC: 0.78, 95% CI: 0.68~0.88, P < 0.001) and SBP (AUC: 0.79, 95% CI: 0.66~0.91, P < 0.01) on a continuous scale using ROC curves, but not FBG (AUC: 0.50, 95% CI: 0.33~0.67, P=0.98) (**Figure 2**).

For boys, the optimal cutoff was 367.5 μmol/L (sensitivity 70.9%, specificity 62.6%) and the AUC was 0.693, (95% CI: 0.622~0.764), P < 0.001.

For girls, the optimal cutoff was 335.5 μmol/L for girls (sensitivity 45.0%, specificity 90.4%) and the AUC was 0.700, (95% CI: 0.582~0.818), P=0.003.

Among four MetS components, in boys, MetS were predicted by WC, TG and SBP on a continuous scale using ROC curves, but not FBG. In girls, MetS were predicted by WC, TG and SBP on a continuous scale using ROC curves, but not FBG.

Discussion

Our results among Chines children and adolescents are consistent with limited data showing that SUA is significantly associated with prevalence of MetS. The results suggest that SUA may be a useful marker for predicting MetS in adolescents, and in particular, may be a better marker than FBG.

Studies of the association between SUA and MetS and its components have been sparse and have reported inconsistent findings. In our

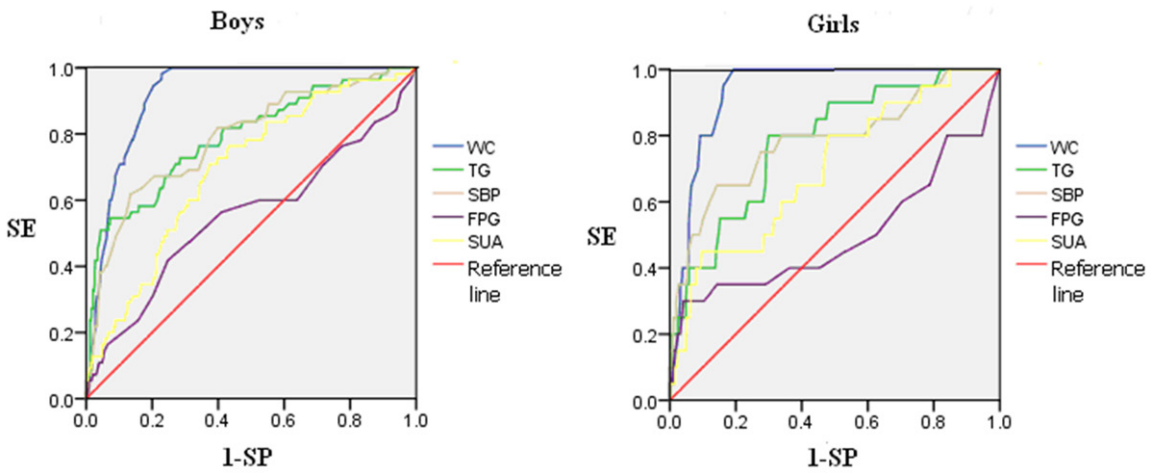

Figure 2. ROC cures of WC, TG, SBP, FBG, and SUA in relation to the presence of Mets.

study, no significant association was found between SUA quartiles and increased FPG in either genders, or with hypertension in girls. In contrast to our study, cross-sectional study [14] of 1370 US adolescents in the National Health and Nutrition Examination Survey (NHANES) 1999~2002 found that among MetS components, SUA was significantly associated with abdominal obesity, hypertriglyceridemia, and hyperglycemia, and showed a borderline association with hypertension. Similarly to the present study, a study [20] of 267 Germany obese adolescents showed that SUA was associated with BMI, SBP and TG, independent of age and gender. In that study, participants were obese and obesity was defined according to BMI, while the study subjects in our study were healthy and we measured obesity by WC. Differences between the present study and two other studies may be related to differences in study populations, subjects, and lifestyle factors. In Japan [15]), where carbohydrates are a main food source, similar to in China, a 2005~2008 study with 958 adolescents reported that in boys, SUA was positively associated with abdominal obesity, hypertension, and dyslipidemia, while in girls, SUA was only associated with abdominal obesity. A study [21] of Chinese adults found that glucose and uric acid absorbed in the renal proximal tubule through a co-transporter competed with each other. When the glucose level was equal to the renal glucose threshold, blood glucose had a clear reabsorption advantage. Uric acid could not be fully reabsorbed, and increased with excretion in urine as SUA decreased. However, the results of our study might differ from the study in adults as we saw no significant association between SUA and FPG in adolescents.

In adults, Reaven, who pioneered MetS studies, stated that hyperuricemia should be considered a component of MetS [22]. A previous study [23] showed that decreasing SUA can prevent or cure MetS. Another study [19] argued that SUA could be seen as a sign of "premetabolic syndrome" among obese adolescents. Similarly, in our analysis, as SUA increased, the prevalence of MetS increased significantly in all subjects. By ROC analysis, our study results suggest that SUA's ability to predict MetS in adolescents is better than FBP, similar to TG and SBP, but not as good as WC. The present study found an optimal SUA cutpoint of 367.5 μmol/L for boys and 335.5 μmol/L for girls for predicting MetS. A study [15] with Japanese junior high school students found that the optimal SUA cutpoint to predict MetS was 6.4 mg/dl (374.4 μmol/L) for boys and 4.9 mg/dl (286.7 μmol/L) for girls. Thus, the present study and the study in Japan are in rough agreement about the optimal SUA cutpoint for boys, but do not agree for the cutpoint for girls. The reasons why the two studies had similar cutpoints for boys but not girls are unclear, but could be due to the fact that in girls, there is a weaker association between SUA and MetS and a relatively low prevalence of MetS.

Insulin resistance is considered a key aspect of MetS and also a common mechanism underlying for hyperuricemia, obesity, hypertension,

increased glucose, dyslipidemia, and other metabolic disorders [24]. A study in Finland [25] found hyperuricemia to be closely correlated with insulin level. Under conditions of insulin resistance, liver fat synthesis increases, which leads to purine metabolic disturbances, causing an increase in SUA. A study [26] of obese Italian teenagers also found that SUA has a close correlation with insulin resistance. We also found that in all subjects, SUA was positively correlated with FINS, HOMA-IR and the prevalence of acanthosis nigricans manifestations.

In our study, SUA was not correlated with age among girls, suggesting that SUA level is not affected by sexual maturation in girls. This result may be due to a low response rate on questionnaire items about menstruation.

In the last decade, MetS prevalence in adolescents has varied considerably because of a lack of consensus on criteria for MetS in adolescents. In recent studies based on NHANES data, the prevalence of MetS in U.S. adolescents varied from 2.0 to 9.6% depending on different definitions of MetS [27]. In the present study, MetS prevalence was 8.1% (11.2% for boys, 5.7% for girls), similar to the prevalence reported in U.S. studies. Additionally, SUA levels in our study were high. These results indicate that metabolic health has become a major public health challenge in northeast China. Many studies have found that MetS correlates with age, gender, race, family history, smoking, alcohol use, dietary style, insufficient physical activity, and family economic conditions, among other factors [28, 29]. Accordingly, improving lifestyle is an efficient way to prevent MetS.

In Conclusion, our study found that SUA is significantly associated with MetS in Chinese adolescents, and can be considered a surrogate marker, superior to FBG, to predict MetS in this population. A marked increase in SUA requires improvements in lifestyle, a decrease in metabolic risk factors, or necessary medical therapy, to prevent the interaction between hyperuricemia and MetS.

This study had several limitations. First, it was based on an observational, cross-sectional design, which prevented us from demonstrating causality in this study. Moreover, because different lifestyles and dietary habits are found in different populations of China, our results may only apply to adolescents in northeast China.

Disclosure of conflict of interest

None.

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