Modern medicine recognizes the metabolic syndrome (MetS) as a cluster of risk factors that predispose patients to various chronic diseases, such as diabetes, dyslipidemia, hypertension, and hyperuricemia. The prevalence of MetS is becoming more prevalent in developing countries, especially in emerging markets like China. This study aimed to investigate the association between serum uric acid (SUA) levels and the development of MetS among Chinese adults.

Materials and Methods

Study participants. A total of 9655 subjects (3664 men and 5991 women) aged ≥20 years were performed annual health check-up in Health Examination Center of Heping District, Tianjin, China in 2008. At baseline, 702 men and 1549 women with MetS and 5 men with low SUA level (<3.0 mg/dl in men and <2.0 mg/dl in women) were excluded from the enrollment. Totally, 7399 subjects (2957 men and 4442 women) were enrolled and they repeated the health check-up in 2011. The medical examination performed for subjects who visited the health examination voluntarily to promote public health through the early detection of chronic disease.

Data collection and measurements. Baseline information on smoking status (yes/no), drinking status (yes/no), habit of regular exercise (yes/no) and past medical history of diabetes, dyslipidemia, hypertension or hyperuricemia were collected by self-reported questionnaire.

Anthropometric measurements were performed by trained health professional personnel using a standardized protocol. Body weight and height were measured without shoes to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was then calculated as weight (in kilograms)/height (in square meters). Waist circumference (WC) was measured midway between the lowest rib and the iliac to the nearest 0.1 cm. Blood pressure was measured by trained nurses with a mercury sphygmomanometer on the right arm of the participants in a comfortable sitting position after at least 5 min rest. Participants were asked to avoid...
vigorous exercise, drinking, and smoking for at least 30 min before the measurement.

Overnight fasting venous blood specimens were drawn. Triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), SUA and fasting plasma glucose (FPG) were measured enzymatically on a auto-Analyzer TBA-40 (Toshiba, Tokyo, Japan).

**Definition of MetS.** The International Diabetes Federation (IDF) criteria was used to define MetS in the present study because this definition considers the ethnic difference for central obesity. According to the IDF criteria, participants are classified as having MetS if they have central obesity (waist circumference ≥90 cm for men and ≥80 cm for women) plus any other two abnormalities of those shown below: (1) Hypertension: systolic blood pressure (SBP) ≥130 mmHg, or diastolic blood pressure (DBP) ≥85 mmHg, or treatment of previously diagnosed hypertension; (2) Hypertriglyceridemia: TG ≥150 mg/dl or specific medical treatment for this lipid abnormality; (3) Low HDL-C: <40 mg/dl in men or <50 mg/dl for women; (4) Hyperuricemia: fasting glucose ≥100 mg/dl or treatment of previously diagnosed diabetes.

**Quartiles of SUA levels within the normal range stratified by gender.** Hyperuricemia was defined as SUA >7.0 mg/dl in men and >6.0 mg/dl in women. SUA concentration within the normal range (≤7.0 mg/dl in men and ≤6.0 mg/dl in women) was categorized into quartiles based on the cut-off points of the entire distribution for men and women separately (men: Q1, <5.3 mg/dl; Q2, 5.3–5.9 mg/dl; Q3, 6.0–6.6 mg/dl and Q4, 6.7–7.0 mg/dl; women: Q1, <4.1 mg/dl; Q2, 4.1–4.6 mg/dl; Q3, 4.7–5.2 mg/dl and Q4, 5.3–6.0 mg/dl).

**Statistical analysis.** Data were expressed as means ± standard deviation (SD) or number (%). Baseline characteristics between the groups with incident MetS and without incident MetS were assessed by Student’s t test or chi-square test. Cox regression analysis was used to assess the relationship between 3-y development of MetS and quartile of SUA level within the normal range and MetS. Overall, a higher SUA concentration significantly increased the risk for MetS and this trend was increased for MetS in both genders. In normouricemic men, Q2, Q3 and Q4 showed higher risks (with unadjusted HR of 2.8- and 5.0-fold increase of the MetS risk in men and women, respectively). This association remained significant after adjustment for compound factors including age, BMI, smoking status, drinking status, habit of regular exercise, SBP, LDL-C, TG, HDL-C and FPG. Participants with hyperuricemia associated a 2.8- and 5.0-fold increase of the MetS risk in men and women, respectively. This association remained significant after adjustment for compound factors including age, BMI, smoking status, drinking status, habit of regular exercise, SBP, LDL-C, TG, HDL-C and FPG. Among participants without hyperuricemia, 630 men and 560 women developed MetS during the 3-year follow-up and the accumulated incidence of MetS was 21.3% in men and 12.6% in women, respectively. We performed a subgroup analysis by gender among participants without hyperuricemia to elucidate the association between SUA level within the normal range and MetS. Overall, a higher SUA concentration significantly increased the risk for MetS and this trend was increased for MetS in both genders. In normouricemic men, Q2, Q3 and Q4 showed higher risks (with unadjusted HR of 1.59, 1.78

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**Table 1. Baseline characteristics of study population stratified for the absence and presence of MetS by gender**

|          | Men          | p    | Women         | p    |
|----------|--------------|------|---------------|------|
| No. of subjects | 776          | 2181 | 749           | 3693 |
| Age (years)     | 54.2 ± 13.4  | 51.1 ± 14.6 | <0.001 | 57.2 ± 12.0  | 46.1 ± 14.0 | <0.001 |
| BMI (kg/m²)     | 26.7 ± 2.2   | 23.6 ± 2.7 | <0.001 | 25.7 ± 2.7   | 22.1 ± 2.7  | <0.001 |
| WC (cm)         | 87.1 ± 5.7   | 79.4 ± 7.3 | <0.001 | 82.9 ± 7.2   | 73.0 ± 6.8  | <0.001 |
| SBP (mmHg)      | 130.0 ± 16.5 | 123.1 ± 16.2 | 0.002 | 126.7 ± 17.7 | 114.3 ± 15.9 | <0.001 |
| DBP (mmHg)      | 84.2 ± 9.5   | 79.8 ± 9.6 | <0.001 | 79.6 ± 10.0  | 73.8 ± 9.6  | <0.001 |
| TC (mg/dl)      | 187.9 ± 28.6 | 184.0 ± 30.6 | 0.002 | 198.9 ± 33.4 | 182.4 ± 31.5 | <0.001 |
| LDL-C (mg/dl)   | 111.9 ± 25.4 | 107.3 ± 26.0 | 0.001 | 118.0 ± 26.6 | 102.2 ± 26.9 | <0.001 |
| HDL-C (mg/dl)   | 45.0 ± 11.7  | 49.6 ± 13.0 | <0.001 | 53.5 ± 13.6  | 55.6 ± 13.4 | <0.001 |
| TG (mg/dl)      | 167.0 ± 104.5 | 132.6 ± 96.3 | 0.001 | 124.6 ± 62.7 | 91.9 ± 56.4 | <0.001 |
| FPG (mg/dl)     | 104.2 ± 24.5 | 99.8 ± 21.9 | <0.001 | 97.6 ± 16.5  | 93.3 ± 24.5 | <0.001 |
| SUA (mg/dl)     | 6.5 ± 1.4    | 6.0 ± 1.1   | <0.001 | 5.4 ± 1.0    | 4.8 ± 1.0   | <0.001 |
| Smoking         | 375 (48.3)   | 1013 (46.4) | 0.368 | 20 (2.7)     | 67 (1.8)    | 0.123 |
| Drinking        | 402 (51.8)   | 1037 (47.5) | 0.042 | 42 (5.6)     | 152 (4.1)   | 0.069 |
| Regular exercise* | 317 (40.9)   | 1206 (55.3) | <0.001 | 340 (45.4)   | 2175 (58.9) | <0.001 |

Data are means ± standard deviation (SD) or number (%). MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; SUA, serum uric acid. *At least once a week.
AUC, areas under the curve; 95% CI, 95% confidence interval. Refer to the legends of Table 1 for other abbreviations.

The maximal factors (HR, 1.62; 95% CI, 1.24–2.11) remained statistically significant after adjustment for compound hazard ratio; 95% CI, 95% confidence interval. Adjusted for age, body mass index, smoking status, drinking status, habit of regular exercise, systolic blood pressure, low-density lipoprotein cholesterol, triglyceride, high-density lipoprotein cholesterol and fasting plasma glucose. MetS, metabolic syndrome; SUA, serum uric acid; HR, hazard ratio; 95% CI, 95% confidence interval.

The optimal cut-off point of SUA as an optional predictor for future development of MetS obtained with a ROC curve. The maximal sensitivity and specificity to predict future MetS were calculated, and 1.92, respectively) relative to Q1. After adjusting for age, BMI, smoking status, drinking status, habit of regular exercise, systolic blood pressure, low-density lipoprotein cholesterol, triglyceride, high-density lipoprotein cholesterol and fasting plasma glucose. MetS, metabolic syndrome; SUA, serum uric acid; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 2. Hazard ratios of 3- y incident MetS according to quartiles of SUA within the normal range before and after adjustment for baseline confounding factors in men and women

| Quartiles of SUA within the normal range | Hyperuricemia | p-trend |
|----------------------------------------|--------------|--------|
| Q1 | Q2 | Q3 | Q4 |
| Men | | | | |
| SUA quartile (mg/dl) | <5.3 | 5.3–5.9 | 6.0–6.6 | 6.7–7.0 | >7.0 |
| No. of subjects | 635 | 642 | 699 | 627 | 354 |
| No. of incident MetS (%) | 101 (15.9) | 157 (24.5) | 189 (27.0) | 183 (29.2) | 146 (41.2) |
| Crude HR (95% CI) | 1.00 (reference) | 1.59 (1.24–2.04) | 1.78 (1.40–2.26) | 1.92 (1.50–2.44) | 2.84 (2.20–3.66) | <0.001 |
| Adjusted HR* (95% CI) | 1.00 (reference) | 1.34 (1.04–1.72) | 1.55 (1.21–1.98) | 1.29 (1.01–1.67) | 1.78 (1.35–2.34) | 0.001 |
| Women | | | | |
| SUA quartile (mg/dl) | <4.1 | 4.1–4.6 | 4.7–5.2 | 5.3–6.0 | >6.0 |
| No. of subjects | 940 | 931 | 1069 | 942 | 560 |
| No. of incident MetS (%) | 75 (8.0) | 92 (9.9) | 177 (16.6) | 216 (22.9) | 189 (33.8) |
| Crude HR (95% CI) | 1.00 (reference) | 1.24 (0.91–1.68) | 2.13 (1.63–2.80) | 3.00 (2.31–3.90) | 4.57 (3.49–5.97) | <0.001 |
| Adjusted HR* (95% CI) | 1.00 (reference) | 0.94 (0.69–1.28) | 1.41 (1.07–1.86) | 1.62 (1.24–2.11) | 1.55 (1.17–2.06) | <0.001 |

Table 3. Optimal cut-off points of risk factors defined by maximizing sensitivity and specificity to predict future metabolic syndrome and their area under the curve in men and women

| SUA (mg/dl) | BMI (kg/m²) | WC (cm) | SBP (mmHg) | DBP (mmHg) | FPG (mg/dl) | TG (mg/dl) | HDL-C (mg/dl) |
|-------------|-------------|---------|------------|------------|-------------|------------|---------------|
| Men | | | | | | | | |
| Cut-off point | 6.3 | 25.0 | 82.5 | 123.0 | 87.0 | 97.4 | 114.6 | 46.2 |
| Sensitivity (%) | 55.5 | 82.6 | 86.5 | 59.0 | 37.9 | 54.5 | 66.1 | 43.7 |
| Specificity (%) | 58.5 | 70.0 | 65.6 | 79.2 | 54.9 | 53.3 | 42.2 |
| AUC | 0.601* | 0.824* | 0.815* | 0.623* | 0.624* | 0.573* | 0.636** | 0.395*** |
| 95% CI | 0.578–0.624 | 0.808–0.840 | 0.799–0.830 | 0.601–0.646 | 0.602–0.647 | 0.549–0.596 | 0.613–0.658 | 0.373–0.418 |
| Women | | | | | | | | |
| Cut-off point | 4.9 | 22.6 | 85.6 | 117.0 | 79.0 | 89.5 | 90.7 | 56.3 |
| Sensitivity (%) | 65.2 | 90.3 | 85.8 | 58.4 | 70.9 | 72.9 | 40.3 |
| Specificity (%) | 57.4 | 61.1 | 72.2 | 58.5 | 43.5 | 60.8 | 56.3 |
| AUC | 0.666** | 0.844* | 0.861* | 0.702** | 0.662** | 0.593** | 0.711** | 0.469*** |
| 95% CI | 0.645–0.687 | 0.830–0.857 | 0.849–0.874 | 0.682–0.722 | 0.641–0.683 | 0.572–0.615 | 0.692–0.729 | 0.477–0.492 |

AUC, areas under the curve; 95% CI, 95% confidence interval. Refer to the legends of Table 1 for other abbreviations. *p<0.05, compared with SUA. **p<0.05, compared with BMI. ***p<0.05, compared with WC.

Discussion

Previously, evidences from cross-sectional studies and cohort studies have demonstrated SUA might be a risk factor for MetS. Our present study differed in several respects. We found this association not only in frank hyperuricemia but also in SUA levels within the normal range. The four quartiles in our study were divided by the distribution of SUA level confined to the normal range (SUA level ≤7.0 mg/dl in men and ≤6.0 mg/dl in women). Results from the current follow-up study are compatible with existing data on SUA as a predictor of the development of MetS. We are of the opinion that SUA level might be considered as a marker to detect the early dysmetabolism, especially the SUA level approaches to the critical value for clinical physician.

Large epidemiologic studies have established a close link between elevated SUA levels and the increasing prevalence of the MetS components, including blood pressure, levels of fasting plasma glucose, insulin, triglycerides, and inversely correlated with HDL-C levels in both adolescents and adults. This raises the possibility that SUA levels could also be included in the new SUA cut-off values identified approximately 40% more patients with MetS.
the definition of the MetS. Improvement of the insulin resistance status and endothelial dysfunction related to hyperuricemia are probably the common underlying condition triggering the development of the above metabolic abnormalities. SUA has been shown to inhibit nitric oxide bioavailability, which is known to be necessary for insulin action in the promotion of glucose uptake. Another mechanism related to hyperuricemia and the development of MetS may involve oxidative stress. SUA as an antioxidant in the extracellular environment can induce oxidative stress in a variety of cells, as demonstrated in adipocytes, and these inflammatory and oxidative changes in adipocytes cause the MetS in obese mice. It seems reasonable to suppose that the ability of hyperuricemia to promote MetS, or at least to worsen insulin resistance states. On the other hand, recent studies also have called attention to another perspective on hyperuricemia, indicating that it may be not only a consequence of insulin resistance states but also a significant predictor of the development of MetS. The strongest evidence of the role of SUA in the development of MetS has been provided by experimental studies in animal models showing that a decrease in SUA levels can reverse features of the MetS. Although researchers have proposed that the hyperuricemia should be included in the definition of MetS, no studies have conducted the optimal cut-off values of SUA as an optional component of MetS for the detection of MetS. It should be noted that, on the basis of results from the present study, elevated SUA even within current normal range could reflect the presence of MetS. Therefore, the traditional cut-off value that was used for diagnosis of hyperuricemia was not appropriate for the identification of patients with MetS. The “normal range” can be altered depending on certain conditions. Our study indicated that the optimal cut-off values for SUA to identify MetS were 6.3 mg/dl in men and 4.9 mg/dl in women. Although they were poor in their MetS discriminatory power (AUC, 0.601 in men and 0.666 in women, respectively), the AUC of SUA to predict future MetS was larger than the AUCs of FPG or HDL-C. Therefore, the SUA discriminatory power in “healthy” patients who currently have elevated SUA levels within normal range.

This study has a few limitations. Our study has several limitations such as short period of follow-up years and sampling size. And information on lifestyle and dietary intake was not available, further longitudinal study will be conducted included these confound factors. In addition, the participants of this study were a group of relatively homogeneous characters, which is a follow-up cohort of annual health check-up program in a single health promotion center in China, and not the representatives of other ethnic group. Thus, the results derived from our research are not applicable to other ethnicities. Large prospective study is needed for the evaluation of predictability of SUA concentrations for future risk of MetS in various ethnic groups. Despite these limitations, our study is the first longitudinal cohort study on the relationship between SUA within the normal range and the development of MetS, and determining an optimal cut-off value of SUA to predict MetS in China.

In conclusion, in this large prospective study in China, higher SUA concentrations within the normal range predicted future development of MetS during a 3-year follow-up.

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Abbreviations

- AUC: areas under the curve
- BMI: body mass index
- 95% CI: 95% confidence interval
- DBP: diastolic blood pressure
- FPG: fasting plasma glucose
- HDL-C: high-density lipoprotein cholesterol
- HR: hazard ratio
- IDF: International Diabetes Federation
- LDL-C: low-density lipoprotein cholesterol
- MetS: metabolic syndrome
- NPV: negative predictive value
- PPV: positive predictive value
- ROC: receiver operating characteristic
- SBP: systolic blood pressure
- SD: standard deviation
- SUA: serum uric acid
- TC: total cholesterol
- TG: triglyceride
- WC: waist circumference

Conflict of Interest

No potential conflicts of interest were disclosed.
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