Serum Concentrations of Uric Acid and the Metabolic Syndrome Among US Children and Adolescents

Earl S. Ford, MD, MPH; Chaoyang Li, MD, PhD; Stephen Cook, MD; Hyon K. Choi, MD, DrPh

Background—The association between concentrations of uric acid and the metabolic syndrome in children and adolescents remains incompletely understood. The objective of this study was to examine how these 2 were associated in a nationally representative sample of US children and adolescents.

Methods and Results—We performed a cross-sectional analysis of 1370 males and females aged 12 to 17 years using data from the National Health and Nutrition Examination Survey 1999–2002. The prevalence of the metabolic syndrome was <1% among participants in the lowest quartile of serum concentration of uric acid, 3.7% in the second quartile, 10.3% in the third quartile, and 21.1% in the highest quartile. Compared with the lowest 2 quartiles of uric acid together (≥291.5 μmol/L), the odds ratios were 5.80 (95% confidence interval, 3.22 to 10.46) for those in the third quartile (>291.5 to ≤339 μmol/L or >4.9 to ≤5.7 mg/dL) and 14.79 (95% confidence interval, 7.78 to 28.11) for those in the top quartile (>339 μmol/L) after adjustment for age, sex, race or ethnicity, and concentrations of C-reactive protein. Starting with the lowest quartile of concentration of uric acid, mean concentrations of serum insulin were 66.2, 66.7, 79.9, and 90.9 pmol/L for ascending quartiles, respectively (P for trend <0.001).

Conclusions—Among US children and adolescents, serum concentrations of uric acid are strongly associated with the prevalence of the metabolic syndrome and several of its components. (Circulation. 2007;115:2526-2532.)

Key Words: epidemiology ■ pediatrics ■ prevention ■ risk factors

The metabolic syndrome comprises several abnormalities that occur together more often than would be expected by chance. Typically, general or central adiposity, elevated blood pressure, dyslipidemia, and hyperglycemia are thought to be part of this syndrome. In addition, several other abnormalities, including those of fibrinolysis, thrombosis, inflammation, and endothelial function, are strongly related to the syndrome. Among US children and adolescents, the prevalence of the syndrome was 4.2% from 1988 through 1994 and 6.4% from 1999 through 2000.

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There continues to be a need to better understand the pattern of risk factor clustering that constitutes the metabolic syndrome and the relationship of the syndrome to emerging risk factors for cardiovascular disease. Although uric acid is not part of any definition of the metabolic syndrome, a number of studies have shown strong associations between concentrations of uric acid and the metabolic syndrome or its components, primarily in adults. Furthermore, little is known about the associations of uric acid and the metabolic syndrome in children and adolescents. A significant association between the 2 in a young population that is mostly free of adult chronic disorders would help to dispel concern that the association could be secondary to the emergence of various conditions or other physiological disturbances in adulthood. Our objective was to examine the associations between serum concentrations of uric acid and the prevalence of the metabolic syndrome in a nationally representative sample of children, adolescents, and young adults from the United States.

Methods

We performed a cross-sectional analysis by using data from the National Health and Nutrition Examination Survey (NHANES) 1999–2002. Detailed information about the methods and procedures of this survey is available elsewhere. In brief, a representative sample of the noninstitutionalized civilian US population was selected through a stratified multistage design. Trained interviewers, using a computer-assisted personal interview system, interviewed the participants at home. The participants were asked to attend the mobile examination center, where they completed additional ques-
tionnaires, underwent various examinations, and provided a blood sample. The study received approval for use of human subjects from the Centers for Disease Control and Prevention.

To define the metabolic syndrome among the young participants, we used a previously proposed modification of the definition by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The participants had to meet 3 of the following 5 criteria: concentration of triglycerides ≥110 mg/dL, high-density lipoprotein cholesterol ≤40 mg/dL, waist circumference ≥90th percentile (sex-specific), glucose concentration ≥100 mg/dL, and systolic or diastolic blood pressure ≥90th percentile (age, height, and sex-specific). For the young participants in NHANES 1999–2000, information to define this syndrome was available only for those aged 12 to 17 years.

The waist circumference was measured at the high point of the iliac crest at minimal respiration to the nearest 0.1 cm at the end of normal expiration with a steel measuring tape. Up to 4 blood pressure measurements were obtained for each participant in the mobile examination center. The participants were seated with their right arm (if usable) resting at the level of the heart. Blood pressure was measured with a mercury-gravity manometer. Child, adult, and large arm cuff sizes were available. Lipid measurements were done at the Johns Hopkins University Lipoprotein Analytical Laboratory. High-density lipoprotein cholesterol concentration, after the precipitation of other lipoproteins with a heparin-manganese chloride mixture, was measured on a Hitachi model 704 analyzer (Roche Diagnostics, Indianapolis, Ind). Plasma glucose concentration was measured by the glucose hexokinase method. Finally, serum triglyceride concentration was determined after hydrolysis of triglycerides to glycerol and oxidation to dihydroxyacetone phosphate and hydrogen peroxide.

Serum uric acid was measured by a colorimetric method in which uric acid is oxidized by uricase to form allantoin and H2O2 (Hitachi model 704 analyzer, Roche Diagnostics). The measurements were performed by the Coulston Foundation in New Mexico in 1999–2001 and by the Collaborative Laboratory Services in Iowa in 2002.

We limited our analyses to the participants aged 12 to 17 years who attended the morning session of the mobile examination center and who had fasted ≥6 hours. We excluded pregnant females. Because no universally accepted threshold exists to define hyperuricemia in children and adolescents, we calculated its prevalence using several thresholds: >327 μmol/L (5.5 mg/dL), ≥357 μmol/L (6 mg/dL), and >416 μmol/L (7 mg/dL). In addition, we estimated the percentage of males who had a concentration of uric acid >460 μmol/L (7.7 mg/dL) and females who had a concentration >340 μmol/L (5.7 mg/dL). We calculated the prevalence of the metabolic syndrome for each quartile of concentration of uric acid. A test for linear trend was performed on the basis of orthogonal contrasts. To examine the association between the metabolic syndrome and concentrations of uric acid, we conducted logistic regression analyses adjusting for age, sex, race or ethnicity, and concentrations of C-reactive protein. Linear trend was assessed by using the medians of the categories of concentrations of uric acid. In addition, to examine the associations between each component of the metabolic syndrome and concentrations of uric acid, we conducted several logistic regression models: once adjusting for age (continuous), sex (men, women), race or ethnicity (white, black, Mexican American, other), and concentration of C-reactive protein (continuous); once adjusting for age, sex, race or ethnicity, concentration of C-reactive protein, and other components of the metabolic syndrome as dichotomized variables; once adjusting for age, sex, race or ethnicity, concentration of C-reactive protein, other components of the metabolic syndrome except abdominal obesity, concentrations of insulin, and body mass index Z score (continuous). A receiver operating characteristic curve for the metabolic syndrome as defined by Cook and colleagues and uric acid was generated, and the C statistic, which reflects the area under the curve and is a measure of predictive ability, was calculated.

ed. The linear and quadratic trends for mean concentrations of uric acid by number of components of the metabolic syndrome were assessed on the basis of orthogonal contrasts. The difference in mean concentrations of uric acid between participants with and without the metabolic syndrome was tested with a t test. To account for the complex sampling design, we used SUDAAN version 9.0 to calculate the means and proportions and to perform regression analyses. If the relative SE for means or percentages exceeded 30%, the estimates were deemed to be potentially unstable.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
A total of 1432 participants aged 12 to 17 years attended the morning session of the mobile examination center. Data allowing the determination of status of the metabolic syndrome were available for 1373 of the participants. After 3 pregnant young women were eliminated, 1370 participants were included in our analytic sample.

![Figure 1. Distribution of serum concentrations of uric acid among 1370 participants aged 12 to 17 years, NHANES 1999–2002.](image)

![Figure 2. Prevalence (95% CI) of the metabolic syndrome by quartiles of serum concentrations of uric acid among 1370 participants aged 12 to 17 years, NHANES 1999–2002. The prevalence estimate of the metabolic syndrome for the lowest quartile of serum concentrations of uric acid fails to meet criteria for reliability or precision and is shown for illustrative purposes.](image)
The prevalence of the metabolic syndrome in our sample was 9.1% (SE 1.3%) (12.4% [SE 2.4] among males and 5.7% [SE 1.4] among females). The concentrations of uric acid ranged from 113.0 μmol/L (1.9 mg/dL) to 719.7 μmol/L (12.1 mg/dL), with a mean of 301.9 (SE 2.0) μmol/L (5.1 mg/dL) and a geometric mean of 292.7 (SE 1.8) μmol/L (4.9 mg/dL). The percentages of children and adolescents with concentrations of uric acid ≤327 μmol/L (5.5 mg/dL), 357 μmol/L (6 mg/dL), and 416 μmol/L (7 mg/dL) were 30.2% (SE 2.0), 22.2% (SE 1.6), and 6.5% (SE 0.6), respectively. In addition, the percentage of males with a concentration of uric acid ≥460 μmol/L (7.7 mg/dL) and females with a concentration ≥340 μmol/L (5.7 mg/dL) was 6.3% (SE 0.9).

Furthermore, 59.9% (SE 6.6) of children and adolescents with the metabolic syndrome and 22.4% (SE 1.6) of those without the syndrome had a concentration of uric acid ≥339 μmol/L (5.7 mg/dL) (P<0.001). The distribution of concentrations of uric acid in our analytic sample is shown in Figure 1. The prevalence of the metabolic syndrome rose from <1% among the participants with concentrations of uric acid ≤249.8 μmol/L (≤4.2 mg/dL) to ~21% among those with concentrations >339 μmol/L (>5.7 mg/dL) (Figure 2). Because of the infrequency with which the metabolic syndrome occurred among those with concentrations of uric acid ≤249.8 μmol/L (≤4.2 mg/dL), we collapsed the 2 lowest quartiles of uric acid into a single reference group. After

### Adjusted Odds Ratios (95% CI) for Associations Between the Metabolic Syndrome and Its Components and Serum Concentrations of Uric Acid Among Participants Aged 12–17 Years, NHANES 1999-2002

<table>
<thead>
<tr>
<th>Serum Concentration of Uric Acid, μmol/L</th>
<th>Sample size</th>
<th>Metabolic syndrome</th>
<th>Metabolic syndrome components</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤291.5 (reference) (≤4.9 mg/dL)</td>
<td>687</td>
<td>1.00</td>
<td>Abdominal obesity</td>
</tr>
<tr>
<td>&gt;291.5 to ≤339 (&gt;4.9 to ≤5.7 mg/dL)</td>
<td>339</td>
<td>5.80 (3.22–10.46)</td>
<td>Model 1*</td>
</tr>
<tr>
<td>&gt;339 (≥5.7 mg/dL)</td>
<td>344</td>
<td>14.79 (7.78–28.11)</td>
<td>Model 2†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 3‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 4§</td>
</tr>
<tr>
<td></td>
<td>P for</td>
<td></td>
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<td></td>
<td>Trend</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age (continuous), sex (men, women), race or ethnicity (white, black, Mexican American, other), and concentration of C-reactive protein (continuous) (n=1370).
†Adjusted for the same set of variables as in model 1 plus the other components of the metabolic syndrome as dichotomized variables (n=1370).
‡Adjusted for the same set of variables as in model 2 plus concentrations of insulin (continuous) (n=1366).
§Adjusted for the same set of variables as in model 3 except dichotomized waist circumference plus body mass index Z score (continuous) (n=1364).
adjustment for age, sex, race or ethnicity, and concentrations of C-reactive protein, a strong independent association between the concentrations of uric acid and the metabolic syndrome remained (Table). We did not find any significant effect modification by sex ($P=0.238$) or by race or ethnicity ($P=0.820$). When uric acid was entered as a continuous variable in the model, the fully adjusted odds ratio was 1.02 (95% confidence interval [CI], 1.01 to 1.02) per 1 μmol/L or 2.52 (95% CI, 1.87 to 3.41) per 59.48 μmol/L (1 mg/dL).

Of the 5 components, abdominal obesity, hypertriglyceridemia, and hyperglycemia were significantly associated with concentrations of uric acid even after adjustment for age, sex, race or ethnicity, concentrations of C-reactive protein, other components of the metabolic syndrome except abdominal obesity, concentrations of insulin, and body mass index $Z$ scores (except model for abdominal obesity) (Table). In addition, the association between high blood pressure and concentrations of uric acid was of borderline significance.

A receiver operating characteristic curve for the metabolic syndrome and concentrations of uric acid is shown in Figure 3. The $C$ statistic was 0.868.

We also conducted a subanalysis among overweight or obese adolescents (body mass index $\geq 85$th percentile). The mean concentrations of uric acid showed an increase with each additional component (Figure 4) ($P$ for linear trend $<0.001$; $P$ for quadratic trend $=0.012$). In addition, concentrations of uric acid were significantly higher among teens with the metabolic syndrome (387.6 μmol/L) than among those without the syndrome (319.7 μmol/L) ($P<0.001$) (Figure 5).

Serum concentrations of insulin also increased as concentrations of uric acid increased. From the lowest to the highest quartile of concentrations of uric acid, the mean concentrations of serum insulin were 66.2 pmol/L (95% CI, 62.8 to 69.6), 66.7 pmol/L (95% CI, 62.4 to 71.0), 79.9 pmol/L (95% CI, 71.5 to 88.3), and 90.9 pmol/L (95% CI, 80.9 to 100.9) ($P$ for linear trend $<0.001$).

**Discussion**

In this nationally representative sample of US children and adolescents, we found a graded positive association between concentrations of serum uric acid and the prevalence of the metabolic syndrome. Our results are consistent with the limited data showing that concentrations of uric acid are significantly associated with the metabolic syndrome. In our analysis, the prevalence of the metabolic syndrome among the youths in the lowest quartile of concentrations of uric acid was almost negligible, whereas $\approx 21\%$ of the children in the highest quartile of concentrations of uric acid had the metabolic syndrome. The association was independent of age, sex, race or ethnicity, and concentrations of C-reactive protein and persisted in both sexes and all racial or ethnic groups. To our knowledge, this is the first population-based study to quantify the prevalence of the metabolic syndrome at different concentrations of uric acid in children and adolescents.

Our results expand on previous studies that showed a close relation between hyperuricemia and the metabolic syndrome in adults $^{3-7}$ and children $^{9,10}$ Several potential mechanisms could account for the elevated concentrations of uric acid among those with the metabolic syndrome. Renal clearance of urate is inversely related to the degree of insulin resis-
tance. Furthermore, higher concentrations of insulin are known to reduce the renal excretion of urate. For example, exogenous insulin can reduce the renal excretion of urate in both healthy and hypertensive subjects. Thus, the reduced renal excretion of urate among patients with the metabolic syndrome may explain the increased frequency of hyperuricemia. This possibility is also supported by the close association between concentrations of uric acid and insulin shown in our results. Insulin may enhance renal urate reabsorption via stimulation of the urate-anion exchanger URAT1 and/or the Na+-dependent anion cotransporter in brush border membranes of the renal proximal tubule. In addition, because serum concentrations of leptin and urate tend to rise together, some investigators have suggested that leptin may affect renal reabsorption. Increased consumption of fructose, which is associated with obesity in childhood, has been shown to elevate concentrations of uric acid, which in turn impairs endothelial function. Finally, in the metabolic syndrome, impaired oxidative phosphorylation may increase systemic adenosine concentrations by increasing the intracellular concentrations of coenzyme A esters of long-chain fatty acids. Increased adenosine, in turn, can result in renal retention of sodium, urate, and water. Some have speculated that chronically increased extracellular adenosine concentrations may also contribute to hyperuricemia by increasing urate production.

We found that concentrations of serum uric acid were significantly associated with all 5 components of the metabolic syndrome after adjustment for age, sex, race or ethnicity, and concentrations of C-reactive protein. However, after additional adjustment for other components of the metabolic syndrome, low concentrations of high-density lipoprotein cholesterol were no longer significantly associated with concentrations of uric acid, and the association between high blood pressure and concentrations of uric acid was of borderline significance. The strongest association was between concentrations of uric acid and abdominal obesity. Previous studies have noted significant associations between concentrations of uric acid and various anthropometric measures in children and adolescents. In addition, the nearly significant association between concentrations of uric acid and elevated blood pressure in our analyses is consistent with a growing literature linking concentrations of uric acid to the development of hypertension in childhood. A number of studies show uric acid to be confounded by other factors more commonly found in adults, such as impaired renal function, use of diuretics, alcohol consumption, diabetes mellitus, and cardiovascular disease. Uric acid has been shown to have a mechanistic role in atherosclerosis both by scavenging nitric oxide and, from studies reducing concentrations of uric acid with allopurinol, by improving endothelial dysfunction. However, uric acid may also be an innocent bystander or just serve as a marker of insulin resistance and central adiposity. The finding of an independent and strong association here is novel because of the absence of chronic factors, which confound studies among adults, among healthy youth. The association of increased uric acid with increasing numbers of components of the syndrome also suggests that there may be differences in endothelial dysfunction even within overweight and obese adolescents. Our findings provide further support for future research to clarify the pathogenetic and predictive roles of concentrations of uric acid among children and adolescents, particularly among those with individual component of the metabolic syndrome.

The high percentage of children and adolescents with the metabolic syndrome who had an elevated concentration of uric acid could be of concern if it were concluded that uric acid was an independent risk factor for cardiovascular disease. However, the independence of the association between concentrations of uric acid and cardiovascular disease remains unsettled. In at least 1 study, however, uric acid was shown to be an independent predictor of cardiovascular disease among participants with the metabolic syndrome. Although it remains unknown whether elevated concentrations of uric acid among young people affect the risk for future cardiovascular disease, it is possible that this marker might help to identify a juvenile group that is at increased risk.

In conclusion, concentrations of uric acid were strongly associated with the prevalence of the metabolic syndrome in this national sample of children and adolescents. Research about the potential consequences of this syndrome on their health is only now emerging. Much remains to be learned about the metabolic syndrome in children and adolescents, including its relationship with uric acid.
Disclosures
Dr Choi has received research funding from TAP Pharmaceuticals. In addition, he has received honoraria from and serves as a consultant to TAP Pharmaceuticals and Saviient. The other authors report no conflicts.

References
Besides the factors included in the various adult definitions of the metabolic syndrome (abdominal or general obesity, hypertriglyceridemia, elevated blood pressure, dyslipidemia, hyperglycemia, insulin resistance, and albuminuria), a number of other abnormalities characterize the syndrome, including those of fibrinolysis, thrombosis, inflammation, and endothelial function. Research conducted primarily among adults has also shown that concentrations of uric acid are increased among those with the syndrome. In our study, the prevalence of the syndrome was <1% among participants in the lowest quartile of serum concentration of uric acid (≤249.8 μmol/L), 3.7% in the second quartile (≤291.5 μmol/L), 10.3% in the third quartile (≤339 μmol/L), and 21.1% in the highest quartile (>339 μmol/L) among US children and adolescents aged 12 to 17 years. Of the 5 components of the syndrome, concentrations of uric acid were significantly associated with abdominal obesity, hypertriglyceridemia, and hyperglycemia, and a borderline significant association was found between concentrations of uric acid and elevated blood pressure. Although uric acid as a risk factor for cardiovascular disease has long been investigated, a renewed interest in this clinical analyte has surfaced in recent years. However, the exact contribution of uric acid to the risk of developing cardiovascular disease remains uncertain among adults and even more so among children. Research has linked increased concentrations of uric acid to increased blood pressure in adults and children. Our results indicate that a substantial percentage of children and adolescents who have elevated concentrations of uric acid, particularly >339 μmol/L, are likely to have multiple cardiometabolic abnormalities.
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