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Racial/ethnic and sex differences in the relationship between uric acid and metabolic syndrome in adolescents: an analysis of National Health and Nutrition Survey 1999-2006

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ABSTRACT

Among adolescents, uric acid is associated with insulin resistance, hypertension, and the metabolic syndrome (MetS); and in adults, high uric acid levels are an independent risk factor for cardiovascular disease and diabetes. The objective was to determine whether the relationship of uric acid with MetS varies in adolescents by race/ethnicity and sex. We used linear regression to evaluate associations between uric acid and other MetS-associated clinical and laboratory measures among 3296 non-Hispanic white, non-Hispanic black, and Hispanic adolescents aged 12 to 19 years participating in the National Health and Nutrition Evaluation Survey (1999-2006). Overall, non-Hispanic white males and females had the highest uric acid levels among the 3 racial/ethnic groups. In each racial/ethnic group, there were higher uric acid levels for those adolescents with vs without MetS. However, the extent of the MetS-related increase in uric acid level varied by race and sex. Among males, MetS was associated with the greatest increases in uric acid among non-Hispanic whites. However, among females the MetS-related increase in uric acid was greater among non-Hispanic blacks and Hispanics. Non-Hispanic white females exhibited the lowest degrees of correlation between levels of uric acid and MetS-associated variables. Uric acid levels did not correlate with insulin levels in non-Hispanic white females. These data suggest that the relationship between uric acid and MetS varies by race/ethnicity and sex. In particular, non-Hispanic white males exhibit a strong relationship and non-Hispanic white females exhibit a relatively poor correlation between uric acid and MetS-related factors. These data may have implications for the use of uric acid as a marker of future risk among adolescents.

1. Introduction

Uric acid is a by-product of purine metabolism that is implicated in worsening insulin resistance [1-3] and appears to contribute to the development of hypertension [3-7]. Given these relationships, it is not surprising that uric acid is tightly linked to the metabolic syndrome (MetS), a constellation of cardiovascular risk factors also associated with insulin resistance [8-11]. In addition, large prospective trials have demonstrated that elevations in uric acid are independently associated with future MetS [12], renal disease [13], cardiovascular disease (CVD) [14-16] and type 2 diabetes mellitus

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[17]. Even among adolescents, elevated levels of uric acid are independently associated with long-term risk for hypertension [6] and carotid artery intima media thickness [18]. This has raised the potential to use elevated levels of uric acid as marker of increased risk.

Among adolescents, uric acid levels are influenced by central obesity [8] and by the intake of fructose and sucrose [19,20]. In addition, sex differences in uric acid are well known, with males having higher levels of uric acid than females, at least in part because estrogen increases excretion of uric acid [21,22].

However, data on racial/ethnic differences in uric acid levels among adolescents are scarce. Many features of MetS itself display racial/ethnic differences [23-25]. Non-Hispanic black adolescents have a greater degree of hypertension and insulin resistance than non-Hispanic whites but have lower rates of MetS overall [26-30]. Our goal was to evaluate the relationship between uric acid and MetS in adolescents on a race/ethnicity- and sex-related basis. We used the National Health and Nutrition Examination Survey (NHANES) 1999-2006 to better define these relationships and to evaluate for potential explanations for any possible sex/ethnic differences.

2. Methods

Data were obtained from NHANES (1999-2006), a complex, multistage probability sample of the US population. These annual cross-sectional surveys are conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention, with randomly selected subjects undergoing anthropometric and blood pressure (BP) measurements, answering questionnaires, and undergoing phlebotomy (http://www.cdc.gov/nchs/nhanes.htm). The National Center for Health Statistics ethics review board reviewed and approved the survey, and participants gave informed consent before participation.

Waist circumference (WC), BP, and laboratory measures of triglycerides, high-density lipoprotein cholesterol, and glucose were obtained using standardized protocols and calibrated equipment [8,31]. Serum uric acid was measured by a colorimetric method in which uric acid is oxidized by uricase to form allantoin and H_2O_2. For NHANES 1999-2002, this was measured by a Hitachi model 704 analyzer (Roche Diagnostics, Indianapolis, IN); and from 2003 to 2006, this was measured by a Beckman Synchron LX20 (Beckman Coulter, Brea, CA). All blood samples used for analyses were obtained following a fast of at least 8 hours before the blood draw.

2.1. MetS classification

Metabolic syndrome was defined by a commonly used pediatric/adolescent adaptation of the Adult Treatment Panel III criteria [8,32-34]. Participants had to meet at least 3 of the following 5 criteria: concentration of triglycerides of at least 110 mg/dL, high-density lipoprotein cholesterol not exceeding 40 mg/dL, WC of at least 90th percentile for age/sex (or Adult Treatment Panel III limit of 102 cm for males and 88 cm for females, whichever was lower) [35,36], glucose concentration of at least 100 mg/dL, and systolic (SBP) or diastolic BP (DBP) of at least 90th percentile (age, height, and sex specific) [37]. Similarly, *hypertension* was defined as systolic or diastolic BP of at least 90th percentile for age, height, and sex.

Data from non-Hispanic white, non-Hispanic black, or Hispanic (Mexican American/other Hispanic) adolescents 12 to 19 years old were analyzed. Children younger than 12 years were excluded because fasting values for triglycerides and glucose were only obtained in participants 12 years and older. Subjects were excluded if they self-reported diabetes, were pregnant, or were taking antihyperlipidemic or antidiabetic medications, as these are all likely to alter lipid and insulin levels in a manner that may not reflect baseline MetS uric acid correlations. Individuals taking antihypertensive medication were classified as having hypertension. Following these exclusions, the study sample consisted of 3296 non-Hispanic white, non-Hispanic black and Hispanic adolescents aged 12 to 19 years with data for all variables tested (52% male). The NHANES includes an oversample of racial/ethnic minorities; and thus, the sample included 28% non-Hispanic whites, 40% Hispanics, and 32% non-Hispanic blacks. This oversampling was accounted for using SUDAAN (version 10; Research Triangle Institute, Research Triangle Park, NC), which accounts for the survey design when estimating standard errors to obtain population-based estimates.

2.2. Statistical analysis

Statistical significance was defined as a P value $< .05$. Statistical analysis was performed using SAS (version 9.2, Cary, NC) and SUDAAN, as mentioned previously. We combined all data sets from the three 2-year cycles (1999-2006) for statistical analyses to increase total sample size. Prevalence rates of MetS were calculated by sex and race/ethnicity and compared via χ^2 tests. Mean uric acid levels were compared among groups using either unpaired t tests or analysis of variance. Linear regression was then used to assess the effect of sex, race/ethnicity, and MetS status on levels of uric acid. All interactions of the 3 covariates (sex, race/ethnicity, and MetS status) were initially included in the model, but removed in a stepwise fashion if the associated interaction P value was $< .15$. We also included education [38], poverty [38], and smoking [15] in the model due to known effects on levels of uric acid. Although potentially important as confounders, drug use and alcohol use were not included in the model because these were not available for NHANES participants younger than 20 years. Education was classified as the highest level obtained for any household member and categorized as follows: less than high school, high school, and greater than high school. Income-to-need ratio was used to measure poverty. Because of the poor reliability of self-reporting of smoking among adolescents [39], serum cotinine was used to identify smokers, with a cutoff of 15 ng/mL as recommended [40]. Because high intake of fructose has been associated with elevations in uric acid levels [19,20], we also included into the model the percentage of calories from added sugars, a component of the Healthy Eating Index [41], using data collected from computer-assisted 24-hour food recall

questionnaires (the Automated Multiple-Pass Method) developed by NHANES [42] and the US Department of Agriculture [43]. Mean levels of uric acid from the final model were estimated and compared among sex and race/ethnicity, as applicable. In comparing uric acid levels and the ratio of uric acid levels among individuals with vs without MetS, Hispanic and non-Hispanic black adolescents were combined into a single "nonwhite" comparator when both of these groups behaved similarly in their differences with non-Hispanic white adolescents. Pearson correlation coefficients were computed to assess the degree of linear association between uric acid and each MetS component and ln(insulin) and the homeostasis model of insulin resistance (HOMA) [44] by race/ethnicity/sex. With the exception of the correlation estimates, all analyses incorporated the sampling weights included in NHANES.

3. Results

3.1. Overall uric acid and MetS values

Values for overall uric acid, individual MetS components, insulin, and HOMA are shown by race/ethnicity for all male and female subjects in Table 1. Non-Hispanic whites had the highest uric acid levels overall in males and females as compared with Hispanics and non-Hispanic blacks. Regarding MetS components commonly associated with elevated uric acid, non-Hispanic black males and females had the highest rates of hypertension (SBP and/or DBP >90th percentile), whereas elevations in WC were highest overall in Hispanic males and non-Hispanic black females. Levels of fasting insulin and HOMA (as an estimate of insulin

Table 1 – Race/ethnicity comparison of MetS components and related factors for all subjects by sex

	Male				Female			
	Non-Hispanic White	Hispanic	Non-Hispanic Black	*P* value [a]	Non-Hispanic White	Hispanic	Black	*P* value [a]
n	473	662	594	–	434	664	469	
Mean age (95% CI), y	15.6 (15.4-15.8)	15.0 (14.7-15.3)	15.3 (15.2-15.5)	<.01	15.4 (15.2-15.7)	15.6 (15.3-15.9)	15.4 (15.1, 15.7)	.57
Percentage with MetS	12.7	13.6	4.8	<.01	5.8	8.1	4.6	.35
Mets components								
WC								
Mean (95% CI), cm	81.9 (80.4-83.5)	83.0 (81.0-85.0)	78.3 (76.9-79.7)	<.01	79.8 (78.2-81.4)	81.8 (79.7-84.0)	82.6 (81.1-84.0)	.03
Percent >90% percentile	15.8	20.8	13.0	.02	21.0	28.9	32.0	<.01
Triglycerides								
Mean (95% CI), mg/dL	98.0 (91.5-104.5)	92.7 (87.5-97.9)	70.3 (66.9-73.8)	<.01 [b]	91.7 (86.4-97.0)	99.4 (84.8-114.0)	68.7 (65.0-72.4)	<.01
Percentage >110	31.0	26.1	10.6	<.01	25.2	24.3	10.5	<.01
HDL								
Mean (95% CI), mg/dL	46.7 (45.6-47.7)	48.5 (47.1-49.9)	54.2 (52.8-55.6)	<.01	52.6 (51.4-53.8)	51.7 (50.3-53.0)	55.3 (53.7-56.9)	.01
Percentage <40	24.0	22.5	10.1	<.01	11.7	14.2	8.7	.12
SBP								
Mean (95% CI), mm Hg	112.5 (111.3,113.8)	111.2 (109.3,113.2)	114.4 (113.5,115.3)	<.01	106.2 (105.1,107.3)	106.7 (105.6,107.9)	109.4 (108.3,110.6)	<.01
Percentage >90% percentile	8.8	5.7	12.5	<.01	3.8	3.9	6.7	.14
DBP								
Mean (95% CI), mm Hg	61.5 (60.4-62.6)	59.0 (57.9-60.0)	60.6 (59.4-61.8)	<.01	63.6 (62.5-64.6)	62.6 (61.5-63.7)	63.3 (62.4-64.2)	.47
Percentage >90% percentile	2.3	2.0	3.0	.41	3.2	2.2	3.7	.55
Fasting glucose								
Mean (95% CI), mg/dL	95.1 (94.4-95.9)	95.9 (95.0-96.9)	92.9 (92.2-93.7)	<.01	91.2 (90.3-92.0)	91.5 (90.8-92.3)	89.4 (88.6-90.2)	<.01
Percentage >100	22.1	28.2	14.4	<.01	9.5	7.4	5.2	.11
MetS-related measures								
Mean (95% CI)								
BMI, kg/m^2	23.0 (22.5-23.5)	23.5 (22.8-24.2)	23.3 (22.8-23.9)	.52	22.9 (22.3-23.5)	24.0 (23.2-24.9)	25.8 (25.2-26.3)	<.01
Insulin, IU/mL	10.4 (9.3-11.5)	11.6 (10.4-12.9)	10.1 (9.5-10.8)	.03 [b]	9.8 (9.1-10.6)	12.6 (11.4-13.7)	13.7 (12.7-14.7)	<.01 [b]
HOMA score	2.5 (2.2-2.8)	2.8 (2.5-3.1)	2.4 (2.2-2.5)	.02 [b]	2.2 (2.1-2.4)	2.9 (2.6-3.2)	3.1 (2.8-3.4)	<.01 [b]
Uric acid, mg/dL	5.8 (5.7-6.0)	5.6 (5.4-5.8)	5.3 (5.2-5.4)	<.01	4.6 (4.5-4.7)	4.4 (4.3-4.6)	4.4 (4.3-4.5)	<.01

[a] χ^2 test comparing percentages; analysis of variance comparing means (overall difference among the groups).
[b] Comparison of ln(triglyceride), ln(insulin), ln(HOMA).

resistance) were also highest in Hispanic males and non-Hispanic black females. The percentage of added sugar did not differ between racial/ethnic/sex groups (data not shown).

3.2. Uric acid linear model

Covariates in the final model of uric acid are shown in Table 2, and mean values by race/ethnicity and sex are shown in Fig. 1A and B. A 3-way interaction between MetS, ethnicity, and sex was significant and thus remained in the model (P = .0495). Although the percentage of added sugar on its own was significantly associated with levels of uric acid, this effect was not significant after adjusting for the other covariates in the model. For each race/ethnicity/sex group, uric acid levels were higher in individuals with MetS compared with those without MetS (Fig. 1A-B).

3.3. Levels of uric acid among adolescents by MetS status

Among males without MetS, both non-Hispanic whites and Hispanics had higher uric acid levels than non-Hispanic blacks (Fig. 1A). Among males with MetS, non-Hispanic whites had higher uric acid levels than the other 2 race/ethnicities (both $P < .05$). Among females without MetS, non-Hispanic whites had higher levels of uric acid than non-Hispanic blacks and Hispanics combined (Fig. 1B; $P < .05$). Among females with MetS, however, there were no significant differences in uric acid levels by race/ethnicity.

Among males, the elevation in uric acid levels between those with and without MetS was greatest with non-Hispanic whites, although the difference in these elevations was not significantly different among the racial/ethnic groups (non-Hispanic white vs nonwhite P value = .1812; Fig. 1C). Conversely, among females, non-Hispanic whites had the lowest elevation in uric acid attributable to MetS; but again, the difference in these elevations was not significantly different among the racial/ethnic groups (non-Hispanic white vs nonwhite P value = .0702; Fig. 1C). However, the pattern of differences in these increases when comparing by race/ethnicity was significantly different between males and females; namely, non-Hispanic white males had the greatest MetS-related increase, whereas non-Hispanic white females had the lowest MetS-related increase. This difference in the pattern of uric acid and MetS between non-Hispanic white males and females was the cause of the significant sex-ethnicity-MetS interaction (P = .0495) mentioned previously.

Table 2 – Linear model results of uric acid

Model covariate	Estimate	95% CI	P value
Education [a]			
Less than high school	0.02	(–0.18 to 0.13)	.78
High school	0.02	(–0.12 to 0.16)	.78
Added sugar (percentage of total calories)	0.005	(–0.001 to 0.011)	.13
Income-to-needs ratio	0.03	(–0.01 to 0.06)	.20
Current smoker	0.13	(–0.06 to 0.32)	.17
Females (vs males)	–1.10	(–1.24 to –0.96)	<.01
Race/ethnicity [b]			
Hispanic	–0.06	(–0.22 to 0.11)	.51
Non-Hispanic black	–0.37	(–0.52 to –0.23)	<.01
MetS vs no mets: females			
Non-Hispanic white	0.64	(0.31-0.96)	<.01
Hispanic	1.38	(0.48-2.29)	<.01
Non-Hispanic black	1.14	(0.59-1.69)	<.01
MetS vs no mets: males			
Non-Hispanic white	1.42	(0.88-1.96)	<.01
Hispanic	0.88	(0.47-1.29)	<.01
Non-Hispanic black	1.03	(0.66-1.40)	<.01

Final model included 3-way interaction among MetS, sex, and ethnicity (interaction P value = .0495); model R^2 = 0.321. Intercept = 5.44 (95% CI, 5.22-5.67).

[a] Highest among household (person who owns/rents house or his/her spouse). Values indicate differences from "more than high school" category.

[b] Values indicate difference from non-Hispanic white.

3.4. Levels of uric acid among adolescents by hypertension, obesity, and insulin status

To investigate if individual MetS components could explain the final model and the resulting racial/ethnic/sex differences of note, we compared mean uric acid levels by sex and race/ethnicity, stratified by hypertension status, obesity status, and insulin status—as each of these indices has been particularly tightly linked to uric acid elevations. For each race/ethnicity/sex group, individuals with hypertension, elevated WC, and elevated insulin had higher uric acid levels compared with individuals with normal levels of these indices (Supplementary Table 1). Among males with and without hypertension, elevated WC, and elevated insulin, non-Hispanic whites had significantly higher uric acid levels than non-Hispanic blacks (but not Hispanics). Among females without these MetS-related findings, non-Hispanic whites had the highest levels of uric acid, whereas among females with elevations in these MetS-related indices, there were no significant race/ethnicity differences in uric acid levels. These findings were thus similar to the findings regarding uric acid levels in groups with and without MetS.

3.5. Uric acid and age

To evaluate for the possibility that differences in levels of uric acid levels were affected by interracial differences in the timing of puberty, we evaluated levels over the age span of adolescence (Supplementary Figure 1). For both males and females, levels of uric acid were similar between races/ethnicities at 12 to 13 years. Non-Hispanic white males had higher uric acid levels starting at 14 to 15 years and continuing through 18 to 19 years, whereas non-Hispanic white females had higher levels starting at 16 to 17 years and continuing to 18 to 19 years.

3.6. Uric acid correlations with MetS components and insulin

Table 3 shows correlations of uric acid with individual components of MetS, as well as with insulin and HOMA. Among all of the components tested, uric acid correlated best

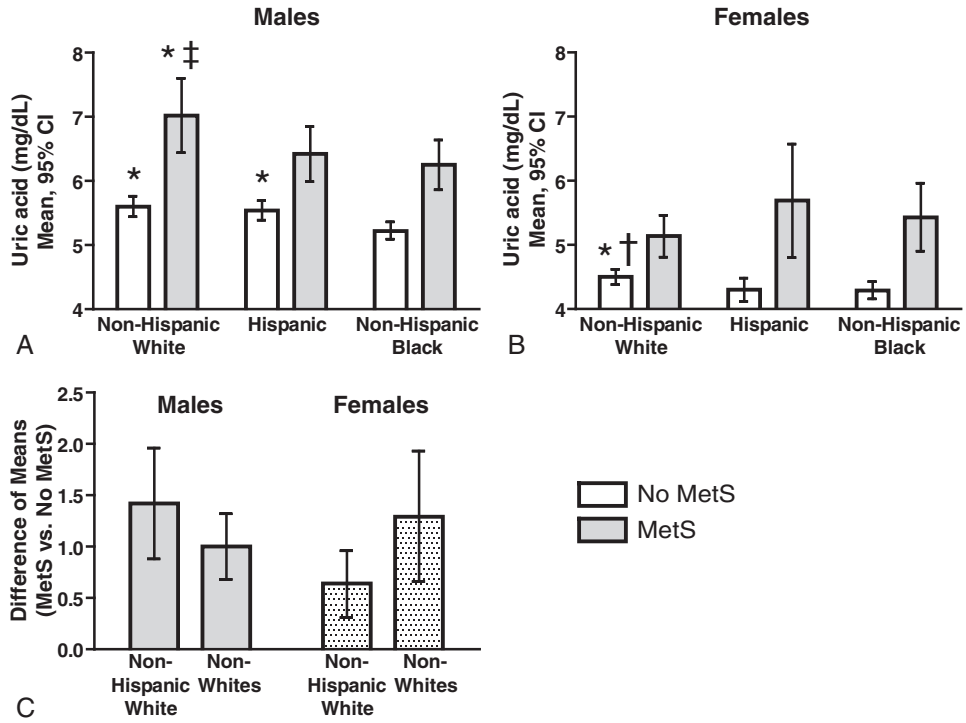

Fig. 1 – Comparison of uric acid levels by race/ethnicity, sex, and MetS status. A and B, Adjusted means of uric acid by sex, race/ethnicity, and MetS status. Estimated means (95% confidence intervals [CIs]) for males (A) and females (B) among adolescents with and without MetS. C, Ratio of adjusted means (and 95% CIs) of uric acid (MetS+/MetS–) for non-Hispanic whites and nonwhites (non-Hispanic blacks and Hispanics combined) among males and females. The pattern of these interethnic differences between whites and other ethnicities is significantly different between non-Hispanic white males and females ($P < .05$). Comparisons between ethnic groups by corresponding MetS status are as follows: *$P < .05$ vs non-Hispanic blacks, ‡$P < .05$ vs Hispanics, and † $P < .05$ vs non-Hispanic blacks and Hispanics combined.

with body mass index (BMI) and WC in all racial/ethnic/sex groups. There were higher degrees of correlation with BP indices among males compared with females. For all measures except triglycerides, non-Hispanic white males had the highest correlation coefficients for all groups. For all measures, non-Hispanic white females had the lowest correlation coefficients of all groups. Non-Hispanic white females were the only group for which uric acid was not correlated with levels of insulin or HOMA (Table 3).

4. Discussion

We found significant racial/ethnic and sex differences in the relationship between uric acid and MetS. Of the racial/ethnic groups studied, non-Hispanic white adolescents had the highest uric acid levels overall despite having both lower fasting insulin levels than Hispanics and less hypertension than non-Hispanic blacks. Interestingly, the pattern of these racial/ethnic differences in the relationship between uric acid and MetS varied between non-Hispanic white males and females. Among males with MetS, non-Hispanic whites had the highest uric acid levels of the 3 ethnic groups and, although not significant, a greater difference in uric acid levels between individuals with and without MetS (Fig. 1C). This suggests that MetS was tightly linked to uric acid in non-Hispanic white males, as is further supported by strong correlations between uric acid and individual MetS components among non-Hispanic white males (Table 3). These associations are consistent with prevailing notions regarding the relationship between uric acid and insulin resistance [3].

Non-Hispanic white females exhibited a different pattern in the relationship between uric acid and MetS. Whereas non-Hispanic white females had the highest uric acid levels overall among the 3 racial/ethnic groups, they did not exhibit an exaggerated increase in uric acid among individuals with MetS as had been seen among males. Indeed, among females with MetS, non-Hispanic whites had lower uric acid levels than the other groups. Among non-Hispanic white females, it was the non-MetS individuals who had notably high uric acid levels. The reason for these sex differences between non-Hispanic white males and females is unclear but may relate to differences in the relationship between uric acid and MetS between these groups.

In general, each racial/sex group exhibited strong correlations between uric acid and the individual components of MetS (Table 3), the strongest associations being with BMI and WC—as has been shown previously [8]—and the weakest with fasting glucose. It is notable, however, that with the exception of BMI and WC, the associations between uric acid and MetS components were lower among non-Hispanic white females as compared with non-Hispanic blacks and Hispanics. Indeed, there was no significant

Table 3 – Correlations between MetS components and uric acid level

Sex	Ethnicity	BMI	WC	SBP	DBP	Triglycerides [a]	HDL	Fasting glucose	Fasting insulin [a]	HOMA [a]
Overall	Non-Hispanic white	**0.43** (0.37-0.48)	**0.47** (0.42-0.52)	**0.37** (0.31-0.42)	0.03 (−0.03 to 0.10)	**0.22** (0.15-0.28)	**−035** (0.41 to −0.30)	**0.21** (0.14-0.27)	**0.18** (0.12-0.24)	**0.20** (0.13-0.26)
	Hispanic	**0.36** (0.31-0.40)	**0.41** (0.36-0.45)	**0.34** (0.29-0.39)	0.00 (−0.05 to 0.05)	**0.25** (0.20-0.30)	**−0.32** (−0.37 to −0.27)	**0.20** (0.15-0.25)	**0.20** (0.14-0.25)	**0.21** (0.16-0.26)
	Non-Hispanic black	**0.35** (0.29-0.40)	**0.36** (0.31-0.42)	**0.33** (0.28-0.38)	0.04 (−0.02 to 0.10)	**0.24** (0.18-0.30)	**−0.28** (−0.34 to −0.23)	**0.19** (0.13-0.24)	**0.16** (0.10-0.22)	**0.18** (0.12-0.23)
Males	Non-Hispanic white	**0.54** (0.47-0.60)	**0.55** (0.48-0.61)	**0.34** (0.26-0.42)	**0.13** (0.04-0.22)	**0.28** (0.20-0.36)	**−0.37** (−0.45 to −0.29)	**0.17** (0.08-0.26)	**0.33** (0.25-0.41)	**0.33** (0.25-0.41)
	Hispanic	**0.46** (0.40-0.52)	**0.46** (0.40-0.52)	**0.26** (0.19-0.33)	**0.10** (0.02-0.17)	**0.31** (0.24-0.37)	**−0.29** (−0.36 to −0.22)	0.05 (−0.03 to 0.13)	**0.30** (0.23-0.37)	**0.30** (0.23-0.36)
	Non-Hispanic black	**0.49** (0.43-0.55)	**0.48** (0.42-0.54)	**0.31** (0.23-0.38)	**0.12** (0.04-0.20)	**0.28** (0.20-0.35)	**−0.31** (−0.38 to −0.23)	**0.12** (0.04-0.20)	**0.27** (0.20-0.35)	**0.27** (0.20-0.35)
Females	Non-Hispanic white	**0.39** (0.30-0.46)	**0.39** (0.30-0.46)	**0.10** (0.00-0.19)	0.01 (−0.09 to 0.10)	**0.13** (0.04-0.22)	**−0.14** (−0.23 to −0.05)	−0.02 (−0.12 to 0.07)	0.06 (−0.03 to 0.16)	0.06 (−0.04 to 0.15)
	Hispanic	**0.40** (0.33-0.46)	**0.39** (0.32-0.45)	**0.20** (0.12-0.27)	0.07 (−0.01 to 0.14)	**0.28** (0.21-0.35)	**−0.27** (−0.33 to −0.19)	0.06 (−0.02 to 0.13)	**0.27** (0.20-0.34)	**0.26** (0.19-0.33)
	Non-Hispanic black	**0.45** (0.37-0.52)	**0.43** (0.36-0.51)	**0.18** (0.09-0.27)	0.06 (−0.03 to 0.15)	**0.20** (0.11-0.28)	**−0.27** (−0.35 to −0.18)	**0.09** (0.00-0.18)	**0.30** (0.22-0.38)	**0.30** (0.22-0.38)

Correlation estimates and corresponding 95% CIs; significant correlations ($P < .05$) in bold.

[a] Natural log of variable was used to achieve normality.

correlation between uric acid and fasting insulin (or HOMA) among non-Hispanic white females. This finding is consistent with the relatively high levels of uric acid in non-Hispanic white females without MetS. Given what appears to be *reciprocal* relationships between uric acid and MetS [3,45], this raises the question about whether processes besides MetS itself contribute to higher uric acid levels in non-Hispanic whites.

Consequently, we investigated for several non-MetS processes that might explain higher levels of uric acid in non-Hispanic white females, examining for potential racial/ethnic differences in added sugar intake [19,20,46-50], obesity [8], and puberty [21,22], each of which is known to affect levels of uric acid. Although consumption of added sugar was associated with uric acid levels in our analysis, we found no differences in added sugar intake among female racial/ethnic groups. Regarding obesity, uric acid retained strong correlations with BMI and WC in non-Hispanic white females (similar to the strength of correlation seen in the other ethnicities); but non-Hispanic white females had overall less obesity compared with the other ethnicities (Table 1), which is also true of non-Hispanic white females with or without MetS [29]. Thus, neither of these considerations appeared to be the cause of the higher levels of uric acid in non-Hispanic white females without MetS.

Considerations regarding the potential effect of racial/ethnic differences in pubertal timing on uric acid levels were not as straightforward, as NHANES 1999-2006 did not include assessment of pubertal status. This is important because estrogen is uricosuric; and thus, lower levels of estrogen are a potential explanation for higher levels of uric acid [21,22]. To assess for the possible effect of differences in pubertal timing, we adjusted for age in its interaction with ethnicity and sex to account for any potential impact of puberty on the ethnic difference in uric acid. In addition, we evaluated uric acid levels across adolescence, from 12 to 19 years (Supplementary Figure 1). Non-Hispanic black girls frequently undergo puberty at younger ages than non-Hispanic whites and Hispanics and can have higher estradiol levels associated with these timing differences [51], although estradiol levels in adulthood have been noted to be similar between these groups [52,53]. Nevertheless, most girls in each ethnic group would have completed puberty by 18 to 19 years, at which point uric acid levels remained higher in non-Hispanic whites. Thus, although we remain uncertain regarding differences in estrogen as a cause of differences in uric acid, our analysis suggests against differences in pubertal timing as the cause.

Genetics may play a role in these processes, supported by the fact that both non-Hispanic white male and female adolescents had higher uric acid levels than other ethnicities. Surveys of uric acid levels in adults have had mixed findings with respect to racial/ethnic differences, reporting higher levels in non-Hispanic whites [54,55] and no difference [56] and higher levels in non-Hispanic blacks [14], potentially owing to differences in underlying MetS-related comorbidities among these studies of adults. In many ways, adolescents represent a more logical group to test for these racial/ethnic differences, given a very low rate of these comorbidities.

Prior reports have noted racial/ethnic differences in other MetS-related factors. Non-Hispanic black adolescents have higher levels of high-sensitivity C-reactive protein and insulin than non-Hispanic whites and Hispanics and also have a greater difference in high-sensitivity C-reactive protein and insulin between individuals with and without MetS [29,32]. The lower uric acid levels in non-Hispanic blacks are thus perhaps surprising, given the known associations between uric acid and both hypertension [4] and insulin resistance [3]—both of which are higher in non-Hispanic blacks as compared with non-Hispanic whites [28,29]. Overall, the lower uric acid levels among non-Hispanic blacks further suggest racial/ethnic differences in the relationship between uric acid and MetS.

These data may have some bearing regarding the utility of elevated uric acid levels as a risk factor for future disease. Although prospective studies have shown a strong association between uric acid levels and future hypertension [6], renal disease [13], CVD [14-16], and diabetes [17], these relationships have not been defined on a race/ethnicity-specific basis; and it is possible that the predictive nature of uric acid is more powerful among some ethnicities than others. Indeed, one study revealed that the association between uric acid and CVD mortality was stronger for non-Hispanic black men and women compared with non-Hispanic whites [14]. A clear limitation of the current study is the cross-sectional nature of NHANES 1999-2006; future prospective studies will be necessary to further define these relationships.

In conclusion, we found higher uric acid levels in non-Hispanic white adolescents compared with non-Hispanic blacks and Hispanics despite lower degree of insulin resistance (compared with both other ethnicities considered) and lower rates of hypertension (compared with non-Hispanic blacks). Uric acid levels were tightly linked to MetS in non-Hispanic white males; but among non-Hispanic white females, uric acid exhibited lower correlations with the components of MetS, with the exception of WC. Although uncertain, these data may have implications for the predictive power of uric acid by race/ethnicity, although future studies are needed.

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Conflict of Interest

The authors have no conflict of interest to declare.

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