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# Carotid intima-media thickness, dietary intake, and cardiovascular phenotypes in adolescents: relation to metabolic syndrome

Daniel M. Croymans[a], Albert Sanchez[b], Jacques D. Barth[c], Christian K. Roberts[a,d,e,*]

[a]Department of Physiological Science, University of California, Los Angeles, CA 90095-1606, USA
[b]Pacific Health Education Center, Bakersfield, CA 93309, USA
[c]Vasctech Foundation, Santa Monica, CA 90403, USA
[d]Department of Epidemiology, University of California, Los Angeles, CA 90095-1606, USA
[e]UCLA Center for Metabolic Disease Prevention, Los Angeles, CA 90095-1606, USA

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**Abstract**

Little is known about the interrelationships between metabolic syndrome (MS), uric acid, and early carotid atherosclerosis with diet in adolescents. We investigated associations among diet, carotid intima-media thickness (cIMT), MS, uric acid, and other cardiovascular risk factors in adolescents. Two hundred forty-nine adolescents from 3 high schools in Central California—a predominately Hispanic (n = 119, 16.1 ± 0.9 years old, 94% Hispanic), a mixed-ethnicity (n = 94, 15.7 ± 1.2 years old), and a Seventh-day Adventist (SDA) (n = 33, 17.0 ± 1.3 years old) high school—were assessed for cIMT, blood lipids, uric acid, blood glucose, systolic and diastolic blood pressure, body mass index (BMI), and dietary intake. Compared with SDA adolescents, the predominately Hispanic and mixed-ethnicity high school adolescents exhibited higher low-density lipoprotein and BMI percentile, whereas adolescents from the SDA and mixed-ethnicity high schools exhibited lower uric acid and fasting glucose levels than those from the Hispanic high school. After adjusting for age and sex, cIMT was only correlated with systolic blood pressure percentile ($r$ = 0.16, $P$ < .01). Controlling for age, levels of uric acid were correlated with BMI percentile (males: $r$ = 0.59, $P$ < .001; females: $r$ = 0.24, $P$ < .01), low-density lipoprotein (males: $r$ = 0.40, $P$ < .001; females: $r$ = 0.20, $P$ < .01), and total cholesterol in males ($r$ = 0.38, $P$ < .001). Despite no significant differences in the high school frequency of MS risk factors, 59% of adolescents had one or more MS risk factors. A relationship was noted between the number of MS risk factors and uric acid ($P$ < .002). Most of the adolescents presented MS risk factors independent of ethnicity or a purportedly healthier lifestyle (SDA). Uric acid association with MS and its risk factors suggests its potentially heightened importance for the assessment of adolescent cardiovascular health.
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## 1. Introduction

Poor diet and lack of physical activity [1] are major contributors to the increased prevalence of childhood obesity and early onset of atherosclerosis [2,3]. Strongly connected to childhood obesity [4], metabolic syndrome (MS) is associated with an increased risk of cardiovascular disease (CVD) in adults [5-7]. The prevalence of MS in adults [8] and in adolescents [9,10] has steadily increased over the last 2 decades. Whereas cardiovascular risk factors are associated with CVD risk later in life [11-14], the relationship of childhood MS and future occurrence of CVD is uncertain.

Metabolic syndrome and its components are associated with increased carotid intima-media thickness (cIMT) in adults [15-17]; but again, there are limited data to support this association in adolescents [18]. The measurement of cIMT by ultrasound imaging is predictive of future CVD [19-22] and may be an important noninvasive measure of early carotid atherosclerosis. Freedman et al [11] noted that body mass index (BMI) during childhood was related to adult cIMT, an association primarily independent of adult BMI. In addition, obese children with greater cIMT than their leaner peers exhibited fewer cardiovascular risk factors and lower cIMT after substantial weight loss [23].

Conflicts of interests: No conflict of interest is to be disclosed.

* Corresponding author. Department of Physiological Science, UCLA, Los Angeles, CA 90095-1606, USA. Tel.: +1 310 825 8499; fax: +1 310 206 9184.

*E-mail address:* croberts@ucla.edu (C.K. Roberts).

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Like MS and its components, serum uric acid may be an important marker of CVD risk [24]. Although uric acid is not part of any MS definition, several epidemiologic studies have noted associations of serum uric acid levels with MS [25-27] and CVD [28-30]. Furthermore, adolescents with MS tend to have higher levels of serum uric acid [31].

The purpose of this study was to (1) determine whether MS risk factors were present in early life and related to cIMT in adolescents from 3 high schools—a predominately Hispanic, a mixed-ethnicity, and a Seventh-day Adventist (SDA) high school—and (2) explore the association between serum uric acid and cardiovascular risk factors among all adolescents. It was hypothesized that adolescents from the SDA high school, primarily from homes of a known health-conscious population that has a lower risk of CVD among adults than the general population [32], were expected to exhibit fewer MS risk factors and overall reduced risk of future CVD development compared with Hispanic and mixed-ethnicity high schools.

## 2. Methods

### 2.1. Study population

This study assessed cIMT in adolescents together with HeartBeat, the adult CVD risk screening program at Pacific Health Education Center. Carotid intima-media thickness is a predictor of CVD for the adult, but similar normative values are not available for adolescents. We thus chose to assess 249 adolescents from 3 high schools in Central California—a predominately Hispanic (n = 119, 16.1 ± 0.9 years old, 94% Hispanic), a mixed-ethnicity (n = 94, 15.7 ± 1.2 years old), and an SDA (n = 33, 17.0 ± 1.3 years old) high school—for height, weight, BMI, cIMT, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), uric acid, blood glucose, systolic and diastolic blood pressure (SBP and DBP, respectively), and dietary intake based on quantitative food frequency questionnaires (Quick Check for Diet Progress by Nutrition Scientific, Pasadena, CA). Blood samples and anthropometric measures were obtained from subjects while they were fasting. Permission for this study was obtained from the Superintendent of Schools and the principal of each high school. The adolescent volunteers signed a consent form and had parental signed consent. The study was approved by the Institutional Review Board of University of Southern California. The teachers cooperated by facilitating participation of the volunteers in their classes. All volunteers participated in the study; there were no exclusion criteria.

### 2.2. Dietary assessment

Diet records were analyzed by using the computerized Nutrient Analysis System (Nutrition Scientific, Inc, Pasadena, CA), which converted dietary intake into an average daily nutrient consumption, as demonstrated in other publications [33,34]. Dietary factors analyzed were as follows: total calories, consumption (grams) of total protein, total carbohydrate, total fat, saturated fat, dietary cholesterol (milligrams per day), meat (servings per day), dairy (servings per day), nuts and grains (servings per day), and fruit/vegetable (servings per day).

### 2.3. Determination of serum lipids, glucose, and uric acid

Fasting blood samples taken from each subject were analyzed for total cholesterol, TG, HDL, glucose, and uric acid levels at LabCorp in Bakersfield, CA, using standardized techniques as previously described [35]. Low-density lipoprotein was calculated by the formula of Friedewald et al [36].

### 2.4. Carotid ultrasonography

Right and left cIMT was obtained using ultrasonography. A linear array 7.5- to 10-MHz transducer using a duplex B-mode scanner (IMT-HeartScan, Prevention Concepts Inc, Santa Monica, CA) was held in place by a stereotactic device; the operating frequency for data collection was 10 MHz. This is the recommended standard probe according to the Screening for Heart Attack Prevention and Education guidelines [37]. This system is interfaced with a standard personal computer equipped with a data acquisition card for attainment of radiofrequency ultrasound signals from the scanner. Optimal image of the far wall of the common carotid artery from multiple angles (at least 4 angles) was determined. Digital images were sent over the Internet to a centralized database; and analysis was performed by the same registered vascular technician, who was blinded to subject identifying information, for all studies. Carotid intima-media thickness was measured using a fully automated, Web-embedded analysis software (ZoeXp, Prevention Concepts Europe BV, Santpoort, The Netherlands), a validated algorithm that analyzes and quantitates cIMT using edge contour detection techniques from digitized images. The coefficients of variation are 3% for intraoperator and 3.1% for interoperator variation [38].

### 2.5. Defining MS risk factors

The MS criteria used were modified from those of the National Cholesterol Education Program's Adult Treatment Panel [39] and the World Health Organization [40], and have been used in previous studies of MS [4,7,41,42]. Age- and sex-specific algorithms provided by the Centers for Disease Control and Prevention were used to calculate SBP and DBP percentiles [43], BMI percentiles, TG percentiles, and HDL percentiles. Equations provided by the Centers for Disease Control and Prevention used to generate $z$ scores of BMI values were then applied to estimate sex-specific BMI-for-age percentiles for each subject. The subjects in our study were classified as having MS if 3 or more of the following criteria were met: (1) BMI greater than or equal to the 95th percentile, (2) fasting glucose greater than or equal to 100 mg/dL, (3) TG greater than or equal to the 95th percentile, (4) HDL less than or equal to the 5th percentile, and (5) SBP or DBP greater than or equal to the 90th percentile.

### 2.6. Statistical analyses

Data were analyzed for homoscedasticity and normality. Data from food frequency questionnaires were inspected for outliers, with under- and overreporters (<800 and >5000 kcal/d for total caloric intake per day, respectively) excluded from the analyses. However, analyses with and without under- and overreporters yielded similar results. Homogeneity of variances across the 3 groups was not upheld. This, along with the absence of normality and unequal sample sizes, prohibited the use of traditional analyses of variance for comparisons between high schools. Thus, nonparametric exploratory analysis and parametric analysis (for combined partial correlations) were used for statistical inference. *P* values were calculated using Pearson and partial Pearson correlation, Fisher exact test, and Kruskal-Wallis equality-of-populations rank test with post hoc analysis by 2-sample Wilcoxon rank sum (Mann-Whitney) test. Significance was set to $\alpha < .01$. All analyses were performed with the use of STATA software (version 10.1; StataCorp, College Station, TX).

## 3. Results

### 3.1. High school differences

Cardiovascular risk factors and dietary data are summarized in Tables 1 and 2, respectively. The predominately Hispanic high school (94% Hispanic) was 78% female, the mixed-ethnicity high school was 52% female, and the SDA high school was 72% female in sampled students.

### 3.2. Cardiovascular risk factors

Both cIMT and uric acid were significantly higher in males than females in combined data (both *P*'s < .001). Between the 3 high schools, there were significant differences in cIMT, BMI percentile, LDL, serum glucose, and serum uric acid (Table 1). Students from the predominately Hispanic high school had lower cIMT compared with those from other high schools, independent of sex (*P* < .04, Table 1). Students from the SDA high school had a significantly lower BMI percentile compared with those from the other high schools (*P* < .02, Table 1). Low-density lipoprotein was 13% and 14% lower in SDA compared with Hispanic and mixed-ethnicity high schools (*P* < .01, Table 1), respectively. The Hispanic high school had a significantly higher fasting glucose compared with the mixed-ethnicity and SDA high schools (*P* < .01). Serum uric acid was significantly lower in SDA students compared with students of other high schools (*P* < .01, Table 1).

### 3.3. Dietary factors

Between the 3 high schools, there were significant differences in protein, dietary cholesterol, meat, dairy, and fruit/vegetable intake. The SDA students had significantly lower protein intake (14%) compared with students from the

Table 1
Cardiovascular risk factors in high schools

| Characteristic[a] | Hispanic (n = 119) | Mixed (n = 94) | SDA (n = 36) | P[b] |
|---|---|---|---|---|
| Sex | | | | |
| Male | 26 | 45 | 10 | |
| Female | 93 | 49 | 26 | |
| Age (y) | 16 (15-17) | 16 (15-17) | 17 (16-18) | |
| Average cIMT (mm) | 0.52 (0.50-0.54)* | 0.53 (0.50-0.56) | 0.54 (0.52-0.55) | .01 |
| Glucose (mg/dL) | 92 (88-96)[‡†] | 89 (85-94) | 88 (83-92) | .001 |
| BMI percentile | 77 (53-93) | 66 (50-89) | 56 (28-80)[§‡] | .02 |
| TG percentile | 45 (29-63) | 34 (27-51) | 40 (27-55) | |
| SBP percentile | 77 (47-93) | 73 (46-98) | 81 (36-89) | |
| DBP percentile | 86 (66-95) | 84 (66-94) | 84 (73-91) | |
| HDL percentile | 35 (15-56) | 41 (20-67) | 42 (21-57) | |
| Total cholesterol (mg/dL) | 161 (144-183) | 159 (140-179) | 149 (130-167) | |
| LDL (mg/dL) | 93 (78-110) | 94 (73-115) | 81 (64-90)[§‡] | .002 |
| Uric acid (mg/dL) | 3.9 (3.2-4.9)[‡†] | 4.6 (3.8-5.6)[†] | 3.5 (3.0-4.0) | .0001 |

Average cIMT refers to averaged value of right and left cIMT.
[a] Data are median (interquartile range).
[b] *P* value calculated using Kruskal-Wallis equality-of-populations rank test with post hoc analysis by 2-sample Wilcoxon rank sum (Mann-Whitney) test.
* *P* < .05 for comparison between schools.
† *P* < .01 for comparison with SDA.
‡ *P* < .01 for comparison with mixed.
§ *P* < .01 for comparison with Hispanic.

predominately Hispanic (20%) and mixed-ethnicity (21%, *P* < .01) high schools. Students from both the mixed-ethnicity and Hispanic high schools had significantly higher consumption of meat and, similarly, cholesterol compared with SDA students (*P* < .01). Students from the predominately Hispanic high school consumed less dairy products compared with students from the SDA and the mixed-ethnicity high schools; they also consumed less fruits/vegetables than the SDA students (all *P*'s < .01).

### 3.4. Combined high school partial correlations

In all subjects, exploratory analysis was performed for cardiovascular risk factors. We ran partial correlations between BMI and cardiovascular risk factors controlling for all variables listed; all were significantly correlated with BMI percentile except glucose and DBP percentile (Table 3). Partial correlation coefficients between uric acid levels and several metabolic measures are shown in Table 4. Body mass index percentile was correlated with uric acid in males ($r$ = 0.59, *P* < .001) and females ($r$ = 0.24, *P* < .01). Before adjustment with BMI percentile, uric acid levels were correlated with TG percentile in females ($r$ = 0.24, *P* < .01) and weakly in males ($r$ = 0.23, *P* < .04). In addition, uric acid was correlated with LDL (males: $r$ = 0.40, *P* < .001; females: $r$ = 0.20, *P* < .01) and with total cholesterol in males ($r$ = 0.38, *P* < .001). Results were attenuated after adjustment with BMI percentile. After adjusting for age and

Table 2
Dietary intake in high schools

| Characteristic[a] | Hispanic (n = 119) | Mixed (n = 94) | SDA (n = 36) | $P^b$ |
|---|---|---|---|---|
| Total calorie (kcal/d) | 1936 (1386-2861) | 2043 (1520-2796) | 1686 (1440-2468) | |
| Protein (%) | 17.4 (15.7-21.3) | 19.1 (16.3-22.3) | 13.1 (11.4-15.2)*‡ | .0001 |
| Protein (g) | 95 (62-131) | 105 (70-134) | 60 (47-79)*‡ | .0001 |
| Carbohydrate (%) | 46.4 (39.0-50.1) | 46.2 (40.1-52.2) | 54.3 (48.3-60.0) | |
| Carbohydrate (g) | 211 (146-336) | 240 (176-350) | 232 (182-310) | |
| Fat (%) | 36.8 (33.6-40.5) | 35.1 (30.5-40.2) | 34.1 (32.0-39.5) | |
| Fat (g) | 78 (53-124) | 82 (54-119) | 65 (52-84) | |
| Saturated fat (%) | 14.0 (12.4-15.4) | 13.8 (10.9-15.1) | 12.9 (10.9-15.4) | |
| Saturated fat (g) | 27 (20-48) | 30 (19-49) | 24 (19-32) | |
| Dietary cholesterol (mg/d) | 287(192-452) | 317 (196-421) | 168 (122-289)*‡ | .001 |
| Meat (servings/d) | 3.0 (1.9-4.8) | 3.3 (2.0-5.3) | 1.6 (0.7-2.8)*‡ | .0001 |
| Dairy (servings/d) | 2.0 (1.1-3.7)‡† | 3.1 (1.8-5.0) | 3.3 (2.5-4.3) | .002 |
| Nuts and grains (servings/d) | 3.5 (2.2-4.8) | 3.6 (2.3-4.9) | 3.7 (2.2-4.8) | |
| Fruit and vegetable (servings/d) | 1.7 (0.8-3.4)† | 2.4 (1.2-4.1) | 3.5 (1.8-4.8) | .01 |

[a] Data are median (interquartile range).
[b] *P* value calculated using Kruskal-Wallis equality-of-populations rank test with post hoc analysis by 2-sample Wilcoxon rank sum (Mann-Whitney) test.
* $P < .01$ for comparison with Hispanic.
† $P < .01$ for comparison with SDA.
‡ $P < .01$ for comparison with mixed.

sex, cIMT was only correlated with SBP percentile ($r = 0.16$, $P < .01$).

### 3.5. Metabolic syndrome

There was no significant difference in the prevalence of MS between all 3 high schools (Fig. 1); however, 59% of adolescents had one or more MS risk factors. In all 249 adolescents (entitled *Combined*), 103 had no MS risk factors, 137 had 1 to 2 MS risk factors, and 9 had at least 3 MS risk factors (Fig. 1). Table 5 depicts the distribution of MS risk factors. Interestingly, serum uric acid levels increased with greater numbers of MS risk factors (Fig. 2, $P < .002$).

## 4. Discussion

Children from the United States are becoming unhealthier, resulting primarily from changes in environmental factors such as inappropriate dietary choices. The Pathobiological Determinants of Atherosclerosis in Youth study exemplified the importance of disease prevention at an early age by demonstrating the early progression of atherosclerosis in 15- to 19-year-old subjects [44]. Accordingly, the accuracy by which we assess disease risk at an early age is of great clinical significance. To better understand the association of cardiovascular risk factors and dietary intake in adolescents from different social and ethnic backgrounds, we examined dietary intake and cardiovascular-related phenotypes in 249 adolescents from 3 high schools.

In adults, SDAs have been known to display a reduced incidence of MS risk factors and CVD, attributed to their lower meat and fat intake, higher fruit and vegetable consumption, reduced smoking, and increased physical activity [1,45,46]. In this study, the trend toward lower cardiovascular risk in SDA adolescents (including lower BMI percentile, LDL cholesterol, and uric acid) may be due,

Table 3
Partial correlation coefficients of BMI percentile with uric acid, glucose, TG percentile, SBP percentile, DBP percentile, HDL percentile, and LDL controlling for age, sex, and all variables listed

| Cardiovascular factors | Correlation coefficients | |
|---|---|---|
| | *r* | *P* |
| Uric acid (mg/dL) | 0.25 | <.001 |
| Glucose (mg/dL) | 0.09 | .18 |
| TG percentile | 0.15 | .02 |
| SBP percentile | 0.17 | .01 |
| DBP percentile | 0.09 | .16 |
| HDL percentile | −0.19 | .003 |
| LDL (mg/dL) | 0.21 | .001 |

Table 4
Partial correlation coefficients of serum uric acid levels with cardiovascular factors among males and females adjusted for BMI percentile and/or age

| Cardiovascular factors | Correlation coefficients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Age adjusted | | | | Age and BMI percentile adjusted | | | |
| | Males (n = 81) | | Females (n = 168) | | Males (n = 81) | | Females (n = 168) | |
| | *r* | *P* | *r* | *P* | *r* | *P* | *r* | *P* |
| Glucose (mg/dL) | 0.14 | .23 | 0.06 | .42 | 0.02 | .83 | 0.03 | .73 |
| BMI percentile | 0.59 | <.001 | 0.24 | <.01 | – | – | – | – |
| TG percentile | 0.23 | .04 | 0.24 | <.01 | 0.02 | .83 | 0.16 | .04 |
| SBP percentile | 0.20 | .07 | 0.12 | .13 | 0.08 | .51 | 0.03 | .68 |
| DBP percentile | 0.09 | .41 | 0.23 | <.01 | 0.00 | .99 | 0.16 | .04 |
| HDL percentile | −0.12 | .29 | −0.20 | .01 | 0.06 | .63 | −0.13 | .09 |
| Total cholesterol (mg/dL) | 0.38 | <.001 | 0.16 | .04 | 0.14 | .23 | 0.12 | .11 |
| LDL (mg/dL) | 0.40 | <.001 | 0.20 | <.01 | 0.14 | .21 | 0.15 | .05 |

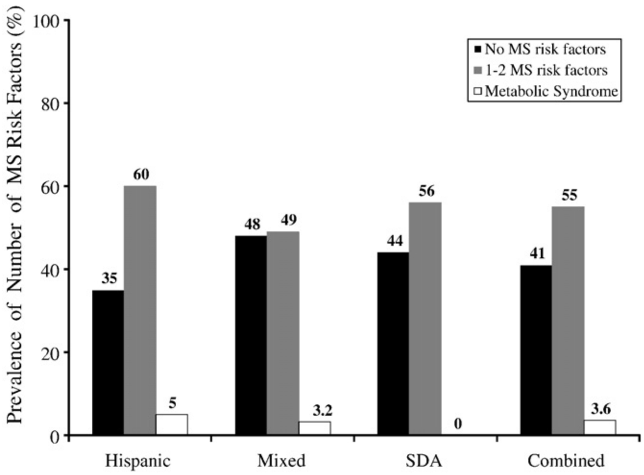


Fig. 1. Prevalence of MS risk factors. Black, gray, and open boxes correspond to adolescents with no MS risk factors, 1 to 2 MS risk factors, and MS (≥3 MS risk factors), respectively. No significant difference between high schools was noted (Fisher exact test, $P < .29$).

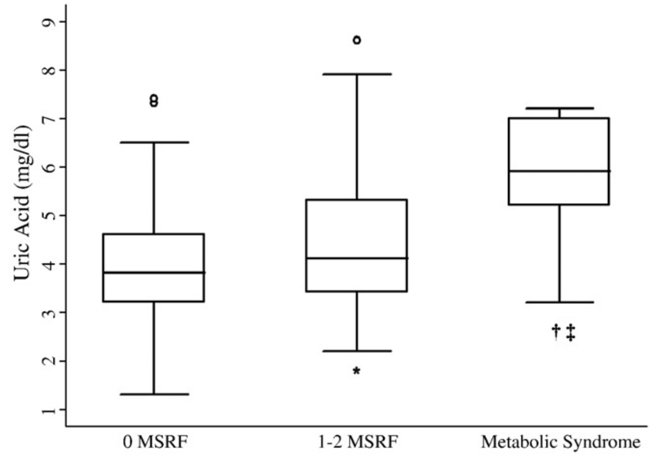


Fig. 2. Uric acid levels in MS. $P$ value calculated using Kruskal-Wallis equality-of-populations rank test with post hoc analysis by 2-sample Wilcoxon rank sum (Mann-Whitney) test. Kruskal-Wallis test gave $P < .002$. *$P < .02$ for comparison with 0 MS risk factor. ‡$P < .01$ for comparison with 1 to 2 MS risk factors. †$P < .003$ for comparison with 0 MS risk factor. Box-and-whisker diagram demonstrates 25th, median, and 75th percentile values; open circles correspond to outliers based on any data point that is more than 1.5 times the interquartile range from either end of the box. MSRF indicates metabolic syndrome risk factor.

in part, to the greater consumption of fruits/vegetables and lower dietary cholesterol. Pan and Pratt [47] showed an inverse relation in the prevalence of MS and Healthy Eating Index and fruit score quartiles in adolescents.

The relationship between uric acid and CVD has been known since the late 19th century [48,49]. In adults, the association of uric acid with hypertension [50], coronary artery disease [51], and even all-cause mortality [28,52] demonstrates its potential clinical importance. The prevalence of MS has been shown to increase with increasing serum uric acid levels even in individuals with normal BMI levels [25]. Furthermore, uric acid may induce endothelial dysfunction and insulin resistance [53]. In our study, the correlations between serum uric acid and known CVD risk factors suggest that uric acid may be a marker of developing disease risk in adolescents. In addition, we noted that greater numbers of MS risk factors were associated with higher levels of serum uric acid. Similar results have been demonstrated in recent studies showing an increased prevalence of MS [54] and carotid atherosclerosis [55] in children with increasing levels of uric acid.

The relationship between diet and uric acid in adolescents is unclear. However, several studies in adults suggest that levels of uric acid are positively associated with meat consumption and negatively associated with dairy consumption [56-58]. Interestingly, in this study, the observed lower serum uric acid levels in SDA adolescents, who consumed less protein and meat and more dairy products, imply a similar association in adolescents.

Table 5
Distribution of MS risk factors

| High school | BMI >95% | HDL <5% | TG >95% | Glucose >100 | SBP or DBP ≥90% |
|---|---|---|---|---|---|
| Hispanic (n = 119) | 19% | 8% | 6% | 8% | 54% |
| Mixed (n = 94) | 13% | 1% | 2% | 3% | 48% |
| SDA (n = 36) | 8% | 3% | 0% | 3% | 50% |
| Combined (n = 249) | 15% | 4% | 4% | 6% | 51% |

Although long-term longitudinal studies are required to corroborate the relationship of adolescent MS, cIMT, and uric acid levels with the future risk of CVD, our results may have clinical relevance. Notably, results from the Bogalusa Heart Study demonstrated the relationship of childhood cardiovascular risk factors and adult risk of CVD [11,12].

The limitations of this study include the following: (1) the cross-sectional design can only examine association and not definitive causation; (2) no measure of physical activity was determined to establish its contribution to the findings noted; and (3) food frequency questionnaire–based dietary intake cannot provide subjects' exact dietary intake but only a representation of general dietary intake patterns.

In all adolescents, after controlling for age and sex, cIMT was positively correlated only with SBP percentile. Interestingly, students from the predominately Hispanic high school have lower cIMT despite exhibiting higher levels of other cardiovascular risk factors compared with students from the SDA and the mixed-ethnicity high schools, agreeing with prior studies [59]. Perhaps the measurement of cIMT alone in adolescents may play a limited role in the assessment of metabolic disease risk. Rather, a more complete assessment of the vascular wall, including lesion number, composition, and vulnerability, might be more appropriate [60-62]. Overall, the uric acid associations with MS and CVD risk factors in adolescents suggest the potential importance of uric acid as a component of disease risk classification at an early age.

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