# The Metabolic Syndrome and Concentrations of C-Reactive Protein Among U.S. Youth

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**OBJECTIVE** — Adults with the metabolic syndrome show biochemical evidence of low-grade inflammation. We sought to examine whether this is true among U.S. youth with the metabolic syndrome.

**RESEARCH DESIGN AND METHODS** — We used data from 1,366 participants aged 12–17 years from the National Health and Nutrition Examination Survey 1999–2000. A modification of the definition of the metabolic syndrome proposed by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults was used. C-reactive protein (CRP) was measured by latex-enhanced nephelometry.

**RESULTS** — Mean and median concentrations of CRP were higher among participants who had the metabolic syndrome (mean 3.8 mg/l, geometric mean 1.8 mg/l) than among those who did not (mean 1.4 mg/l, geometric mean 0.4 mg/l). The percentage of participants with a concentration of CRP >3.0 mg/l was 38.4% among those with the metabolic syndrome and 10.3% among those without the syndrome ($P = 0.007$). Of the five components of the syndrome, only abdominal obesity was significantly and independently associated with log-transformed concentrations of CRP in multiple linear regression analysis.

**CONCLUSIONS** — Our results show that a large percentage of children and adolescents with the metabolic syndrome have elevated concentrations of CRP. Whether the elevated concentrations of CRP among children and adolescents who have the metabolic syndrome predict future adverse health events remains to be determined.

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The metabolic syndrome has generated a great deal of interest in recent years. Comprised of a constellation of anthropometric, physiologic, and biochemical abnormalities, the metabolic syndrome is a risk factor for cardiovascular disease and diabetes among adults. However, research about the metabolic syndrome among children and adolescents and the implications of having the metabolic syndrome is limited.

Among adults, components of the metabolic syndrome and the metabolic syndrome itself are associated with measures of inflammation, such as concentrations of C-reactive protein (CRP) (1–4). This low-grade inflammation, which has been associated with an increased risk for cardiovascular disease and diabetes (5,6), may provide a mechanism for the increased risk of these conditions experienced by individuals who have the metabolic syndrome.

Little is known about whether children and adolescents who have the metabolic syndrome have evidence of inflammation. Because the roots of many adult diseases herald back to childhood, establishing whether young people who have the metabolic syndrome also show evidence of increased inflammation may help to identify children and adolescents who are at high risk for developing cardiovascular disease and diabetes and allow for early prevention of possible adverse health events.

## RESEARCH DESIGN AND METHODS

— We performed a cross-sectional analysis using data from National Health and Nutrition Examination Survey (NHANES) 1999–2000. Detailed information about the methods and procedures of this survey is available elsewhere (7). In brief, a representative sample of the noninstitutionalized civilian U.S. population was selected through a stratified multistage design. Trained interviewers, using a computer-assisted personal interview system, interviewed participants at home. Participants were asked to attend the mobile examination center where they completed additional questionnaires, underwent various examinations, and provided a blood sample. The study received human subject approval from the Centers for Disease Control and Prevention, Atlanta, Georgia.

To define the metabolic syndrome among the young participants, we used a previously proposed modification of the definition proposed in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP/ATP III) (8). Participants had to meet three of the following five criteria: concentration of triglycerides ≥110 mg/dl, HDL cholesterol ≤40 mg/dl, waist circumference ≥90th

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**Abbreviations:** CRP, C-reactive protein; NHANES, National Health and Nutrition Examination Survey.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

**Table 1—*Unadjusted mean concentrations ± SE, geometric mean concentrations ± SE, and percentage ± SE of CRP >3.0 mg/l by presence or absence of metabolic syndrome or its five components among 1,366 participants aged 12–17 years, National Health and Nutrition Examination Survey 1999–2000***

| Metabolic syndrome or components | Sample size | | Mean ± SE (mg/l) | | | Geometric mean ± SE (mg/l) | | | % ± SE of CRP >3 mg/l | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | *P* | Yes | No | *P** | Yes | No | *P* |
| Metabolic syndrome (original NCEP/ATP III) | 80 | 1,286 | 3.8 ± 1.1 | 1.4 ± 0.1 | 0.038 | 1.8 ± 0.4 | 0.4 ± 0.03 | <0.001 | 38.4 ± 10.0 | 10.3 ± 1.0 | 0.007 |
| Metabolic syndrome (modified NCEP/ATP III) | 85 | 1,281 | 3.9 ± 1.1 | 1.4 ± 0.1 | 0.030 | 1.8 ± 0.4 | 0.4 ± 0.03 | <0.001 | 38.1 ± 9.8 | 10.3 ± 1.0 | 0.007 |
| Abdominal obesity | 292 | 1,074 | 3.6 ± 0.4 | 1.1 ± 0.2 | <0.001 | 1.9 ± 0.2 | 0.4 ± 0.02 | <0.001 | 36.0 ± 4.0 | 6.5 ± 0.9 | <0.001 |
| Hypertriglyceridemia | 254 | 1,112 | 1.8 ± 0.3 | 1.5 ± 0.2 | 0.436 | 0.7 ± 0.1 | 0.4 ± 0.03 | 0.014 | 14.4 ± 3.4 | 11.1 ± 1.2 | 0.370 |
| Low HDL cholesterol | 230 | 1,136 | 2.1 ± 0.4 | 1.4 ± 0.2 | 0.132 | 0.7 ± 0.1 | 0.4 ± 0.03 | 0.002 | 16.1 ± 4.0 | 10.8 ± 1.0 | 0.207 |
| High blood pressure | 135 | 1,231 | 3.0 ± 0.9 | 1.4 ± 0.1 | 0.099 | 0.9 ± 0.2 | 0.5 ± 0.03 | 0.019 | 22.5 ± 5.9 | 10.9 ± 1.0 | 0.053 |
| Hyperglycemia ≥110 mg/dl | 12 | 1,354 | 1.3† | 1.6 ± 0.2 | — | 0.7† | 0.5 ± 0.03 | — | 27.6† | 11.6 ± 1.1 | — |
| Hyperglycemia ≥100 mg/dl | 44 | 1,322 | 2.4† | 1.5 ± 0.1 | — | 0.6† | 0.5 ± 0.03 | — | 18.4† | 11.6 ± 1.1 | — |

**P* value calculated based on log-transformed concentration of CRP. †Unstable estimates.

percentile (sex specific), glucose concentration ≥110 mg/dl, and systolic or diastolic blood pressure ≥90th percentile (age, height, and sex specific). Because a lower threshold of hyperglycemia at ≥100 mg/dl has been previously proposed by Grundy et al. (9), we also included this revised definition of hyperglycemia in our analyses and created a modified definition of the metabolic syndrome using the revised definition of hyperglycemia while keeping the other criteria unchanged. For young participants in NHANES 1999–2000, information to define this syndrome was available only for those aged 12–17 years who attended the mobile examination center. To remain consistent with a previous analysis of the metabolic syndrome among adolescents from NHANES III (8), we used a fasting time of ≥6 h.

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 four blood pressure measurements were obtained for each participant in the mobile examination center. 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. HDL cholesterol concentration, after the precipitation of other lipoproteins with a heparin-manganese chloride mixture, was measured on a Hitachi 717 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). To maximize the number of young participants available for analysis, we used measurements of glucose and triglycerides from the biochemistry panel, since the reference measurements for these two variables were only conducted for participants of the morning examination. Glucose concentration was measured using the glucose hexokinase method. Finally, triglyceride concentration was determined after hydrolysis of triglycerides to glycerol and oxidation to dihydroxyacetone phosphate and hydrogen peroxide.

CRP was measured by latex-enhanced nephelometry (N high-sensitivity CRP assay) on a BN II nephelometer (Dade Behring, Deerfield, IL) at the University of Washington Medical Center, Seattle, Washington. Two levels of control materials from Bio-Rad Laboratories (Hercules, CA) were used for quality control purposes, and day-to-day coefficients of variation (CVs) ranged from 4.93 to 7.84%.

*T* tests were performed to compare mean and log-transformed concentrations of CRP. We examined the independent contribution of the five components of the metabolic syndrome to CRP concentration in multiple linear regression analyses. For regression analyses, CRP concentration was log transformed to improve the distribution of this variable. In addition, we dichotomized concentrations of CRP into ≤3.0 and >3.0 mg/l and used logistic regression analysis to examine the independent contribution of the five components to having a concentration of CRP >3.0 mg/l. To account for the complex sampling design, SUDAAN version 8.0 was used to calculate means and proportions and to perform linear regression analyses (10). Sampling weights were used to calculate proportions, measures of central tendency, and regression estimates. If the relative SE for means or percentages exceeded 30%, the estimates were deemed to be unstable.

**RESULTS** — A total of 1,782 participants aged 12–17 years attended the mobile examination center. Complete information for the five variables needed to assess the metabolic syndrome was available for 1,554 children and adolescents. The sample size fell to 1,370 after excluding participants who had fasted <6 h and those who were pregnant. After excluding an additional four participants who did not have a value for concentration of CRP, 1,366 participants remained in the analytic sample. Among the 1,366 participants, CRP concentrations ranged from 0.1 to 65.2 mg/l (geometric mean 0.5 mg/l, median 0.4 mg/l).

Among all 1,366 participants, 57.6% had no components, 26.0% had one component, 11.1% had two components, 4.1% had three components, and 1.2% had four components. No participants had all five components. The prevalence of the metabolic syndrome was 5.2% (6.3% among males and 4.1% among females, $P = 0.233$). Furthermore, 17.9%

**Table 2 —*Results of multiple linear regression analysis with concentration of log-transformed CRP as the dependent variable among 1,366 participants aged 12–17 years, National Health and Nutrition Examination Survey 1999–2000***

| Independent variables | Regression coefficient | SE | *P* |
|---|---|---|---|
| Age (years) | 0.103 | 0.031 | 0.002 |
| Sex | | | |
| Male vs. female (ref.) | −0.077 | 0.123 | 0.534 |
| Abdominal obesity | | | |
| Yes vs. no (ref.) | 1.677 | 0.125 | <0.001 |
| Hypertriglyceridemia | | | |
| Yes vs. no (ref.) | −0.051 | 0.141 | 0.720 |
| HDL cholesterol <40 mg/dl | | | |
| Yes vs. no (ref.) | 0.163 | 0.130 | 0.215 |
| High blood pressure | | | |
| Yes vs. no (ref.) | 0.255 | 0.171 | 0.142 |
| Glucose ≥110 mg/dl | | | |
| Yes vs. no (ref.) | 0.040 | 0.261 | 0.878 |

had a large waist circumference, 21.0% had hypertriglyceridemia, 18.3% had a low concentration of HDL cholesterol, 7.1% had high blood pressure, 0.8% had a concentration of glucose ≥110 mg/dl, and 2.7% had a concentration of glucose ≥100 mg/dl.

Mean and geometric mean concentrations of CRP were higher among participants who had the metabolic syndrome (mean 3.8 mg/l, geometric mean 1.8 mg/l) than among those who did not (mean 1.4 mg/l, geometric mean 0.4 mg/l) (Table 1). Among adolescents with the metabolic syndrome, 38.4% had a concentration of CRP >3.0 mg/l, a concentration considered to place adults at high risk for cardiovascular disease. In comparison, 10.3% of adolescents without the syndrome had such a concentration of CRP ($P = 0.007$).

Of the five components of the metabolic syndrome, mean concentration of CRP was higher only among those with abdominal obesity (Table 1). However, mean concentrations of log-transformed CRP were higher among participants with abdominal obesity, hypertriglyceridemia, low HDL cholesterol, and high blood pressure compared with participants without those conditions. In multiple logistic regression analysis with age, sex, and all five components of the metabolic syndrome added as independent variables, only abdominal obesity was significantly and independently associated with log-transformed concentration of CRP (Table 2). When the same five components were examined as continuous variables in another linear regression model, only waist circumference was significantly associated with concentrations of log-transformed CRP. Results from an analogous logistic regression model with dichotomized concentration of CRP as the dependent variable and the five components added as continuous independent variables yielded similar conclusions.

**CONCLUSIONS** — Studies have previously demonstrated that adults with the metabolic syndrome show evidence of low-grade inflammation. We have now shown that children and adolescents with the metabolic syndrome are more likely than those without this syndrome to show evidence of low-grade inflammation. The percentage of children and adolescents with an elevated concentration of CRP (>3.0 mg/l) was almost four times higher among those with the metabolic syndrome compared with those who did not have the syndrome. However, abdominal obesity was the component that was responsible for much of the difference in concentrations of CRP.

The association between obesity and elevated concentrations of CRP in children and adolescents has been clearly established (11–21). In univariate analysis, concentrations of CRP have also been significantly associated with the other four components of the metabolic syndrome (11,13,16–18). However, after adjustment for an anthropometric measure, many of these associations were seriously weakened and often failed to achieve statistical significance.

No studies have thus far shown that children and adolescents with evidence of low-grade inflammation are more likely to develop cardiovascular disease or diabetes than those without such evidence. However, obesity in childhood does increase the risk for diabetes in childhood and a variety of diseases in adulthood (22).

To maximize our sample size, we decided to use nonreference measurements of concentrations of glucose and triglycerides because these were obtained for children who attended any of the three examination sessions. However, when we used reference measurements for the young participants who attended the morning examination, we obtained very similar results. Unfortunately, the sample size was inadequate to provide results separately for males and females.

Our results suggest that the presence of the metabolic syndrome and abdominal obesity among children and adolescents may be laying the foundation for the emergence of cardiovascular disease and diabetes later in life through early low-grade inflammation. To reduce the potential adverse effects of the inflammation that accompanies the metabolic syndrome, children and adolescents with this syndrome should avoid excessive energy intake, limit sedentary behavior, and increase their participation in activities that increase their energy expenditure.

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