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Inflammation and Changes in Metabolic Syndrome Abnormalities in US Adolescents: Findings from the 1988–1994 and 1999–2000 National Health and Nutrition Examination Surveys

Sarah D. de Ferranti,[1] Kimberlee Gauvreau,[1] David S. Ludwig,[2] Jane W. Newburger,[1] and Nader Rifai[3*]

Background: **Understanding of C-reactive protein (CRP) in adult metabolic syndrome is increasing; however, this relationship in children is less clear.**

Methods: **We compared the prevalence of metabolic abnormalities and metabolic syndrome in fasting 12- to 19-year-olds from the 1999–2000 and 1988–1994 National Health and Nutrition Examination Survey (NHANES). In the more recent dataset we explored the relationship between metabolic abnormalities and CRP as measured by a high-sensitivity assay.**

Results: **The prevalence of central obesity, low HDL-cholesterol, and hypertension increased between the 2 surveys. Three or more abnormalities (metabolic syndrome) were found in 12.7% [95% confidence interval (CI), 10.0%–15.4%] of fasting adolescents from the 1999–2000 survey, compared with 9.2% (95% CI, 7.8%–10.6%; $P < 0.001$) in the 1988–1994 dataset, with increases also seen in sex and ethnic/racial subgroups. Increases in metabolic syndrome were primarily attributable to increasing body mass index (BMI); prevalence of BMI at or above the 85th percentile increased from 25.9% to 30.5%. Metabolic syndrome was much more prevalent in overweight compared with normal-weight adolescents (38.6% vs 1.4%; $P < 0.001$). Median CRP increased with increasing numbers of metabolic abnormalities and was higher in adolescents with metabolic syndrome than in those without. CRP was higher in adolescents with BMI at or above the 85th percentile than those with normal BMI.**

Conclusions: **Metabolic abnormalities and the metabolic syndrome phenotype are increasingly prevalent in US adolescents, attributable in part to the increasing incidence of overweight. Adolescents with more metabolic abnormalities have higher CRP, which may be an indicator of greater metabolic derangement and future cardiovascular risk.**

Metabolic abnormalities in children have become more prevalent with the epidemic of obesity in childhood and adolescence. Although studies have examined the clustering of metabolic abnormalities *(1–3)*, the metabolic syndrome phenotype continues to be less well understood in children than in adults in terms of criteria, prevalence, and clinical implications. Abnormalities such as overweight, hypertension, and lipid derangements are known to track from childhood to adulthood, and the collected abnormalities may similarly track *(4)*. Adult metabolic syndrome, although the subject of some debate recently, is associated with cardiovascular disease *(5)* and diabetes mellitus *(6)*, and was defined by the Adult Treatment Panel III (ATP III)[4] as 3 or more of the following: hypertriglyceridemia, low HDL-cholesterol, high fasting glucose, excessive waist circumference, and hypertension *(7)*. Recent factor analysis supports this definition *(8)*. Using a definition based closely on ATP III in analyses of the National Health and Nutrition Examination Survey

[1] Department of Cardiology; [2] Department of Medicine, Division of Endocrinology; and [3] Department of Laboratory Medicine and Pathology, Children's Hospital, Boston, MA.

* Address correspondence to this author at: Department of Laboratory Medicine, Children's Hospital, 300 Longwood Ave., Boston, MA 02115. Fax 617-713-4347; e-mail nader.rifai@tch.harvard.edu.

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[4] Nonstandard abbreviations: ATP III, Adult Treatment Panel III; NHANES, National Health and Nutrition Examination Survey; CRP, C-reactive protein; BMI, body mass index; CI, confidence interval; and IQR, interquartile range.

(NHANES) III, we recently reported that 63.4% of US adolescents have at least 1 metabolic abnormality and that nearly 1 in 10 have 3 or more abnormalities consistent with a metabolic syndrome phenotype *(9)*.

C-reactive protein (CRP) is increased in adults with elements of the metabolic syndrome, such as hypertension *(10)* and increased body mass index (BMI) *(11)*, and correlates with triglyceride and HDL-cholesterol concentrations *(12)*. In children, there is less information about CRP concentrations and metabolic syndrome; however, CRP is higher in children with metabolic abnormalities *(13, 14)*. We sought to explore changes over time in the prevalence of the metabolic syndrome phenotype in US adolescents by comparing 2 NHANES datasets, 1999–2000 and 1988–1994. We also evaluated the relationship between metabolic abnormalities, metabolic syndrome, and CRP concentrations in the more recent dataset.

Materials and Methods

NHANES is a national dataset of blood testing and anthropomorphic measurements weighted to represent the population of noninstitutionalized US civilians, not living on Indian reservations, ages 2 years and older *(15, 16)*. It uses a multistage, stratified sampling design. In 1999, NHANES became a continuously enrolling and reporting survey. Our sample was drawn from participants in the surveys ages 12 to 19 years who underwent physical examinations and fasted for at least 8 h before blood testing. Human subjects approval for NHANES was obtained from the CDC. A parent or guardian gave consent for participation, and 12- to 17-year-olds also gave assent.

CRP was measured in the 1999–2000 survey by a high-sensitivity assay (hsCRP), a latex-enhanced nephelometry method (BN II nephelometer; Dade Behring) with a lower limit of detection of 0.1 mg/L. Acceptable day-to-day CVs (4.93%–7.84%) have been reported for this assay in this dataset *(17)*. Participants with CRP concentrations <0.1 mg/L had a value assigned to them of 0.1 mg/L in the 1999–2000 NHANES dataset. The 1988–1994 survey did not use a high-sensitivity CRP assay; the lower limit of detection of that assay was 3.0 mg/L, with values below this cutoff being assigned a value of 2.1 mg/L *(18)*. Both assays are felt to be accurate at CRP concentrations >3.0 mg/L.

statistical methods

Because the NHANES surveys have complex sampling designs, estimates and SEs were calculated in Stata, Ver. 9 (StataCorp), with the sampling weights provided to make prevalence estimates representative of the civilian, noninstitutionalized US population. Sampling weights are adjusted for nonresponse. We calculated the prevalence of individual metabolic abnormalities as well as the metabolic syndrome, as defined previously *(9)*, for the entire sample and according to sex, age group, race or ethnicity, and BMI at or above the 85th percentile for age and sex. Metabolic syndrome was defined as 3 or more of the following: (*a*) fasting triglycerides ≥1.1 mmol/L (100 mg/dL); (*b*) HDL-cholesterol <1.3 mmol/L (50 mg/dL), except in boys 15 to 19 years of age, in whom the cutpoint was <1.2 mmol/L (45 mg/dL); (*c*) fasting glucose ≥6.1 mmol/L (110 mg/dL); (*d*) waist circumference above the 75th percentile for age and sex based on the 1988–1994 NHANES dataset; and (*e*) systolic blood pressure above the 90th percentile for sex, age, and height. The same criteria for metabolic abnormalities were used for both datasets. For estimates of prevalence, adolescents missing information on metabolic criteria were assumed not to have met that criterion to give more conservative estimates of prevalence. BMI percentiles for both datasets were calculated by use of standard CDC data curves. We compared the distributions of these variables in NHANES 1999–2000 with those previously reported in NHANES III (1988–1994), using the χ^2 test, again incorporating the sampling weights.

We calculated the median and interquartile range of CRP for all adolescents with recorded CRP values and by subgroups according to patient characteristics and metabolic abnormalities. Because CRP does not follow a gaussian distribution, we used nonparametric methods for analysis and report percentiles and medians rather than means. CRP concentrations were compared by use of the Wilcoxon rank-sum test for characteristics with 2 categories (e.g., sex and normal BMI vs BMI at or above the 85th percentile) and by use of the Kruskal–Wallis test for those with 3 or more categories (e.g., number of metabolic abnormalities and race or ethnicity). Comparisons were repeated excluding those with CRP >10 mg/L because very high CRP concentrations can indicate inflammatory disorders or infections.

Results

The 1999–2000 dataset included 1527 fasting 12- to 19-year-olds. Low HDL-cholesterol, hypertriglyceridemia, and central obesity remained common, whereas hyperglycemia and hypertension were infrequent, as we found in 1988–1994 (Fig. 1). Prevalence of 3 of the 5 individual metabolic abnormalities increased in the more recent sample compared with 1988–1994, with the greatest increase seen in central obesity. Subgroup analysis by age grouping and sex revealed that changes between the 2 datasets generally were similar to those in the overall group. Notably, the prevalence of hypertriglyceridemia increased in non-Hispanic blacks and Mexican Americans, in contrast to the prevalence in the group overall and in non-Hispanic whites, in whom the prevalence of hypertriglyceridemia decreased (data not shown).

The prevalence of the metabolic syndrome phenotype increased from 9.2% [95% confidence interval (CI), 7.8%–10.6%] to 12.7% (95% CI, 10.0%–15.4%; P <0.001) from NHANES 1988–1994 to 1999–2000 in US adolescents; this represents an increase of 38%. Increases in prevalence estimates of the metabolic syndrome phenotype were

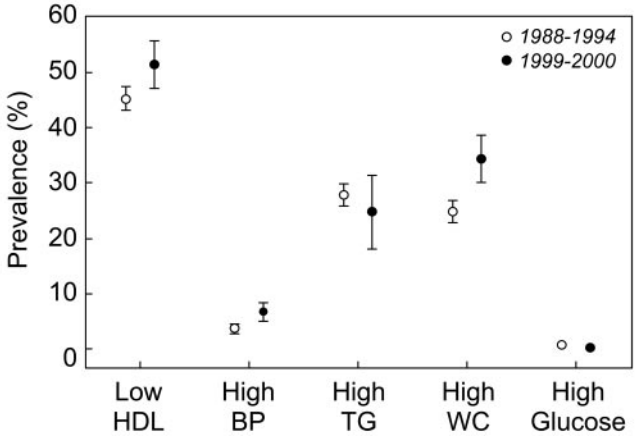

Fig. 1. Estimated prevalence of individual metabolic abnormalities, shown with 95% CIs (*error bars*), in fasting 12- to 19-year-olds.

For each abnormality, estimates from the 1988–1994 dataset are shown on the *left* and estimates from the 1999–2000 NHANES dataset are on the *right*. *High TG*, fasting triglycerides ≥1.1 mmol/L (100 mg/dL); *Low HDL*, HDL-cholesterol <1.3 mmol/L (50 mg/dL), except in boys 15–19 years of age, for whom the cutpoint was <1.2 mmol/L (45 mg/dL); *High glucose*, fasting glucose ≥6.1 mmol/L (110 mg/dL); *High WC*, waist circumference above the 75th percentile for age and sex; *High BP*, systolic blood pressure above the 90th percentile for sex, age, and height. Hyperglycemia prevalence estimates are based on small numbers of participants with small CIs and are less reliable than estimates of other metabolic abnormalities.

seen in subgroups as well (Table 1). The largest increases were seen in non-Hispanic blacks, followed by Mexican Americans. Of note, the prevalence estimate for metabolic syndrome in non-Hispanic blacks was based on a small number of participants and may appear artificially low in the 1988–1994 survey. Analysis of ethnic/racial subgroups by sex revealed similar changes for males and females (data not shown).

As has been reported in the past *(19)*, CRP did not follow a gaussian distribution but was skewed, with lower values being more common. Median CRP for those 1471 adolescents with recorded CRP values was 0.5 mg/L [interquartile range (IQR), 0.1–1.6 mg/L]. Girls had slightly higher median CRP than boys (0.5 vs 0.4 mg/L; $P = 0.01$) and Mexican Americans had higher CRP than other racial/ethnic subgroups (0.8 vs 0.4–0.5 mg/L; $P < 0.0001$). Median CRP increased with older age, from 0.3 mg/L in 12- to 13-year-olds to 0.7 mg/L in 18- to 19-year-olds ($P < 0.0001$). Median CRP was higher in children with individual metabolic abnormalities compared with adolescents without those metabolic abnormalities, although the IQRs overlapped (Fig. 2; $P < 0.0001$); the number of children with hyperglycemia and measured CRP was too small to allow reliable calculations. Median CRP concentrations increased incrementally by the number of metabolic abnormalities (Fig. 3; $P < 0.0001$). The results were similar in analyses excluding those with CRP >10 mg/L.

Of fasting adolescents 12–19 years of age in the NHANES 1999–2000 survey, 30.5% had a BMI at or above the 85th percentile. This represents an increase of 18% from NHANES 1988–1994, in which the prevalence of high BMI was 25.9%, consistent with previous reports *(20, 21)*. Consistent with previous reports *(3)*, the metabolic syndrome phenotype was highly prevalent in the overweight adolescents (found in more than one third) and rare in teens with normal BMI (Table 1). As expected from previous research *(22)*, CRP was higher in adolescents with BMI at or above the 85th percentile compared with those with normal BMI: median, 1.6 mg/L (IQR, 0.6–3.9 mg/L) vs 0.3 mg/L (0.1–0.7 mg/L); $P < 0.0001$. In the subgroups with 0, 1, and 2 metabolic abnormalities, median CRP was higher in those with high BMI than in those with normal BMI. Only 12 individuals in the sample had both a normal BMI and 3 or more metabolic abnormalities. Median CRP was higher for these normal-weight adolescents with metabolic syndrome than for the 201 adolescents with high BMI and 3 or more abnormalities [2.1 mg/L (IQR, 1.3–6.1 mg/L) vs 1.6 mg/L (0.9–3.3 mg/L); $P < 0.0001$].

Table 1. Metabolic syndrome phenotype prevalence estimates from the NHANES 1988–1994 and 1999–2000 datasets.[a]

	1988–1994		1999–2000	
	No. in sample	Prevalence of MetS[b] (95% CI)	No. in sample	Prevalence of MetS (95% CI)
Total	1960	9.2 (7.8–10.6)	1527	12.7 (10.0–15.4)
Male	891	9.5 (7.5–11.5)	775	13.8 (10.3–17.2)
Female	1069	8.9 (7.1–10.7)	752	11.6 (8.3–14.9)
12–15 years	978	10.3 (8.3–12.3)	781	13.6 (10.4–16.8)
16–19 years	982	8.3 (6.5–10.1)	746	11.9 (8.3–15.5)
Non-Hispanic white	520	10.9 (8.4–13.4)	313	12.5 (8.1–16.9)
Non-Hispanic black	657	2.5 (1.3–3.7)[c]	383	10.2 (6.4–14.0)
Mexican American	688	12.9 (10.4–15.4)	692	16.9 (15.1–18.6)
BMI <85th percentile	1350	1.5 (0.7–2.3)[c]	931	1.4 (0.5–2.2)[c]
BMI ≥85th percentile	584	31.2 (28.3–34.1)	590	38.6 (32.9–44.4)

[a] The unweighted number of participants included in each subset analysis is noted for both surveys; sample size varied because some participants were missing race/ethnicity and BMI. All comparisons, $P < 0.001$.

[b] MetS, metabolic syndrome phenotype.

[c] Estimate may be unreliable because of small sample size.

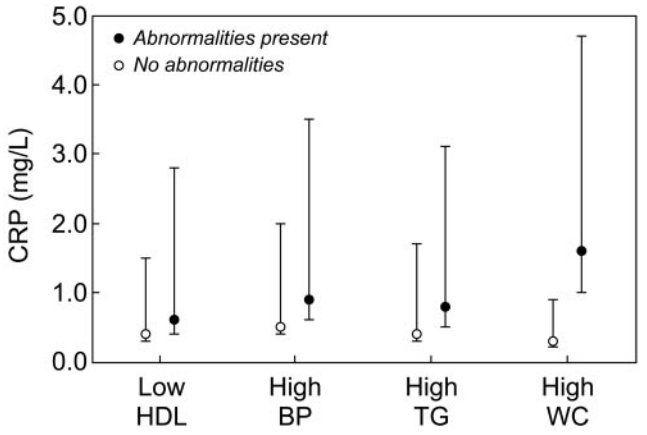

Fig. 2. Median (IQR; *error bars*) CRP (mg/L) of children with and without metabolic abnormalities in the 1999–2000 NHANES dataset.

For all abnormalities, median CRP differed between the 2 groups ($P < 0.0001$). *High TG*, fasting triglycerides ≥1.1 mmol/L (100 mg/dL); *Low HDL*, HDL-cholesterol <1.3 mmol/L (50 mg/dL), except in boys 15–19 years of age, in whom the cutpoint was <1.2 mmol/L (45 mg/dL); *High WC*, waist circumference above the 75th percentile for age and sex; *High BP*, systolic blood pressure above the 90th percentile for sex, age, and height. Hyperglycemia is not shown because the small number of cases with this abnormality makes the estimates unreliable.

Discussion

We found increases in most individual metabolic abnormalities and a significant and concerning increase of 38% in the prevalence of an adolescent metabolic syndrome phenotype between the 1988–1994 and 1999–2000 NHANES surveys. Particularly alarming was the change in central obesity from 25% to 34% of 12- to 19-year-olds, which likely played a central role in the increase in the metabolic syndrome overall. Also concerning, if confirmed, would be the tripling in the prevalence of the metabolic syndrome phenotype in non-Hispanic blacks; this finding may be an artifact because of small sample size and should be reevaluated in other studies with a larger sample size. Median CRP concentrations were higher for adolescents with the metabolic syndrome phenotype than in those without it, and CRP increased with greater numbers of metabolic abnormalities in the group overall and in overweight youth, supporting an association between metabolic syndrome and CRP in the pediatric age range. In overweight children with metabolic syndrome, CRP concentrations were higher than in overweight children without metabolic syndrome, suggesting that the combination of metabolic abnormalities has a greater effect on inflammation than weight alone. The few with normal weight who had metabolic syndrome had higher CRP concentrations than those who were overweight and had metabolic syndrome, leading one to suspect that they represent a different disease group, perhaps one worthy of further investigation.

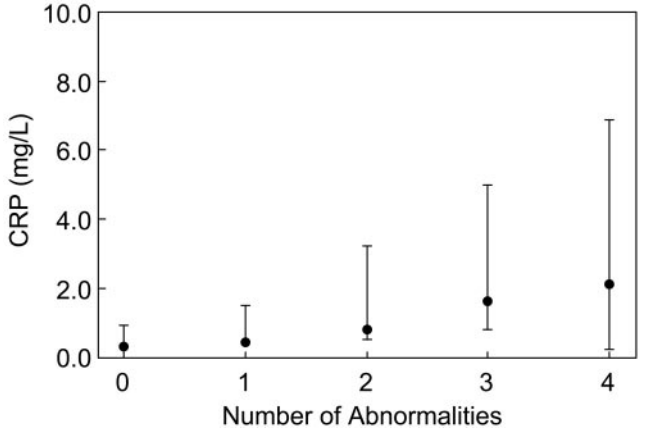

Fig. 3. Median (IQR; *error bars*) CRP (mg/L) by number of metabolic abnormalities in the 1999–2000 NHANES dataset (significant difference in CRP between groups, $P < 0.0001$).

No participants had all 5 metabolic abnormalities.

Previous studies have also reported that CRP concentrations in children are associated with individual components of the metabolic syndrome *(1, 13, 14)*. The relationship with obesity is particularly well documented *(14, 18, 22–25)*. Higher blood pressure and dyslipidemias are also correlated with CRP in some reports, whereas the relationship between CRP and insulin resistance in children is less clear *(13, 19, 22, 26, 27)*. Our findings were also consistent with reports of CRP concentrations in children from the 1999–2000 NHANES database, including findings that CRP is higher in girls compared with boys, in Mexican Americans compared with non-Hispanic whites, and in overweight adolescents compared with normal-weight adolescents *(28)*.

Addressing an issue that has been less well investigated in children, we evaluated the relationship between a metabolic syndrome phenotype and CRP concentrations. Weiss et al. *(27)* found no relationship between CRP and a metabolic syndrome phenotype in obese children; however, they studied a selected referral population with a higher rate of overweight, and used a more restrictive definition of metabolic syndrome than ours, which we based on the ATP III definition for adults. Ford et al. *(17)* examined mean (not median) CRP concentrations in adolescents with metabolic syndrome who had fasted >6 h; however, they used a less restrictive definition with lower HDL-cholesterol, higher triglyceride, and higher waist circumference cutpoints than ATP III and did not address changes in the CRP concentration with increasing numbers of metabolic abnormalities.

Previous research has demonstrated that individual components of the metabolic syndrome track from childhood to adulthood, suggesting that metabolic syndrome might also track into adulthood *(4)*. In fact, childhood obesity predicts the development of metabolic syndrome in adulthood, lending credence to the theory that excess adipose tissue is an initiating event for the metabolic syndrome *(29)*. However, it is unknown whether CRP concentrations track from childhood to adulthood. Furthermore, the long-term cardiovascular risks of increased CRP in childhood, as well as clinically useful cutpoints for CRP in pediatrics, are unknown. In adults, metabolic

syndrome and CRP are correlated and predict worse cardiovascular outcomes. Lee et al. *(30)* reported that CRP increased incrementally with greater numbers of metabolic abnormalities in adult men and women. The Women's Health Study showed that CRP correlated with metabolic syndrome, and the risk of cardiovascular disease events doubled in women with metabolic syndrome and CRP >3.0 mg/L compared with women with metabolic syndrome and CRP <3.0 mg/L *(31)*. In the West of Scotland Coronary Prevention Study, CRP was higher in men with metabolic syndrome and was an independent predictor of cardiovascular disease and diabetes in multivariate analyses *(32)*. Our findings of the association between metabolic syndrome and CRP in children are consistent with research in adults.

There are several limitations to our findings. The primary limitation is the use of a single CRP measurement. In adults, repeat CRP measurements are recommended, as concentrations are affected by multiple factors, including recent infections and inflammatory conditions *(33)*. These factors, perhaps more common in children who have frequent minor illnesses, are partially offset by the lower rate of chronic disease in children. We attempted to evaluate whether this was a significant confounder by repeating the analysis after excluding those with CRP >10 mg/L, who might have had acute infections or chronic inflammatory conditions, and our findings were not significantly changed. A second limitation is that study outcomes depend on the definition of metabolic syndrome, a problem inherent to any extrapolation of the adult definition to a pediatric population. There is no agreed on definition of metabolic syndrome in children. The cutpoints used for our definition were extrapolated from those used in adults; they could not be based on cardiovascular outcomes because of the young age of our population. However, the same definition was used in both datasets, allowing valid comparisons between the two, showing increases in the prevalence of metabolic abnormalities and the metabolic syndrome phenotype as we have defined them. Future studies should examine CRP in children with metabolic syndrome, as it relates to measures of preclinical disease, such as endothelial function. A third limitation was our inability to evaluate detailed changes in CRP between the 2 surveys because a high-sensitivity CRP assay was not used in the earlier survey. Although the more sensitive assay was not used in the earlier dataset, there is evidence to support an increase in CRP concentrations over that time period. In the earlier survey, 8.3% of 12- to 19-year-olds had a CRP >3.0 mg/L; in the later survey, 11.0% of adolescents had CRP >3.0 mg/L. Although the assay used in the earlier dataset does not detect CRP <3.0 mg/L, it is thought to be accurate for CRP concentrations ≥3.0 mg/L *(18)*. The assays used by the 2 surveys have different limits of detection; however, both used reagents and instruments from the same manufacturer (Dade Behring), and both are calibrated against CRM 470, the international standard for calibration of proteins. Another limitation is that, for participants missing data, we assumed they did not meet that criterion for a metabolic abnormality. This may have caused us to underestimate the prevalence of the metabolic syndrome; however, we followed the same procedure in both datasets, allowing us to demonstrate increases in prevalence between the 2 time periods with consistency. Finally, although NHANES is highly representative of most of the US population, the dataset did not include those living on American Indian reservations. The rates of obesity and diabetes mellitus type 2 are particularly high in some American Indian populations *(34)*, who therefore are likely to have higher rates of metabolic syndrome.

In summary, we found that CRP is increased in adolescents with metabolic abnormalities and the metabolic syndrome phenotype in a manner consistent with the association documented previously in adults. The prevalence of metabolic syndrome has increased, in large part related to the increase in central obesity in adolescents. The impact of these data may be far-reaching, given the association between CRP, metabolic syndrome and cardiovascular disease *(31, 32)*, and metabolic syndrome and diabetes mellitus type 2 *(5)*. Pediatric practitioners should be aware of the clustering of metabolic abnormalities, particularly in overweight children, and public health efforts should target those affected children for risk-reducing lifestyle changes such as weight loss, exercise, and dietary modifications. Future studies should explore whether CRP concentrations have a role in clinical management and assessment of cardiovascular risk in the pediatric population.

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