Low-Grade Systemic Inflammation in Overweight Children

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ABSTRACT. *Objective.* **Human adipose tissue expresses and releases the proinflammatory cytokine interleukin-6, potentially inducing low-grade systemic inflammation in persons with excess body fat. To limit potential confounding by inflammation-related diseases and subclinical cardiovascular disease, we tested the hypothesis that overweight is associated with low-grade systemic inflammation in children.**

Design and Setting. **The third National Health and Nutrition Examination Survey, 1988–1994, a representative sample of the US population.**

Participants. **A total of 3512 children 8 to 16 years of age.**

Outcome Measures. **Elevated serum C-reactive protein concentration (CRP; ≥.22 mg/dL) and white blood cell count (10^9 cells/L).**

Results. **Elevated CRP was present in 7.1% of the boys and 6.1% of the girls. Overweight children (defined as having a body mass index or a sum of 3 skinfolds (triceps, subscapula, and supra-iliac) above the gender-specific 85th percentile) were more likely to have elevated CRP than were their normal-weight counterparts. After adjustment for potential confounders, including smoking and health status, the odds ratio (OR) was 3.74 (95% confidence interval [CI]: 1.66–8.43) for overweight boys and the OR was 3.17 (95% CI: 1.60–6.28) for overweight girls, based on the body mass index. Based on the sum of 3 skinfolds, these ORs were 5.11 (95% CI: 2.36–11.06) and 2.89 (95% CI: 1.49–5.59) for boys and girls, respectively. Overweight was also associated with statistically significant higher white blood cell counts. The results were similar when restricted to healthy, nonsmoking, nonestrogen-using children.**

Conclusions. **In children 8 to 16 years of age, overweight is associated with higher CRP concentrations and higher white blood cell counts. These findings suggest a state of low-grade systemic inflammation in overweight children.** *Pediatrics* **2001;107(1). URL: http://www.pediatrics.org/cgi/content/full/107/1/e13; *inflammation, obesity, children.***

ABBREVIATIONS. CRP, C-reactive protein; BMI, body mass index; NHANES III, third National Health and Nutrition Examination Survey; OR, odds ratio; CI, confidence interval; SD, standard deviation; SE, standard error.

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C-reactive protein (CRP) is an acute-phase protein and a sensitive marker for systemic inflammation. In a recent meta-analysis of 7 prospective studies, elevated serum CRP concentration has been shown to predict future risk of coronary heart disease.[1] CRP concentrations well below the conventional clinical upper limit of normal of 1 mg/dL have been associated with a twofold to threefold increase in risk of myocardial infarction, ischemic stroke, peripheral arterial disease, and coronary heart disease mortality in healthy men and women.[2–6] These findings demonstrate the potential detrimental consequences of elevated CRP concentrations on health.

Several factors are known to increase CRP concentrations. Smoking[7–9] and hormone replacement therapy[10,11] have been associated with elevated CRP concentration in middle-aged and elderly persons. In addition, several inflammation-related diseases, such as respiratory disease,[8] rheumatoid arthritis,[12] diabetes mellitus,[9,13,14] and (subclinical) cardiovascular disease,[9] have been associated with elevated CRP concentrations. Moreover, recent studies have reported a positive relationship between body mass index (BMI) and CRP concentrations.[5,8,9,15–18]

The elevated CRP concentrations in overweight persons might be explained by the expression of the cytokine interleukin-6 in adipose tissue[19–21] and its release into the circulation.[21,22] Interleukin-6 is a proinflammatory cytokine that stimulates the production of acute-phase proteins, including CRP, in the liver.[23,24] Higher adipose tissue content of interleukin-6 has been associated with higher serum CRP concentrations in obese persons.[25] The release of interleukin-6 from adipose tissue may induce elevated CRP concentrations in persons with excess body fat.

Previous studies investigating the association between body fatness and CRP were primarily conducted in middle-aged and elderly adults in whom the observed association may have been confounded by disease. Rheumatoid arthritis, diabetes mellitus, and cardiovascular disease are prevalent diseases in older adults and are clearly associated with both obesity[26–28] and increased CRP concentrations.[1,8,12,13,16] To limit the potential confounding by inflammation-related diseases and subclinical cardiovascular disease, we investigated the association between overweight and systemic inflammation in children.

This study tested the hypothesis that overweight is associated with low-grade systemic inflammation as

measured by serum CRP concentration and white blood cell count. The study population included 3512 children 8 to 16 years of age who were participants of the third National Health and Nutrition Examination Survey (NHANES III), 1988–1994, a representative sample of the US population.

METHODS

Survey Design

NHANES III was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention.[29] The survey had a complex, stratified, multistage, probability-cluster design for selecting a sample of ~40 000 persons representative of the noninstitutionalized civilian population of the United States. Children <5 years of age, persons 60 years of age and older, Mexican Americans, and non-Hispanic blacks were sampled at higher rates than were other persons. Eighty-seven percent of all eligible children 8 to 16 years of age were interviewed in their household, of whom 5065 (81%) were subsequently examined in a mobile examination center (n = 5052) or in their homes (n = 13). Of the 4018 children who had complete data on anthropometry, 506 children were excluded from the statistical analyses because of missing data on serum CRP concentration or white blood cell count. A total of 3512 children (1725 boys and 1787 girls) were available for the statistical analyses.

Anthropometry

Body weight and height were measured using standardized procedures previously described.[30] BMI was calculated as weight in kilograms divided by height in meters squared and used as an indicator of total body fat.[31–33] Skinfolds were measured on the right side of the body using a Holtain T/W skinfold caliper (Holtain Ltd., Crymych, UK) and recorded to the nearest .1 mm. The triceps skinfold, subscapular skinfold, and the supra-iliac skinfold were measured using standardized procedures and locations.[30] The sum of 3 skinfolds was calculated and used as an indicator of subcutaneous body fat.

Children were considered overweight when they had a BMI or a sum of 3 skinfolds above the gender-specific 85th percentile, as proposed by a consensus conference.[34] The cutpoints for overweight were created based on the 85th percentile of the total population of boys and girls 8 to 16 years of age included in the NHANES III study (n = 4220 for BMI and n = 4042 for the sum of 3 skinfolds). The cutpoints for the BMI were >23.66 kg/m^2 for boys and >24.52 kg/m^2 for girls. The cutpoints for the sum of 3 skinfolds were >56.90 mm for boys and >68.27 mm for girls.

Inflammation Markers

Serum CRP

Serum specimens for the measurement of CRP were shipped on dry ice to the laboratory, stored at -70°C, and analyzed within 2 months after phlebotomy. CRP was analyzed using a modification of the Behring Latex-Enhanced CRP assay on the Behring Nephelometer Analyzer System (Behring Diagnostics, Westwood MA).[35] Both within-assay and between-assay quality control procedures were used and the coefficient of variation of the method was 3.2% to 16.1% through the period of data collection. The assay was designed primarily to detect inflammation in patients, and it was included as part of the NHANES III cohort originally to help detect inflammation as a confounding variable for interpretation of nutrition markers. The assay could detect a minimal concentration of .22 mg/dL, and values below this level were classified as undetectable. Because a majority of individuals had values less than the minimal detectable concentration, in this analysis CRP is treated as a categorical rather than as a continuous variable. The population was divided into 2 categories based on CRP concentration: undetectable (<.22 mg/dL) and elevated (≥.22 mg/dL).

White Blood Cell Count

White blood cell count was assessed using a quantitative, automated hematology analyzer (Coulter Counter Model S-PLUS JR [Beckman Coulter Inc., Fullerton, CA]).[36] Lower detection limit was .4 (10^9 cells/L). Both within-assay and between-assay quality control procedures were used, and the coefficient of variation of the method was <3.0% through the period of data collection. White blood cell count was used as a continuous variable in the analyses.

Potential Confounders and Effect Modifiers

Race and disease prevalence were based on proxy report, usually by the mother or father of the child (95.1%). Race was defined as non-Hispanic white, non-Hispanic black, Mexican American, or other. Respiratory disease prevalence was determined through report of physician-diagnosed chronic bronchitis or asthma or report of having a cold in the past few days. Other diseases included physician-diagnosed cardiovascular disease including hypertension, high cholesterol or rheumatic heart disease, or diabetes mellitus defined as current use of blood glucose regulators. Smoking status was based on self-report and categorized as never and former/current smoking. In children 12 years of age and older, serum cotinine concentration was measured by high-performance liquid chromatography and atmospheric pressure chemical ionization tandem mass spectroscopy.[37] Children with a serum cotinine concentration >10 ng/mL[38] were categorized as former/current smokers, regardless of self-report. Estrogen use was based on self-report and included oral contraceptive medications and implants. The stage of sexual maturation was assessed during the physical examination using the criteria of Tanner.[39] Children were categorized into prepubertal (Tanner stage < 5) and postpubertal (Tanner stage = 5).

Statistical Analyses

Two outcome variables were defined: elevated CRP concentration (≥.22 mg/dL), which was contrasted with undetectable CRP, and white blood cell count, which was used as a continuous variable. Within each gender, the relationship between overweight and CRP concentration category was examined by means of multiple logistic regression analysis. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for the BMI as a categorical variable with normal weight (BMI equal or below gender-specific 85th percentile) as the reference category and for BMI as a continuous variable, expressed per 4 kg/m^2 (~1 standard deviation [SD]) increment. Similar analyses were performed for the sum of 3 skinfolds using an increment of 23.0 mm, corresponding to the SD. Within each gender the relationship between overweight and white blood cell count was examined using linear regression analyses, with BMI or the sum of 3 skinfolds as a categorical variable (1 = above gender-specific 85th percentile, 2 = equal or below gender-specific 85th percentile) and as a continuous variable, expressed per SD increment. Adjustments were made for potential confounders, including age, race, smoking status, sexual maturation stage, estrogen use (girls only), respiratory disease, and other diseases shown to be associated with low-grade inflammation in adults. Racial differences in the association between overweight and inflammation status were assessed in analyses stratified by gender and race and were tested by using product terms. To assess potential effect modification by smoking status, disease status, or estrogen use, the analyses were repeated restricted to healthy, never smokers among boys and girls, with an additional exclusion of estrogen users among girls. Analyses were performed using SAS (SAS Institute, Inc, Cary, NC) and SUDAAN (Research Triangle Institute, Research Triangle Park, NC) and incorporated sampling weights to account for oversampling and nonresponse to the household interview and examination.[36] Variance estimates were calculated with SUDAAN, incorporating the complex sampling design of NHANES III.[36]

RESULTS

Elevated CRP (≥.22 mg/dL) was present in 7.6% of the boys and 6.1% of the girls. Mean white blood cell count was 7.1 × 10^9/L (standard error [SE]: .1) for boys and 7.3 × 10^9/L (SE: .1) for girls. Other characteristics of the study population are shown in Table 1.

The relationship of BMI category or skinfolds category with the prevalence of elevated CRP concentration is shown in Fig 1. A higher prevalence of

TABLE 1. Characteristics of the Study Population: NHANES III, 1988–1994

	Boys (n = 1725)	Girls (n = 1787)
Age (y)	12.0 (.1)*	12.0 (.1)
BMI (kg/m^2)	19.7 (.1)	20.1 (.2)
Triceps skinfold (mm)	11.8 (.2)	15.8 (.3)
Subscapula skinfold (mm)	9.6 (.2)	12.7 (.4)
Supra-iliac skinfold (mm)	12.4 (.3)	14.8 (.5)
Sum of 3 skinfolds (mm)	33.8 (.7)	43.3 (1.1)
White blood cell count (10^9/L)	7.1 (.1)	7.3 (.1)
Elevated CRP (≥.22 mg/dL)	7.6	7.7
Former/current smoking	7.1	6.1
Respiratory disease		
Current cold	20.5	20.2
Asthma†	8.2	7.9
Chronic bronchitis†	2.7	1.6
Other disease		
Hypertension†	.1	.1
High cholesterol†	.2	.1
Rheumatic heart disease†	.3	.0
Diabetes	.3	.1
Postpubertal (Tanner stage = 5)	21.3	25.4
Estrogen use (oral contraceptives or implants)	—	2.3

* Data are percentages or means (standard error).
† Based on self-report of physician-diagnosed disease.

elevated CRP concentration was observed in boys and girls with a BMI or sum of 3 skinfolds above the gender-specific 85th percentile, the proposed cut-point for overweight in children. Based on BMI, an elevated CRP concentration was observed among 20.6% and 18.7% of the overweight boys and girls, respectively. Based on the sum of 3 skinfolds, these percentages were 19.8% and 16.1%, respectively. The prevalence of elevated serum CRP concentration among overweight children (category 5, Fig 1) was higher compared with the prevalence at all other categories, the only exception being the difference between category 5 and category 4 of the sum of 3 skinfolds in girls (P = .2). In boys and girls, the prevalence of elevated serum CRP concentration did not differ among categories 1 to 4. These results could be interpreted as a threshold effect in the association between overweight and elevated serum CRP concentration.

Based on BMI—after adjustment for potential confounders including age, race, smoking, respiratory and cardiovascular disease, diabetes mellitus, sexual maturation stage, and estrogen use (girls only)—overweight boys were 3.74 and overweight girls were 3.17 times more likely to have elevated CRP, compared with their normal weight counterparts (Table 2). Based on the sum of 3 skinfolds these numbers were 5.11 and 2.89 for boys and girls, respectively. Per 1 SD increase in BMI, boys were 1.65 and girls were 1.60 times more likely to have elevated CRP. Per 1 SD in the sum of 3 skinfolds, these numbers were 1.68 and 1.61. In addition, overweight boys and girls had higher white blood cell counts than did normal weight children (Table 2). No effect modification by race was observed ($P > .12$).

To avoid any potential effect modification by disease, smoking, or estrogen use, the analyses were repeated restricted to 2419 healthy, never-smoking, nonestrogen-using children. The positive association between overweight and elevated CRP remained statistically significant after adjustment for age, race, and sexual maturation stage (Table 3). Similar results were observed for white blood cell count.

DISCUSSION

In this study we observed a higher prevalence of elevated CRP concentration in overweight children compared with normal weight children, even after carefully controlling for disease and other factors known to influence CRP concentrations. Being overweight was also associated with a higher white blood cell count, confirming the presence of low-grade systemic inflammation. A positive association between BMI and CRP concentration has been repeatedly observed in adults.[5,8,9,15–18] Our study extends these important findings to children in whom the prevalence of any confounding subclinical disease is very low.

Overweight at young age is associated with dyslipidemia[42,43] and insulin resistance.[44,45] Prospective studies have shown that overweight in childhood is an important determinant of overweight in adulthood.[46–48] Moreover, childhood overweight is associated with the metabolic syndrome in adulthood, independent of adult weight,[49] and is a more powerful predictor of cardiovascular morbidity and mortality than is overweight in adulthood.[50] The prevention and management of childhood overweight is important to reduce these potential health risks.

To our knowledge, this is the first study reporting an association between childhood overweight and inflammation. Although the health effects of low-grade systemic inflammation in children are unknown, in healthy adults it has been shown to increase the risk for cardiovascular disease and diabetes mellitus.[2–6,51] Moreover, CRP induces the production of tissue factor, a potent procoagulant, in monocytes.[52] Because of the reported adverse health effects of systemic inflammation in adults, the inflammation observed in overweight children may be an additional risk factor for future disease. Whether the low-grade systemic inflammation in overweight children might partly explain their increased risk for cardiovascular disease and diabetes mellitus in adulthood is unknown. More information is needed about the long-term health impact of inflammation and other adipose tissue-related factors, such as plasma levels of plasminogen activator inhibitor type 1, fibrinogen, and factor VII[53] in overweight children.

The BMI is a clinical indicator of overweight in adults.[40] Its use as an indicator of overweight in children is still being discussed.[41] Therefore, we used 2 anthropometric measures of body fat in the study: the BMI as an indicator of overall body fat, including the visceral fat depots, and the sum of 3 skinfolds as an indicator of subcutaneous body fat. Classification of overweight using the BMI or using the sum of 3 skinfolds consistently showed a higher prevalence of low-grade systemic inflammation in overweight children.

Two potential limitations regarding the assessment of elevated serum CRP concentration should be discussed. First, in this study we used a single CRP

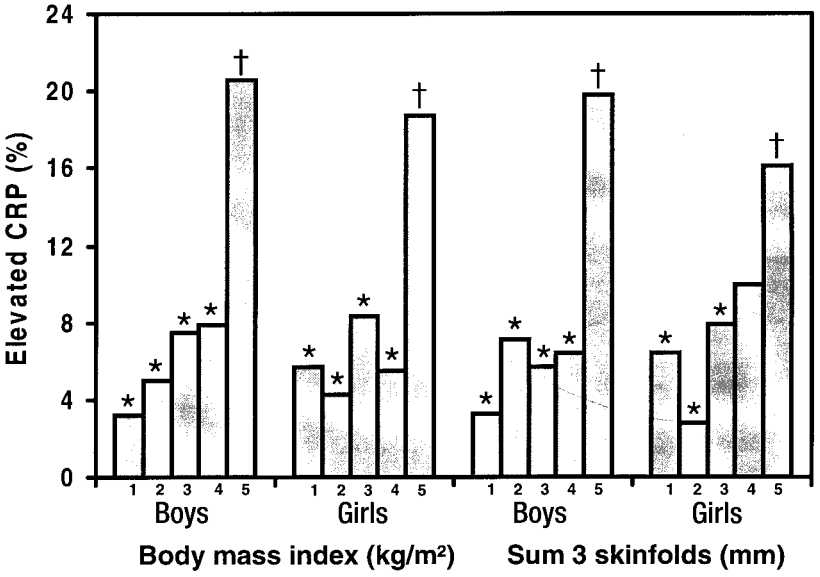

Fig 1. Prevalence of elevated (≥.22 mg/dL) serum CRP concentration by categories of BMI and sum of 3 skinfolds (triceps, subscapula, and supra-iliac skinfold) in 3512 children 8 to 16 years of age, NHANES III, 1988–1994. The categories were defined according to percentiles of the distribution: æ25th percentile = 1; 25.1–50th = 2; 50.1- 75th = 3; 75.1–85 = 4; and >85th = 5 = overweight. *$P < .05$ versus highest category; †$P < .05$ versus lowest category.

TABLE 2. Adjusted OR (With 95% CI) for Elevated Serum CRP Concentration and Adjusted Mean White Blood Cell Counts (With SE) in 3512 Children 8 to 16 years of Age, According to BMI or Sum of Three Skinfolds: NHANES III, 1988–1994

	Boys (n = 1725)	Girls (n = 1787)
Elevated CRP (≥.22 mg/dL)*	OR (95% CI)	OR (95% CI)
BMI (kg/m²)		
>85th vs ≤85th percentiles	3.74 (1.66–8.43)	3.17 (1.60–6.28)
Per 1 SD increment	1.65 (1.26–2.16)	1.60 (1.25–2.05)
Sum 3 skinfolds (mm)†		
>85th vs ≤85th percentiles	5.11 (2.36–11.06)	2.89 (1.49–5.59)
Per 1 SD increment	1.68 (1.26–2.22)	1.61 (1.19–2.16)
White blood cell count (10^9/L)*		
	Mean (SE)	Mean (SE)
BMI (kg/m²)		
≤85th percentile	6.99 (.08)	7.16 (.09)
>85th percentile	7.57 (.20)‡	8.31 (.30)‡
Per 1 SD increment	.39 (.09)§	.37 (0.09)§
Sum 3 skinfolds (mm)†		
≤85th percentile	6.93 (.07)	7.18 (.09)
>85th percentile	7.85 (.20)‡	8.07 (.29)‡
Per 1 SD increment	.38 (.08)§	.40 (.12)§

* Adjusted for age, race, smoking, respiratory and cardiovascular disease, diabetes mellitus, sexual maturation stage, and estrogen use (girls only).
† Sum of triceps, subscapula and supra-iliac skinfold.
‡ $P < .05$ versus ≤85th percentile.
§ $P < .05$.

TABLE 3. Adjusted OR (With 95% CI) for Elevated Serum CRP Concentration and Adjusted Mean White Blood Cell Counts (With SE) in 2419 Healthy, Never Smoking, Nonestrogen-Using Children 8 to 16 Years of Age, according to BMI or Sum of Three Skinfolds, NHANES III, 1988–1994

	Boys (n = 1178)	Girls (n = 1241)
Elevated CRP (≥.22 mg/dL)*	OR (95% CI)	OR (95% CI)
BMI (kg/m²)		
>85th vs ≤85th percentile	8.03 (2.43–26.50)	6.71 (2.86–15.75)
Per 1 SD increment	2.42 (1.55–3.78)	2.03 (1.41–2.90)
Sum 3 skinfolds (mm)†		
>85th vs ≤85th percentiles	12.68 (4.62–34.83)	5.67 (2.39–13.42)
Per 1 SD increment	2.74 (1.8–4.09)	2.02 (1.25–3.25)
White blood cell count (10^9/L)*		
	Mean (SE)	Mean (SE)
BMI (kg/m²)		
≤85th percentile	6.82 (.11)	7.13 (.09)
>85th percentile	7.21 (.24)	8.43 (.35)‡
Per 1 SD increment	.42 (.10)§	.34 (.09)§
Sum 3 skinfolds (mm)†		
≤85th percentile	6.77 (.11)	7.16 (.09)
>85th percentile	7.49 (.20)‡	7.93 (.31)‡
Per 1 SD increment	.36 (.09)§	.38 (.11)§

* Adjusted for age, race, and sexual maturation stage.
† Sum of triceps, subscapula and supra-iliac skinfold.
‡ $P < .05$ versus ≤85th percentile.
§ $P < .05$.

measurement, which may not accurately reflect long-term inflammation status. The biological variability of CRP is substantial, with reported values ranging between 10.6% and 63.0%.[54–57] However, because random misclassification caused by biological variability will lead to underestimation of true associations, this limitation is unlikely to explain the study findings. Second, the definition of elevated serum CRP concentration was based on the detection level of the CRP assay. The conventional cutpoint for elevated CRP concentration (a concentration >1 mg/dL) was not used because the prevalence of elevated serum CRP concentration using this criteria was too low (only 1.6% in boys and 1.8% in girls) to be used as the study outcome. However, when the analyses were repeated using the 95th percentile of serum CRP concentration as the cutpoint for elevated CRP (4–11 years of age: >.37 mg/dL for boys and >.68 mg/dL for girls, and for 12–19 years of age: >.65 mg/dL for boys and >.67 mg/dL for girls),[35] similar results were obtained. For example, among healthy, nonsmoking, nonestrogen-using children, overweight boys were 6.12 (95% CI: 1.23–30.52) and 7.11 (95% CI: 2.52–20.06) times more likely to have an elevated CRP concentration based on the BMI and the sum of 3 skinfolds, respectively. For overweight girls these numbers were 5.59 (95% CI: 2.20–14.22) and 3.77 (95% CI: 1.42–9.99), respectively. Thus, using a more extreme cutpoint to define elevated CRP in children did not change the conclusions of the study.

Measurements of the serum concentration of interleukin-6 were not available in the present study. Although the results support the hypothesis that interleukin-6 produced by adipocytes increases CRP concentration, direct assessment of interleukin-6 concentration is needed in future studies to further test this hypothesis.

CONCLUSION

The results of this large-scale cross-sectional study show that overweight is associated with higher CRP concentrations and higher white blood cells counts in children, which could not be explained by disease or other factors associated with inflammation. In children, subclinical disease is unlikely to explain these findings. These data suggest a state of low-grade systemic inflammation in overweight children.

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