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ELEVATED BLOOD PRESSURE, RACE/ETHNICITY, AND C-REACTIVE PROTEIN IN CHILDREN AND ADOLESCENTS

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Abstract

Objective—Adult hypertension is independently associated with elevated C-reactive protein (CRP) after controlling for obesity and other cardiovascular risk factors. The objective of the current study was to determine in a nationally representative sample of children whether the relationship between elevated blood pressure and CRP may be evident prior to adulthood.

Patients and Methods—Cross-sectional data for children 8 to 17 years who participated in NHANES from 1999 to 2004 were analyzed. Bivariate analysis compared children with CRP > 3 mg/L to those with CRP ≤ 3 mg/L for BP and other cardiovascular risk factors. Multiple linear regression was used to evaluate the relation between elevated BP and CRP.

Results—Among 6112 children, 3% had systolic BP ≥ 95th percentile and 1.3% had diastolic BP ≥ 95th percentile. Children with CRP > 3 mg/L had higher SBP compared to children with CRP ≤ 3 mg/L (109 mm vs 105 mm Hg, $p < 0.001$). Obesity, HDL cholesterol < 40 mg/dl, and Hispanic ethnicity were independent predictors of elevated CRP. Diastolic BP did not differ between groups. Linear regression showed that SBP ≥ 95th percentile was independently associated with CRP in males ($p = 0.018$), but not females ($p = 0.94$). Subset analysis by race/ethnicity demonstrated that the independent association of elevated SBP with CRP to be largely limited to Black males ($p = 0.01$).

Conclusions—These data indicate that there is interplay between race/ethnicity, elevated SBP, obesity, and inflammation in children, a finding that has potential implications for disparities in cardiovascular disease later in life.

Keywords

C-reactive protein; inflammation; ethnicity; hypertension; NHANES

INTRODUCTION

C-reactive protein (CRP) is a nonspecific marker of systemic inflammation.^{1,2} There is evidence that chronic inflammation plays a role in the pathogenesis of atherosclerosis and modest elevations of high sensitivity CRP (> 3 mg/L) may therefore be useful as a marker of increased risk for atherosclerotic diseases.^{2,3} In adults, elevated CRP and elevated blood pressure (BP) are both independent determinants of cardiovascular risk. Furthermore, elevated BP is itself an independent predictor of increased CRP, leading to the hypothesis that adult hypertension leads to atherosclerosis, in part, via chronic inflammation.^{4–10}

Both autopsy studies and clinical studies suggest that atherosclerosis can develop during adolescence and is more prevalent in adolescents with elevated BP.^{11,12} These findings, together with the potential role of chronic inflammation in the pathogenesis of atherosclerosis, have led investigators to study the relationship between elevated CRP, BP, and other cardiovascular risk factors in children and adolescents. Most previous studies have not shown an independent association between elevated BP and CRP in children, after controlling for adiposity and dyslipidemia.^{13–17} Two prior studies of cardiovascular risk factors in children in the National Health and Nutrition Examination Survey (NHANES) 1999–2000 reported conflicting results regarding an association between elevated BP and CRP level.^{16,18}

The objective of the current study was to re-examine the relationship between CRP and elevated BP in the larger 1999 – 2004 NHANES sample of US children and adolescents, with particular emphasis on subjects with BP measurements in the hypertensive range (BP 95th percentile).¹⁹

METHODS

NHANES Study Population, Data Collection, and Laboratory Analyses

The National Health and Nutrition Examination Survey (NHANES) is a national survey of the civilian noninstitutionalized US population. Starting in 1999, the survey has been conducted continuously, evaluating approximately 5,000 persons annually, using a multistage stratified cluster sampling design.²⁰ Participants complete a detailed home interview followed by a physical examination and laboratory evaluation in a mobile examination center. Since 1999, BP has been measured in NHANES in subjects 8 years and older.²¹ The study physician measured the BP three times by auscultation using a mercury manometer after the subject sat quietly for 5 minutes. The first and fifth Korotkoff sounds were determined according to standard recommendations by the American Heart Association. The first reading was discarded and the average of the second and third measurements was recorded as the final BP reading.²²

All subjects 8 to 17 years old who participated in NHANES from 1999 to 2004 were to have CRP, cotinine, homocysteine, total cholesterol, and HDL cholesterol determined. Triglycerides, insulin levels, and glycohemoglobin were only measured in subsamples and were therefore excluded from the current analysis.²¹

CRP was measured by a high-sensitivity assay using latex-enhanced nephelometry (Dade Behring Nephelometer II Analyzer System, Dade Behring Diagnostics Inc., Somerville, NJ) at the University of Washington Medical Center, Seattle, Washington. The lower limit of detection of the assay was 0.1 mg/L. The upper limit of normal was 10 mg/L. Homocysteine was measured in plasma by an automated fluorescence polarization immunoassay (Abbott Homocysteine Assay, NHANES 1999–2001 - Abbott Imx, NHANES 2002–2004 – Abbott AxSym, Abbott Diagnostics). Cotinine, a metabolite of nicotine, was measured in serum by

isotope dilution – high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (ID HPLC-APCI MS/MS, Organic Analytical Toxicants Branch, Division of Laboratory Sciences, National Center for Environmental Health). Total cholesterol was measured enzymatically ((Hitachi 704 Analyzer, Lipoprotein Analytical Laboratory, Johns Hopkins University School of Medicine, Baltimore, MD). The method for HDL cholesterol changed during the study period. During NHANES 1999–2002, HDL cholesterol was determined after precipitation of other lipoproteins with a polyanion-divalent cation mixture. During NAHANES 2003–2004, HDL cholesterol was determined directly after the apoB-containing lipoproteins were reacted with a blocking agent (Hitachi 704 Analyzer, Lipoprotein Analytical Laboratory, Johns Hopkins University School of Medicine, Baltimore, MD).^{23–25}

Analysis

Data sets from NHANES 1999–2000, 2001–2002, and 2003–2004 were merged to create a single dataset with subjects from 1999–2004. Participants aged 8 to 17 years who had CRP levels and systolic and/or diastolic BP measurements available were included in the current analysis. Participants with CRP > 10 mg/L and those on corticosteroids were excluded to avoid children with acute inflammation. Participants taking estrogens and those taking stimulants were excluded because of their known effects on CRP and BP, respectively.^{26,27}

There are currently no guidelines associating CRP level and cardiovascular risk in children, but adults with CRP > 3 mg/L (upper tertile of population distribution) are considered to be at 1.5 to 2.0 fold increased risk for cardiovascular disease, relative to adults with CRP < 1 mg /L (lower tertile of population distribution).² In the absence of pediatric specific guidelines, the bivariate analysis compared children and adolescents with CRP > 3 mg/L to those with CRP ≤ 3 mg/L for demographic characteristics, BP, and other potential cardiovascular risk factors, including body mass index (BMI), total cholesterol, HDL cholesterol, homocysteine, and smoking (cotinine). Mexican American and Other Hispanic subjects were analyzed together as Hispanic. Independent associations between elevated BP and CRP as a continuous variable were then adjusted for covariates by multiple linear regression analysis. All variables found to be significantly different between subjects with CRP > 3 mg/L and those with CRP ≤ 3 mg/L were included as independent variables in the regression models. The effect of BP was evaluated both categorically (≥ 95th percentile for age, gender, and height¹⁹) and continuously (BP index). BP index was defined as the subject's BP divided by the 95th percentile BP for age, gender and height.¹⁹ The effect of BP 90th percentile was also analyzed for consistency with previous studies.^{16,28} Multiple linear regressions were performed separately for males and females, since previous studies have shown gender differences in associations between CRP and cardiovascular risk factors in children.²⁹

Statistics

Bivariate associations between baseline demographic characteristics, BP, and other cardiovascular risk factors of children who had CRP > 3 mg/L versus those with CRP ≤ 3 mg/L were compared using χ^2 analyses and 2-sided unpaired *t* tests. Independent associations between CRP and BP controlling for potential confounders were investigated by using multiple linear regressions with log-transformed CRP as the dependent variable. In regression analyses, CRP was log-transformed to improve the distribution of this variable. SUDAAN software (Research Triangle Park Institute, Research Triangle Park, NC) was used to produce weighted national estimates and to adjust standard errors, accounting for the complex sampling design of NHANES. Descriptive data are presented as unweighted counts and weighted percentages. A *p* value < 0.05 was considered significant.

RESULTS

Among the 7458 children 8 to 17 years included in NHANES from 1999 – 2004, 301 were missing both a systolic and diastolic BP measurement, and an additional 688 were missing a CRP measurement. Of the remaining 6469 children, 204 had a CRP level > 10 mg/L and were therefore excluded from the current study. Twenty-one children were excluded for use of estrogens, 122 for use of stimulants, and 10 for use of corticosteroids. Of the remaining 6112 children, 3058 (50.7%) were male and 3054 (49.3%) female; 1510 (59.7%) were White, 2391 (18.8%) Hispanic, 1984 (15.5%) Black, and 227 (6%) other race/ethnicity. Six hundred ten children (8.8%) had CRP > 3 mg/L and 1183 (17%) had BMI 95th percentile. Subjects with CRP ≤ 3 mg/L had a median CRP of 0.30 mg/L with an interquartile range of 0.70 mg/L. Subjects with CRP > 3 mg/L had a median CRP of 4.6 mg/L with an interquartile range of 2.4 mg/L. Four hundred fourteen (6%) had systolic BP (SBP) 90th percentile. Of those, 219 (53%) had SBP 95th percentile (a three-fold increase in the available number of subjects with SBP 95th percentile compared with the NHANES 1999–2000 sample). Two hundred forty-nine children had diastolic BP (DBP) 90th percentile, and of those, 91 had DBP 95th percentile, representing 4% and 1.3% of the total sample, respectively.

Table 1 compares baseline demographics and laboratory values of subjects with CRP > 3 mg/L and subjects with CRP ≤ 3 mg/L. Subjects with higher CRP were more likely to be slightly older, to be of minority race/ethnicity, to have higher BMI, to have higher SBP, and to have low HDL cholesterol. The groups were comparable in gender distribution, DBP, total cholesterol, homocysteine, and cotinine levels.

To evaluate the effect of elevated SBP on CRP, multiple linear regression analysis was performed. Systolic BP was analyzed both categorically (90th percentile and 95th percentile) and continuously (SBP index). Based on results of the bivariate analysis, the multivariate regression models were adjusted for age, BMI percentile, race/minority, SBP, and low HDL cholesterol. Because of limited sample size, children whose race was categorized as other were not included in the regression analysis. The analysis was limited to SBP because DBP did not differ between CRP groups. Table 2 shows the results of regression analysis by gender. In this adjusted analysis, males with SBP 95th percentile had significantly higher log-transformed CRP compared to males with lower SBP ($\beta = 0.38$, $P = 0.018$). By contrast, SBP 95th percentile did not have an independent effect on log-transformed CRP in females ($P = 0.94$). Regardless of gender, BMI percentile was a strong predictor of CRP. Hispanic ethnicity and low HDL cholesterol were also independently associated with log-transformed CRP in both males and females. Systolic BP was not independently associated with CRP when the SBP variable was defined as SBP 90th percentile or when SBP index was used (data not shown).

To further investigate the relationship between elevated SBP and CRP in males, multivariate regressions were repeated separately by race/ethnicity categories (Table 3). The regression models included age, BMI percentile, low HDL cholesterol, and SBP 95th percentile, with log-transformed CRP as the dependent variable. In these adjusted analyses, there was an independent association between SBP 95th percentile and log-transformed CRP in Black males ($\beta = 0.46$, $P = 0.01$), but not White or Hispanic males. BMI percentile remained independently associated with CRP regardless of race/ethnicity (Black males, $\beta = 0.015 \pm 0.0014$, $P < 0.001$; White males, $\beta = 0.018 \pm 0.002$, $P < 0.001$; Hispanic males, $\beta = 0.022 \pm 0.0012$, $P < 0.001$). Age remained independently associated with CRP in White males ($\beta = 0.0048 \pm 0.002$, $P = 0.004$) and Hispanic males ($\beta = 0.007 \pm 0.001$, $P = 0.006$) but not Black males ($\beta = 0.001 \pm 0.001$, $P = 0.31$). Low HDL remained independently associated with

CRP in Black males ($\beta = 0.35 \pm 0.10$, $P = 0.002$) but not White males ($\beta = 0.21 \pm 0.12$, $P = 0.09$) or Hispanic males ($\beta = 0.083 \pm 0.11$, $P < 0.46$).

DISCUSSION

Cross-sectional studies in adults show that CRP is elevated in subjects with elevated BP, after adjusting for obesity and other cardiovascular risk factors.^{4–10} In addition, prospective studies show that elevated CRP and hypertension are both independent determinants of cardiovascular risk and that their predictive value is additive.^{2,5,10} An analysis of the Woman's Health Study showed that participants with both elevated CRP and high BP went on to have the poorest cardiovascular disease event-free survival.⁵ Such findings suggest that inflammation and hypertension may act together to promote atherosclerosis, underscoring the importance of any potential relationship between elevated BP and CRP.^{5,10}

In contrast to studies in adults, most previous studies of CRP and cardiovascular risk factors in children have not found an independent effect of BP on CRP, after controlling for the strong influence of BMI on CRP.^{13–17} Two previous reports evaluating the effect of cardiovascular risk factors on high-sensitivity CRP in NHANES 1999–2000 both found that adiposity was the best predictor of CRP.^{16,18} In the first report, SBP analyzed as a continuous variable was found to be independently associated with CRP in girls aged 12 to 17 years.¹⁸ By contrast, a subsequent NHANES 1999–2000 study found that high SBP, defined as SBP $\geq 90^{\text{th}}$ percentile, was not associated with increased CRP in adjusted analysis.¹⁶

The current study evaluated the effect of high SBP on CRP in children and adolescents in NHANES 1999–2004, a dataset with a three-fold greater number of children with elevated SBP compared with NHANES 1999–2000. The larger sample size allowed the current study to focus on children with SBP elevation in the hypertensive range (SBP $\geq 95^{\text{th}}$ percentile).¹⁹ Multivariate analysis revealed that SBP $\geq 95^{\text{th}}$ percentile was independently associated with higher CRP in male subjects. In subset analysis, the association of high SBP and CRP was found to be largely limited to Black males. In contrast to these findings, neither SBP $\geq 90^{\text{th}}$ percentile nor SBP index was independently associated with higher CRP, a result that underscores the importance of focusing on subjects with the highest elevation of SBP. The current analysis also found that Hispanic ethnicity was independently associated with elevated CRP regardless of gender and BP status. A previous report of CRP concentration distribution among US children also found that Mexican Americans had the highest CRP concentrations among race and ethnic groups.³⁰ The propensity of Hispanic youth toward elevated CRP, and therefore possibly early atherosclerosis, is particularly notable in light of the greater likelihood of Hispanic adolescents to develop left ventricular hypertrophy in the face of elevated BP and obesity.³¹

Similar to previous studies, the current analysis found that BMI was a strong determinant of CRP. In addition, low HDL cholesterol, a lipid abnormality often associated with obesity, was a significant independent predictor of CRP in the primary analysis regardless of gender, SBP, and ethnicity. These findings confirm the importance of obesity and its associated lipid abnormalities as significant cardiovascular risk factors already prevalent in childhood and adolescence. Less than 10% of children had a CRP > 3 mg/L, a level that represents the upper tertile in adults. In addition, increasing age in the current study was independently associated with higher CRP, a finding that has been described previously.³⁰ Taken together, these results suggest that inflammation may become more prominent as age increases.

Clinical studies of carotid intima-media thickness suggest that adolescents with primary hypertension are at increased risk for the development of atherosclerosis during youth.¹²

Autopsy studies confirm the increased prevalence of early atherosclerotic lesions in the coronary arteries and aorta in adolescents with elevated BP.¹¹ Such findings, along with the recent increased prevalence of obesity-associated hypertension in childhood, demonstrate the importance of understanding the pathogenesis of atherosclerosis in overweight youth with elevated BP.³² The current study results suggest there is an interplay between race/ethnicity, elevated BP, and inflammation during childhood and adolescence. The reasons for these findings are unclear, but recent studies in adults have also found racial and gender differences in the effects of CRP on cardiovascular risk.^{33–35} Given the potential importance of chronic inflammation in the pathogenesis of atherosclerosis, the current study findings have potential implications for the development of atherosclerosis in youth and subsequent disparities in atherosclerotic cardiovascular disease later in life,^{36,37} and the potential use of inflammatory markers to identify children and adolescents at risk for development of hypertension and atherosclerotic diseases later in life.

The current study has several limitations. The cross-sectional study design limits inference on the causal relationship between cardiovascular risk factors and increased CRP. Participants in NHANES had a single CRP determination. For clinical determination of cardiovascular risk in adult patients, the American Heart Association and the Centers for Disease Control and Prevention recommend that CRP be measured twice, optimally two weeks apart.² In addition, participants in NHANES had BP measured on a single day. Few children with elevated BP in NHANES will actually have persistent hypertension and many children with elevated BP at a single sitting will ultimately have white-coat hypertension. The focus on SBP 95th percentile in the current analysis may have lessened this limitation compared with previous studies as the likelihood of white-coat hypertension decreases with increased elevation of clinic BP.³⁸ Triglycerides, insulin levels, and glycohemoglobin were not included in the analysis because these tests were only performed in subsamples of the subjects in NHANES. The impact of not having these measures available for the current analysis is unknown, but previous studies in children and adults have found that insulin resistance and the metabolic syndrome are both associated with elevated CRP.²⁸

In summary, the current study showed that elevated SBP is independently associated with increased CRP in males, an effect most evident in Black males by subset analysis. In addition, Hispanic ethnicity was found to be independently associated with elevated CRP, regardless of gender. Obesity was found to be a strong predictor of CRP, a result consistent with previous studies. These findings hold potential implications for the future cardiovascular health of minority youth and are particularly notable given the recent increase in the prevalence of pediatric hypertension and obesity. Further studies of racial and ethnic differences in chronic inflammation early in life may lead to a better understanding of differences in cardiovascular outcomes among minority groups of middle-aged and older adults.

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Abbreviations

CRP	C-reactive protein
SBP	systolic blood pressure
DBP	diastolic blood pressure
BMI	body mass index
NHANES	National Health and Nutrition Examination Survey

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Table 1

Bivariate analysis comparing subjects with CRP ≥ 3 mg/L to subjects with CRP < 3 mg/L.

Characteristic (mean $\pm$ SE)	CRP ≥ 3 mg/L n = 5502	CRP < 3 mg/L n = 610	P - Value
Male (%)	50.8	49.5	NS
Age (y)	13.1 $\pm$ 0.07	13.4 $\pm$ 0.18	0.046
Race/Ethnicity (%)			
White/Hispanic/Black/Other	60.3 / 18.3 / 15.4 / 5.9	53.4 / 23.7 / 16.5 / 6.4	0.0015
BMI (kg/m ²)	20.9 $\pm$ 0.11	26.32 $\pm$ 0.4	< 0.001
BMI percentile	62.2 $\pm$ 0.7	82.5 $\pm$ 1.7	< 0.001
SBP (mm Hg)	105 $\pm$ 0.3	109 $\pm$ 0.5	< 0.001
SBP index	0.85 $\pm$ 0.002	0.87 $\pm$ 0.004	< 0.001
DBP (mm Hg)	59 $\pm$ 0.4	60 $\pm$ 0.75	NS
DBP index	0.72 $\pm$ 0.005	0.73 $\pm$ 0.009	NS
Total Cholesterol (mg/dl)	163.2 $\pm$ 0.71	166.74 $\pm$ 2.6	NS
HDL < 40 mg/dl (%)	17.5	31.2	< 0.001
Homocysteine (μ mol/L)	5.42 $\pm$ 0.05	5.74 $\pm$ 0.08	NS
Cotinine (ng/ml)	8.59 $\pm$ 0.93	10.48 $\pm$ 3.21	NS

Table 2

Multiple linear regression analysis of associations with log-transformed CRP. Each regression model includes all the variables in the table.

Characteristic	Female (n = 3054)			Male (n = 3058)		
	Beta	SE	P - value	Beta	SE	P - value
Age (months)	0.003	0.001	0.005	0.004	0.001	< 0.001
Race/Ethnicity						
White (ref)	---	---	---	---	---	---
Hispanic	0.27	0.058	< 0.001	0.24	0.06	< 0.001
Black	0.12	0.067	0.067	-0.04	0.05	0.46
BMI percentile	0.019	0.001	< 0.001	0.018	0.0014	< 0.001
SBP 95th %	0.014	0.19	0.94	0.38	0.15	0.018
HDL < 40 mg/dl	0.42	0.098	< 0.001	0.25	0.09	0.012

Table 3

Subset analysis comparing the effect of SBP 95th percentile on log-transformed CRP in separate analyses in White, Hispanic, and Black males. Each regression model included age, BMI percentile, HDL, and SBP 95th percentile, with log-CRP as the dependent variable.

Race/Ethnicity	Beta-Coefficient for SBP 95th percentile	Beta SE	P – value
White Males (n = 731)	0.31	0.34	0.36
Hispanic Males (n = 1184)	– 0.05	0.14	0.70
Black Males (n = 988)	0.46	0.17	0.01