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Predictors of Inflammation in U.S. Children Aged 3–16 Years

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Abstract

Background—Little is known about the correlates of low-grade inflammation in U.S. children.

Purpose—This study describes the factors associated with increased levels of C-Reactive Protein (CRP) in U.S. children and tests whether differences in CRP by socioeconomic factors emerge in childhood.

Methods—Data were analyzed in 2009 from 6004 children aged 3 to 16 years from the National Health and Nutrition Examination Survey, 1999–2004, a representative sample of the U.S. non-institutionalized population. Tobit regression models are used to evaluate associations between predictors including BMI-for-age, skinfold body fat measures, chronic infections, environmental tobacco exposure, low birth weight and sociodemographics and continuous high-sensitivity C-reactive protein (CRP) in mg/L.

Results—CRP levels were higher in U.S. children with lower family income, and these differences are largely accounted for by differences in adiposity and recent illness. Mexican-American children had higher levels of CRP compared to both whites and blacks, but these differences were not explained by physical risk factors.

Conclusions—Increased adiposity is associated with higher CRP concentrations in U.S children aged 3–16 years, and both socioeconomic and race/ethnic differences exist in systemic inflammation in U.S. children. Increased childhood obesity and low-grade inflammation may contribute to later life chronic disease risk.

Introduction

C-reactive protein (CRP) is an acute phase protein produced in the liver, and is an important component of the nonspecific innate immune system response to infection and injury. In recent years, CRP has received increased attention as a sensitive marker of systemic inflammation. CRP levels typically rise quickly in the 24–72 hours following infection or injury, with a half-life of approximately 18 hours. Concentrations typically remain elevated until roughly 1 week after the resolution of an infection.[1,2] Chronically elevated levels of CRP are thought to play

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an important role in atherogenesis and the development of cardiovascular disease, in part through facilitating the uptake of lipids and macrophages to vessel walls.[3–5] Elevated levels of inflammatory markers have also been associated with a variety of other acute and chronic ailments including functional limitations, cognitive impairment, and depression.[6–8]

With growing evidence for the role of inflammation role in the pathophysiology of many of the chronic diseases of aging, differential exposure to inflammation over the life course may contribute to existing differences in morbidity and mortality. Previous studies identified socioeconomic differences in inflammation in U.S. adults,[9,10] but little is known about the factors associated with inflammation in U.S. children. The current study examined whether differences in CRP also exist in childhood in the U.S., and whether such differences are accounted for by physical risk factors such as adiposity, environmental tobacco smoke, and chronic infections. A better understanding of the determinants of systemic inflammation at early ages could have important implications for primary prevention of many inflammation-related chronic diseases.

Social factors associated with CRP

Levels of CRP are associated with social factors in many countries. Levels of inflammatory markers including CRP are inversely associated with SES in U.S. adults.[9–11] No differences in CRP by SES during childhood and adolescence were found in a recent study from Finland, [12] but to our knowledge no studies have examined the relationship of CRP levels to SES in U.S. children. Previous descriptive analysis of the 1999–2000 NHANES data identified higher levels of CRP among Mexican-American children compared to whites and blacks, but did not examine socioeconomic factors or test for potential mediators.[13] Findings of associations between CRP and race/ethnicity in U.S. adults have been mixed, with some studies indicating the highest levels in African Americans, while others indicated higher levels in Mexican Americans.[14–16]

Physical risk factors associated with CRP levels

Body fat is associated with increased levels of CRP, likely due to the expression of inflammatory cytokines in adipose tissue.[17,18] Oxidative stress associated with smoking and secondhand smoke has been associated with higher levels of CRP.[19,20] In developing countries, prenatal undernutrition reflected in low birth weight has been associated with immune function later in life[21] and low birth weight has been found to be associated with higher CRP levels in adults in Finland and the U.K.[22,23]

Infections elicit an inflammatory response from the innate immune system on entry into the body, and chronic infections may elicit a persistent inflammatory response.[24–26] Many of these infections such as cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), and *H Pylori* are often acquired early in life and remain with the host for life. Overall pathogen burden over the life course may contribute to an inflammatory burden that leads to earlier onset of morbidity and mortality.[27,28] Recently, differences in the burden of chronic infections was identified in U.S. children by family income and race/ethnicity, but the implications of these differences for inflammation are not known.[29]

METHODS

Sample

Participants come from the 1999–2004 U.S. National Health and Nutrition Examination Survey (NHANES). The NHANES are nationally representative, cross-sectional surveys of the non-institutionalized U.S. population, and include interview, examination, and laboratory measures. NHANES uses a stratified multistage sampling technique, with oversamples of

children aged 12–19 years, people aged ≥60 years, blacks, and Mexican Americans. Trained interviewers, using a computer-assisted personal interview system, interviewed participants at home. Participants were asked to subsequently attend the mobile examination center where they were asked to complete additional questionnaires, undergo various examinations and to provide biological specimens, including a blood and urine samples. For children aged <15 years, a parent or guardian provided interview information. 9390 children aged 3–16 years were interviewed in the NHANES household survey, 8579 of whom (91.3%) participated in the examination. Of those examined, 7211 (84.1%) agreed to have blood drawn and had a valid CRP value. In both cases, respondents not participating in the examination and not having blood drawn were more likely to be younger, higher income, and white. 6566 of these respondents (91%) had all the requested data on parental education and family income. An additional 562 respondents were missing information on BMI or cotinine, leaving a final analysis sample of 6004 children aged 3–16 years. Those missing information on parental SES, BMI, and cotinine did not have significantly different CRP concentrations than those who did not have missing information. The NHANES data are publicly available and the analysis was approved by the IRBs of Hunter College and the University of Michigan.

Measures

Outcome Measure—Serum CRP samples were analyzed by high-sensitivity latex-enhanced nephelometry on a BMII Nephelometer (Dade Behring).[30] The lower limit of detection was . 10 mg/L (32.3% of the sample). CRP values were log-transformed due to a right skewed distribution.

Physical Risk Factors—Serum was tested for seropositivity to 6 pathogens: cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), Hepatitis A (HAV), *Helicobacter Pylori (H Pylori)*, Cryptosporidium, and Toxoplasmosis, which were examined individually in relation to CRP as well as collectively as a proxy for pathogen burden. Confirmatory factor analysis (CFA) was used to construct an infection burden index using information from the six individual infection serostatus indicators. Within the CFA framework, the burden of infection is conceptualized as a latent (unobserved) variable measured by a number of observed variables, referred to as factor indicators. The measurement error in the factor indicators is included in the regression model that describes their association with the latent variable. Another advantage to CFA results from the practical constraints of the NHANES data, where some infections were measured for only a subset of the sample. CFA allowed the use all observations with one or more infection data points by using a full-information maximum likelihood estimation under the assumption that the data were missing at random (MAR), meaning that the mechanism causing the data to be missing was not related to the data.[31] Infections were tested in different years and for different age group subsamples determined by NCHS, thus once age is taken into account the lack of information is independent of the model covariates or of the outcome itself. A latent infection burden score for each individual was calculated using the posterior distribution of the burden variable, based on the model and the data specific to the person.

Low birth weight was coded as 1 if the child was born weighing less than 2500 grams, =0 otherwise. BMI was calculated as ($kg/m^{2)}$ from measured height and weight during the exam, and converted to age- and gender-specific z-scores based on the 2000 CDC growth charts.[32] To better capture body fatness, two additional measures of adiposity were included: triceps and subscapular skinfold measurements.[33,34] 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. Children were coded as having had a recent illness if their caregiver reported that they had experienced a head or chest cold, stomach or intestinal illness with vomiting, diarrhea, flu, pneumonia or ear infection in the last 30 days. White blood cell (WBC) count,

reflecting current immune activity, was included as a marker of other, unreported infection or illness. Serum cotinine, a byproduct of nicotine, was included as a continuous measure of firsthand or secondhand smoke exposure, log-transformed. Household smoker was coded as =1 if a smoker currently resides with the child, =0 otherwise.

Social Factors

Sociodemographic characteristics of the child were reported by the primary caregiver. Age in years at the time of exam was coded continuously. Race/ethnicity was coded as 1=non-Hispanic white, 2=non-Hispanic black, 3=Mexican-American, 4=other. Family income was categorized into quartiles for analysis (top income quartile as reference). Education of the family reference person was coded as 1=less than high school education, 2=completed high school, and 3=greater than high school education. Foreign born=1 if the child was born outside of the U.S., =0 otherwise.

Because of the high percentage (32.3%) of respondents at the lower detection limit (.10 mg/L), Tobit regression models were utilized to account for left censoring of the dependent variable.[35] The associations between ln(CRP) and combined physical risk factors were tested first (Model 1). Next, the associations between CRP concentrations and combined social predictors including race, gender, parental education, and family income were examined (Model 2). Finally, both physical and social predictors were examined together to determine the most important risk factors in fully adjusted models and to what degree social differences in CRP levels are accounted for by physical risk factors (Model 3). All models were adjusted for continuous age.

Sensitivity analyses were conducted by running all analyses excluding observations with CRP >10mg/L (2.22% of the sample), to exclude those with CRP levels indicating current or recent acute infection. Models excluding all respondents reporting recent illness in the last 30 days (23.02% of the sample) were also run. There were no substantive differences in the results with these exclusions (available on request).

Analyses were conducted in 2009 using Stata 10.1 (2007, StataCorp, College Station, TX) and Mplus version 5.1 (2008, Muthén and Muthén, Los Angeles, CA), with proper adjustments for the NHANES complex survey design, including 6-year examination (MEC) sample weights constructed as suggested in the NHANES analytic guidelines.[36]

Results

Table 1 presents weighted summary statistics for the 1999–2004 NHANES sample. The mean concentration of CRP in the sample was 1.22 mg/L, with 8.46% of the sample having CRP levels above 3 mg/L. Age-adjusted associations between individual infections and CRP indicated that seropositivity to herpes simplex virus-1(HSV-1) and hepatitis A were associated with higher CRP levels while seropositivity to cytomegalovirus(CMV), *H Pylori*, cryptosporidium and toxoplasmosis were not significantly associated with levels of CRP.

Table 2 presents results from sequential models with multivariate adjustment for physical risk factors alone, social risk factors alone, and finally social and physical risk factors together. Among the physical factors (Model 1), BMI-for-age and skinfold thickness, recent illness, white blood cell count (WBC), and the infectious burden score were significantly positively associated with CRP levels, while low birth weight and the smoking-related variables were not significantly associated. In the social risk factors model (Model 2), family income in the bottom two quartiles of the distribution compared to the top quartile and Mexican-American race/ethnicity were associated with higher CRP levels, while black race/ethnicity, parental education, household size, and being foreign-born were not significantly associated. Results

from fully adjusted models with both social and physical predictors are presented in Model 3. Increased BMI-for-age and skinfold thickness remained strongly predictive of higher CRP levels after adjusting for social factors, as did recent illness and higher WBC. Higher serum cotinine levels but not household smoking were significantly associated with higher CRP levels. Infectious burden was not associated with CRP in the fully adjusted model. The association of family income with CRP in the full model moved close to zero, suggesting that proximate physical risk factors mediate the relationship between family income and CRP levels in U.S. children. Despite the reduction in the association of family income in fully adjusted models, the association of Mexican-American race/ethnicity remained strong after adjustment for the most common physical risk factors for inflammation (β=0.516, $p<0.001$). Interestingly, while black race/ethnicity was not associated with CRP levels in the model when it was adjusted for social factors only (Model 1: β=0.082, $p=0.413$), this coefficient increased in magnitude and significance after adjustment for physical risk factors (β=0.251, $p=0.005$), suggesting that blacks may have more favorable distributions of some of the physical risk factors for CRP, but once these are held constant, they have higher CRP levels than whites. Examining the race/ethnic associations with the physical risk factors, blacks had higher BMI than whites (β=0.51, $p=0.012$), higher subscapular skinfold measures (β=0.44, $p=0.15$), but *lower* tricep skinfold measures (β=–0.62, $p=0.04$). Blacks also had lower white blood cell counts than whites (β=–1.18, $p=<.001$), with no difference in reported recent illness. The significant coefficient for blacks versus whites in the fully adjusted model thus suggests that black children have higher CRP levels than would be expected given their lower levels of WBC and triceps skinfold measures.

Additional sensitivity analyses were conducted. Since the timing of exposures may be important for regulation of the inflammatory response, each of physical and social risk factors was interacted with age in minimally adjusted models to look for differences in associations by age. Of all the predictors, only age significantly modified the association of CRP with the adiposity measures, with higher BMI-for-age and greater skinfold thickness being less strongly associated with CRP with increasing age. Results stratified by race/ethnicity showed very similar results within all three racial/ethnic categories for all predictors except for the highest category of parental education, which was associated with lower CRP levels for blacks and Mexican Americans, but not for whites. All analyses were also conducted using structural equation models in MPlus to incorporate the uncertainty in the infection burden score when modeling its effect on CRP, with almost to identical results.

Discussion

This study is the first to examine the physical and social risk correlates of C-reactive protein concentrations in U.S. children. Major strengths of this study include a nationally representative sample of U.S. children with oversamples of non-Hispanic black and Mexican-American children, and the use of a high-sensitivity CRP assay. CRP concentrations varied by age, gender, race/ethnicity, and family income level. Differences by family income level were mediated by differences in adiposity and the presence of recent illness, while the higher concentrations found for Mexican Americans remained even after adjustment for all social and physical risk factors. While black children did not have higher CRP concentrations relative to whites in unadjusted models, they did have higher CRP concentrations than would be expected given their physical risk profile, including significantly lower white blood cell counts compared to white children.

Some evidence for a positive relationship between pathogen burden and CRP levels in U.S. children was found. Seropositivity to HSV-1 and Hepatitis A were associated with higher CRP levels in age-adjusted models, as was the infectious burden factor score. In fully adjusted models, the estimate for pathogen burden was close to zero and no longer significant. To

examine the possibility that pathogen burden might raise CRP in younger children but lead to lower long-run levels, all age–pathogen interactions were tested, but none was significant. Unfortunately this type of cross-sectional analysis cannot test whether early-life pathogen burden influences inflammation beyond age 16 years, as was recently found in the Phillipines.[37]

These findings confirm that adiposity is a major contributor to levels of low-grade inflammation, even in children. This is consistent with the findings of Visser, et al. who found that overweight children (as defined by BMI and skinfold tests) aged 8–16 years were more likely to have CRP levels >2.2mg/L in the 1988–1994 NHANES III sample.[18] This study expands on those findings with more recent data, a wider age range, and the use of continuous high-sensitivity CRP measure to capture more subtle differences in inflammation. The finding that adiposity was a stronger risk for elevated CRP at younger ages may suggest that prevention of obesity is especially important during the earlier stages of immune system development. These results are also consistent with earlier findings that serum cotinine is predictive of higher levels of inflammation in children.[20] Low birth weight was not associated with higher levels of CRP in this sample, although it has previously been found to be associated with higher CRP levels in adults.[22]

An important finding of this study was that socioeconomic differences in CRP exist in childhood in the U.S., something that was not found to be true in Finland.[12] These differences seem to be largely mediated by BMI and recent illness. While BMI is a known chronic determinant of CRP, it is not currently known whether more frequent exposure to acute illness contributes to chronically elevated CRP levels. Future work should examine this question to better understand whether more frequent common infections among lower-income children contributes to chronically higher levels of inflammation that were not picked up by the current measures of chronic infections.

Mexican-American children have significantly higher levels of CRP compared to white or black children, and these results could not be explained by adiposity or other risk factors. Non-Hispanic black children showed elevated CRP levels compared to whites only in fully adjusted models, but had significantly lower levels than Mexican-American children. This is somewhat consistent with previous results from the 1999–2000 NHANES which found that Mexican-American adult women had the highest CRP concentrations, with no differences observed between white and non-Hispanic black women.[14] Other studies however, have found the highest CRP concentrations in black adults rather than Hispanics.[16] Future work should investigate what unmeasured risk factors might account for these race/ethnic differences, and whether Mexican Americans have higher CRP levels than other Hispanic groups that have been included in other studies.

This study has several limitations. Nonresponse at each stage of the NHANES interview, examination, and blood draw reduced sample size and may have led to a less representative analysis sample. While many of the physical risk factors were objectively measured, recall bias for predictors such as family income and education make have contributed to measurement error. Finally, while the use of confirmatory factor analysis to construct the infectious burden index took account of some measurement error, the available infections that contributed to the index are unlikely to be representative of the overall pathogen environment in childhood that may contribute to inflammation.

While the detrimental health effects of a chronic inflammatory state at older ages are well known, the long-run consequences of low-grade inflammation that begins in childhood are not well known. In light of the obesity epidemic that will continue to contribute to higher levels

of inflammation in U.S. children, the long-term consequences for cardiovascular and disability risk could be high.

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Table 1

Descriptive statistics: NHANES 1999–2004, ages 3–16 years

	M or proportion	SE	*n*
Physical risk factors			
Age (years)	9.96	(0.056)	6004
BMI-for-age	0.42	(0.031)	6004
Tricep skinfold measure (mm)	13.38	(0.159)	6004
Subscapular skinfold measure (mm)	9.93	(0.155)	6004
Recently sick	23.02%		6004
Low birth weight	7.00%		6004
Mother smoked	18.94%		6004
Household smoker	24.51%		6,004
Lab Measures			
CRP mg/L	1.22	(0.066)	6004
CRP > 3 mg/L	8.46%		6004
CRP > 10 mg/L	2.22%		6004
Cotinine ng/mL	2.86	(0.444)	6004
White blood cell count, 1000 cells/uL	7.17	(0.054)	6004
Infection Seropositivity			
CMV	38.04%		4592
HSV-1	32.04%		1999
H. pylori	9.87%		1787
Cryptosporidium	44.06%		1505
Toxoplasmosis	3.88%		4952
Hepatitis A	19.23%		6003
Social Factors			
Male gender	52.74%		6004
Race			6004
Non-Hispanic white	61.68%		
Non-Hispanic black	15.24%		
Mexican-American	12.66%		
Other race/ethnic groups	10.41%		
Family Income	$46,582	($1,404)	6004
Family Income: Quartile 1	$8,230	($221)	
Family Income: Quartile 2	$20,435	($205)	
Family Income: Quartile 3	$38,927	($403)	
Family Income: Quartile 4	$89,281	($1,056)	
Parental education			
Less than high school	23.23%		6004
Finished high school	27.00%		6004
Beyond high school	49.77%		6004
Foreign-born	5.62%		6004

	M or proportion	SE	*n*
Household size	4.54	(0.041)	6004

Weighted sample M's

Note: The sample size of individual infections varied due to differences in the ages and years of eligible samples:

CMV: all years, ages 6–16 years

HSV-1: 1999–2002, ages 6–13 years; 2003–2004, ages 14–16 years

H Pylori: 1999–2000: ages ≥3 years

Cryptosporidium: 1999–2000, ages 6–16 years

Toxoplasmosis: all years, ages 6–16 years

Hepatitis A: all years, ages ≥3 years

Table 2

Tobit Models for ln(CRP): NHANES 1999–2004, ages 3–16 years

	Model 1		Model 2		Model 3	
	Coefficient	**P-value**	**Coefficient**	**P-value**	**Coefficient**	**P-value**
Physical Risk Factors						
Age	–0.003	0.011	0.002	0.053	–0.002	0.019
BMI-for-age	0.220	<0.001			0.206	<0.001
Tricep skinfold measure	0.037	<0.001			0.042	<0.001
Subscapular skinfold measure	0.062	<0.001			0.058	<0.001
Recently sick	0.605	<0.001			0.606	<0.001
Low birth weight	0.000	0.999			–0.017	0.909
Household smoker	–0.021	0.791			0.039	0.644
ln(Cotinine)	0.035	0.140			0.054	0.026
White blood cell count	0.153	<0.001			0.156	<0.001
Infectious burden factor score	0.198	0.032			0.055	0.583
Social Factors						
Male gender	0.111	0.104	–0.131	0.086	0.121	0.069
Race: black			0.082	0.413	0.251	0.005
Race: Mexican American			0.609	<0.001	0.516	<0.001
Race: Other			0.341	0.020	0.244	0.070
Family income: Quartile 1			0.242	0.025	–0.034	0.786
Family income: Quartile 2			0.320	0.009	0.013	0.896
Family income: Quartile 3			0.158	0.228	–0.031	0.793
Parental education: Finished high school			0.103	0.363	0.124	0.128
Parental education: Beyond high school			–0.092	0.488	0.051	0.633
Foreign-born			–0.145	0.203	0.001	0.989
Household size			–0.024	0.409	0.047	0.042