Origins of "the flame within": Social and physical predictors of inflammation in U.S. children aged 3-17.

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Abstract:

Infectious exposures may link early environments to later life patterns of chronic disease and aging by contributing to a higher lifetime inflammatory burden [1-3]. There is growing evidence of socioeconomic differences in inflammation in U.S. adults[4, 5], as well as potential influences of childhood socioeconomic status on levels of inflammation in adulthood in other countries[6-8]. Little is known about what factors are associated with inflammation in U.S. children and whether differences in inflammation by socioeconomic factors emerge in childhood. While infectious exposures are thought to be important determinants of CRP historically and in developing countries, the relationship between CRP and pathogen exposure has not been explored in U.S. children. This paper uses data from the U.S. National Health and Nutrition Examination Survey from years 1999-2004 to 1.) describe the distribution of C-reactive (CRP) protein in U.S. children ages 3-16 by age, gender, and race/ethnicity; and 2) examine the association between markers of household socioeconomic status, low birth weight, infections, household smoking, and body-mass index with high-sensitivity C-reactive protein (CRP), a marker of inflammation, in U.S. children aged 3-16. We find socioeconomic differences in CRP in U.S. children, and these differences are largely accounted for by differences in adiposity and recent illness. Mexican-American children have higher levels of CRP compared to both whites and blacks, but these differences are not easily explained by physical risk factors.

Introduction

Infectious exposures may link early environments to later life patterns of chronic disease and aging by contributing to a high lifetime inflammatory burden [1-3]. There is growing evidence of socioeconomic differences in inflammation in U.S. adults[4, 5], as well as potential influences of childhood socioeconomic status on levels of inflammation in adulthood in other countries[6-8]. Little is known about what factors are associated with inflammation in U.S. children and whether differences in inflammation by socioeconomic factors emerge in childhood. While infectious exposures are thought to be important determinants of CRP historically and in developing countries, the relationship between CRP and pathogen exposure has not been explored in U.S. children. This paper will use data from the U.S. National Health and Nutrition Examination Survey from years 1999-2004 to 1.) describe the distribution of C-reactive (CRP) protein in U.S. children ages 3-16 by age, gender, and race/ethnicity; and 2) examine the association between markers of household socioeconomic status, low birth weight, infections, household smoking, and body-mass index with high-sensitivity C-reactive protein (CRP), a marker of inflammation, in U.S. children aged 3-16. The results will help shed light on whether socioeconomic differences in inflammation begin early in life in the United States, and if so, what the potential pathways may be.

Background

CRP is an acute phase protein produced in the liver, and is an important component of the non-specific innate immune system response to infection and injury. Interleukin-6 (Il-6) is the primary inflammatory cytokine responsible for upregulation of CRP. 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 a week after

the resolution of an infection[9, 10]. Chronically elevated levels of CRP are thought to play an important role in atherogenesis and the development of cardiovascular disease, in part through facilitating the uptake of lipids and macrophages to vessel walls[11-13]. 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[14-16]. Systemic inflammation has even been suggested as the key to understanding almost all age-related diseases, coined "inflammaging."[17-19].

Physical risk factors associated with CRP levels

Infections elicit an inflammatory response from the innate immune system upon entry into the body, and chronic infections may elicit a persistent inflammatory response[20-22]. 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[2, 19]. 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[23].

Obesity is another major factor associated with higher CRP levels, a result of the over-expression of inflammatory cytokines in adipose tissue[24]. Smoking and second-hand smoke are also associated with higher levels of CRP[25, 26]. Recent evidence suggest a role for micronutrients such as vitamin D in immune function and resistance to infections, and vitamin D deficient adults have been found to have increased levels of the inflammatory cytokine tumor necrosis factor alpha (TNF-α)[27-30]. In developing countries, pre-natal undernutrition reflected in low birth weight has been associated with immune function later

in life[3], and low birth weight has been found to be associated with higher CRP levels in adults in Finland and the U.K[31, 32].

Hygeine hypothesis

The "hygiene hypothesis" was first proposed in 1989 by Strachan et al, suggesting that modern under-exposure to infectious agents may contribute to immature and pro-allergic immune responses[33]. This idea is consistent with theory suggesting that early environments can model immune and inflammatory responses for the remainder of the life course[3]. It remains unclear whether high pathogen burden early in life would predispose the immune system to a pro-inflammatory state as suggested by the hypothesis of Crimmins and Finch[1, 2], or whether better immune system "education" by a large number of pathogens early in life leads to better regulation of the inflammatory response and lower overall levels of inflammation later in life[34].

Social risk factors associated with CRP

Levels of CRP are associated with social factors in many countries. Levels of inflammatory markers including CRP have been found to vary by socioeconomic status (SES) in U.S. adults [4, 5, 35]. Miller and Chen examined whether parental socioeconomic status during childhood influenced later expression of a pro-inflammatory phenotype in U.S. adolescents, finding that children whose parents owned their own home during ages 2-3 had better inflammation regulation in adolescence than those children whose parents did not own their own home[36]. No differences in CRP by socioeconomic status during childhood and adolescence were found in a recent study from Finland[6], but to our knowledge no studies have examined the relation of CRP levels to socioeconomic status in U.S. children.

Our analyses will examine the physical and social correlates of CRP in U.S. children aged 3-16, and test whether physical risk factors for elevated CRP mediate any relationship between social factors and CRP levels.

Sample:

Participants come from the 1999-2004 U.S. National Health and Nutrition Examination Survey (NHANES). In 1999, the NHANES became a continuously operating survey. The NHANES are nationally representative, cross-sectional surveys of the non-institutionalized U.S. population, and include interview, examination, and laboratory measures. NHANES uses stratified multi-stage sampling technique, with oversamples of older persons, 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 under 15 years of age, a parent or guardian provided interview information. The baseline sample includes 6338 children age 3-16 whose serum was tested for CRP.

Measures:

Outcome Measure:

Serum CRP samples were analyzed by high-sensitivity latex-enhanced nephelometry on a BMII Nephelometer (Dade Behring). For the purposes of analysis, CRP values were log-transformed due to right skewness.

Physical Risk Factors

Serum was also 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 we look at individually in relation to CRP as well as collectively as a proxy for pathogen burden. Not all pathogens were tested in each year or for all ages, leading to different final sample sizes for analyses involving individual infections. Low birth weight was coded as 1 if the child was born weighing less than 5.5lbs, =0 otherwise. BMI is calculated as ($kg/m^{2)}$ from measured height and weight during the exam. Two additional measures of adiposity were included in sensitivity analyses: triceps and subscapular skinfold measurements. 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, which reflects current immune activity, was also included as a marker of other, unreported infection or illness. Serum cotinine, a by-product of nicotine, was included as a continuous measure of second-hand smoke exposure, log-transformed. Maternal smoking was coded as =1 if the mother reported smoking during pregnancy with the child, =0 otherwise. Household smoker was coded as =1 if a smoker currently resides with the child, =0 otherwise. Serum levels of vitamin D were included as a continuous variable, log-transformed due to skewness.

For a small sub-sample of children (n=557), data were available on urinary levels of triclosan, the primary ingredient in anti-bacterial soap. We include log-transformed triclosan as a proxy for home hygiene for this sub-sample.

Sociodemographic characteristics of the child are reported by the primary caregiver. Age in years at the time of exam is coded continuously. Race/ethnicity is coded as 1=Non-Hispanic white, 2=Non-Hispanic black, 3- Hispanic. SES was operationalized as the ratio of family income to the poverty line and education level of the household reference person. The poverty-income ratio was calculated by the National Center for Health Statistics based on self-reported family income from all sources and accounts for family size, composition, and location. Education is 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 United States, =0 otherwise.

Methods

The mean and percentile distribution of CRP across sex, age, race/ethnicity, and family income was first examined, adjusting for the complex survey design. Next, linear regression models are used to model continuous levels of CRP as a function of age, sex, and covariates of interest. Confirmatory factor analysis (CFA) was used to construct an infection burden index using information from the six individual infection serostatus dummies. 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. Besides accounting for measurement error in the burden of infection construct, another advantage to CFA results from the practical constraints of the NHANES data, where some infections have only been measured in a subset of the survey. CFA allows the use all observations with one or more infection data points by using a full-information maximum likelihood estimation under the

assumption of ignorable missingness. We calculated a latent infection burden score for each individual using the posterior distribution of the burden variable, based on the model and the data specific to the person. We conducted sensitivity analyses by running all analysis excluding observations with CRP > 10mg/L (2.47% of the sample), sometimes recommended to exclude those with current or recent acute infection. There were no substantive differences in the results with this exclusion (available upon request).

Analyses were conducted 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.

Results

Table 1 shows weighted summary statistics for the 1999-2006 NHANES sample. The mean level of CRP in the sample was 1.32 mg/L, with 9.51% of the sample having CRP levels above 3mg/L. Distributions of CRP by age, sex, race/ethnicity, and family income level are presented in Table 2. In general, mean CRP levels rise with age and are higher for females in the sample. There are also differences by race/ethnicity and family income, with Mexican-American children and those with lower family income showing higher levels in these unadjusted statistics.

Table 3 shows the association of physical risk factors with ln(CRP) in age and sex adjusted models run separately for each risk factor. Risk factors associated with higher CRP in children included reporting an illness within the last four weeks, higher body mass index, having a mother who smoked during pregnancy, currently living with a smoker in the household, higher levels of serum cotinine, and a higher white blood cell (WBC) count Seropositivity to herpes simplex virus-1(HSV-1), *H Pylori* (p=0.069), toxoplasmosis (p=.098),

and hepatitis A was also associated with higher CRP levels in age and sex adjusted models, as was the factor score for latent burden of infection (p=.051). Being born low birth weight, serum levels of vitamin D, urinary levels of triclosan, and seropositivity to cytomegalovirus(CMV) and cryptosporidium were not significantly associated with levels of CRP in U.S. children.

Table 4 shows results from models with simultaneous adjustment for all physical risk variables that were available in the full sample (BMI, recent illness, low birthweight, maternal smoking during pregnancy, household smoking, serum cotinine, WBC, and latent infection burden score. In this fully adjusted model, only BMI, recent illness, and white blood cell count (WBC) are significantly associated with CRP levels, while all smoking variables become insignificant. Overall infectious burden remains positively related to CRP levels, but insignificant at conventional levels (p=0.153).

Table 5 shows results from models estimating both the separate and combined effects of physical and social variables on CRP levels in U.S. children. Model 1 examines the social correlates of CRP in U.S., finding significantly higher CRP levels for Mexican-American children and children with a lower family income. In models adjusted only for age, sex, and sociodemographics, being born outside the U.S. is associated with lower CRP (p=0.07), as is a larger household size. Parental education levels and black (compared to white) race were not associated with CRP levels. Model 2 summarizes the results for the physical correlates alone previously shown in Table 3.

Model 3 combines the social correlates along with the first group of physical risk factors (BMI, low birth weight, and household smoking). Of the physical risk factors, increased BMI remains strongly predictive of higher CRP levels in models that include sociodemographics, and household smoking is also associated with higher CRP levels. After

adjusting for BMI and smoking, the association of lower family income with higher CRP drops in half. The previous association of being foreign-born goes to zero, seemingly fully mediated by differences in BMI. The association of CRP with Mexican-American race/ethnicity remains strong after adjustment for these risk factors. Model 4 shows results from further adjustment for the laboratory measures including serum cotinine, white blood cell count, and the infectious burden score. White blood cell count and BMI remain strongly predictive of CRP levels in the fully adjusted models, while cotinine and infectious burden are not associated with CRP. The coefficient on family income is greatly diminished in the fully adjusted model, and no longer statistically significant ($p=0.379$), suggesting that the more proximate physical risk factors included in the model 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 remains strong even after adjustment for the most common physical risk factors for inflammation.

Additional sensitivity analysis were conducted. Since the timing of exposures may also be important for regulation of the inflammatory response, we interacted each of our physical and social risk factors with age in minimally adjusted models to look for differences in associations by age. Out of all the predictors, there was only a significant age interaction for BMI, with higher BMI being less associated with CRP with increasing age. Results stratified by race/ethnicity showed very similar results within all three racial/ethnic categories for all predictors. The only exception was the highest category of parental education, which was associated with lower CRP for blacks and Mexican-Americans, but not for whites. Since BMI may not capture adiposity well for children, we also included subscapular and skinfold measures to our models, both with and without BMI. Both

skinfold measures were significant predictors of CRP net of BMI, and BMI remained a strong predictor even including the skinfold measurements. Inclusion of these additional measures of adiposity did not change results for any other covariates and did not explain any additional portion of the effect of Mexican-American race/ethnicity on CRP levels.

Discussion

This is the first study to examine the association of physical and social risk factors with C-reactive protein in U.S. children. CRP concentrations varied by age, sex, race/ethnicity, and family income level. Differences by family income level were largely accounted for by differences in body mass index and the presence of recent illness, while the higher levels found for Mexican-Americans remained strong even after adjustment for all social and physical risk factors.

Our results did not provide definitive evidence for or against the hygiene hypothesis suggestion that low early pathogen exposure might bias immune system regulation in the direction of increasing inflammation. We found weak evidence for a positive relationship between pathogen burden and CRP levels in U.S. children. Several infections including HSV-1, *H Pylori*, toxoplasmosis, and Hep A were associated with higher CRP levels in age and sex 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 statistically significant. To examine the possibility that pathogen burden might raise CRP in younger children but lead to lower long-run levels, we tested all age-pathogen interactions, but none were significant. This does not rule out the possibility that early-life influences of pathogen burden on inflammation emerge beyond the age of 16, as was found in the Phillipines[34]. Using levels of urinary triclosan as a proxy for home hygiene in a small subsample, the

coefficient suggested that increased exposure to triclosan was associated with lower CRP, but this estimate was not statistically significant. In looking at household variables that might proxy higher pathogen exposure, a larger household size and being born outside of the U.S. were significantly associated with lower CRP in models including all sociodemographic variables, findings that could be consistent with they hygiene hypothesis. On the other hand, both of these effects diminished and became statistically insignificant upon the inclusion of BMI and markers of recent illness, tempering any conclusions.

Our findings confirm that adiposity is a major contributor to levels of low-grade inflammation, even in children. We also confirm evidence that second-hand smoke exposure is predictive of higher levels of inflammation in children[26], although these results did not remain strong in fully adjusted models. Low birth weight was not associated with higher levels of CRP in this sample, though it has previously been found to be associated with higher CRP levels in adults[31].

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[6]. These differences seem to be largely mediated by BMI and recent illness. While individual pathogens and our burden of chronic infections measure did not predict CRP in adjusted models, future work should explore socioeconomic differentials in recent illness, since these results raise the possibility that lower income children are infected with common ailments more frequently, which contributes to chronically higher levels of inflammation that were not picked up by the specific pathogen measures. In exploratory analysis, higher income kids were more likely to be reported to have been sick in the last 30 days, but lower income children had higher levels of WBC indicating recent infection.

Mexican-American children also have significantly higher levels of CRP compared to white or black children, and these results could not be explained by BMI or other risk factors. Future work should investigate what unmeasured risk factors might account for these differences, including dietary patterns.

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 likely continue to contribute to higher levels inflammation in U.S. children, the long-term consequences for cardiovascular and disability risk could be high. Inflammation has also been related to cognition, and future work should investigate the potential role of low-grade inflammation in children on cognition and learning, especially in light of the socioeconomic differences identified here.

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Table 1: Descriptive Statistics: NHANES 1999-2004, Ages 3-16

	Mean or proportion	Standard Error	N
Age	10.01	(0.054)	6,338
Male	52.06%		6,338
Physical Correlates			
BMI	19.40	(0.110)	6,338
Recently sick	23.11%		6,338
Low birth weight	6.91%		6,338
Mother smoked	21.66%		6,338
Household smoker	24.65%		6,338
Race			6,338
Non-Hispanic white	61.07%		
Non-Hispanic black	15.53%		
Mexican American	12.73%		
Other race/ethnic groups	10.67%		
Social Correlates			
Poverty income ratio	2.34	(0.059)	6,338
Parental education: less than high school	23.41%		6,338
Parental education: finished high school	27.22%		6,338
Parental education: beyond high school	49.37%		6,338
Foreign born	5.64%	(0.006)	6,338
Household size	4.53	(0.040)	6,338
Lab Measures			
CRP mg/L	1.32	(0.067)	6,338
CRP > 3 mg/L	9.51%		6,338
CRP > 10 mg/L	2.47%		6,338
Cotinine ng/mL	2.87	(0.422)	6,338
Triclosan ng/mL	63.97	(16.358)	557
White blood cell count, 1000 cells/uL	7.21	(0.053)	6,338
Vitamin D ng/mL	26.46	(0.444)	4,048
Infection Seropositivity			
CMV	38.08%		4,855
HSV-1	32.07%		2,115
H. pylori	10.18%		1,892
Cryptosporidium	44.29%		1,598
Toxoplasmosis	4.01%		5,232
Hepatitis A	19.31%		6,337

TABLE 2. Percentiles of CRP concentration (mg/L) in U.S. children aged 3-16, NHANES 1999-2004

		Percentile					
Total	**Mean**	**1**	**25**	**50**	**75**	**95**	**99**
Age, years	1.61	0.1	0.1	0.4	1.3	6.8	21.1
3-7	1.36	0.1	0.1	0.3	0.9	5.8	18.2
8-12	1.58	0.1	0.1	0.4	1.25	6.8	22.1
13-16	1.78	0.1	0.2	0.5	1.5	7.1	21.1
Sex							
Male	1.53	0.1	0.1	0.4	1.2	6.4	20.4
Female	1.71	0.1	0.1	0.4	1.4	7.4	21.4
Race/ethnicity							
White	1.34	0.1	0.1	0.3	0.9	5.3	19.9
Black	1.55	0.1	0.1	0.4	1.1	6.8	20.8
Mexican-American	1.91	0.1	0.2	0.5	1.7	7.7	21.9
Income							
<Poverty Line	1.77	0.1	0.1	0.4	1.5	7.7	21.4
1-2X the Poverty Line	1.73	0.1	0.1	0.4	1.3	7.7	23
2-3X the Poverty Line	1.58	0.1	0.1	0.4	1.2	6.5	17.6
>3X the Poverty Line	1.36	0.1	0.1	0.4	1.1	5.4	18.5

Table 3: OLS regressions for ln(CRP) in NHANES 1999-2004, Ages 3-16

	Coefficient	P-value	N
BMI	0.154	<0.001	6,338
Recently sick	0.535	<0.001	6,338
Low birth weight	-0.109	0.157	6,338
Mother smoked	0.159	0.029	6,338
Household smoker	0.201	0.003	6,338
Lab Measures			
ln(Cotinine)	0.059	0.002	6,338
ln(Triclosan)	-0.063	0.238	557
White blood cell count	0.178	<0.001	6,338
ln(Vitamin D)	-0.140	0.146	4,048
Infection Seropositivity			
CMV	-0.053	0.464	4,855
HSV-1	0.280	0.005	2,115
H. pylori	0.268	0.069	1,892
Cryptosporidium	0.024	0.824	1,598
Toxoplasmosis	0.197	0.098	5,232
Hepatitis A	0.204	0.019	6,337
Infectious burden factor score	0.128	0.051	6,338

Note: Each coefficients represents a separate regression with the covariate of interest, adjusted for age and sex.

Table 4: Physical Predictors of ln(CRP): NHANES 1999-2004, Ages 3-16

	Coefficient	P-value
BMI	0.139	<0.001
Low birth weight	-0.056	0.533
Mother smoked	0.032	0.613
Household smoker	0.008	0.877
Recently sick	0.410	<0.001
Lab Measures		
ln(Cotinine)	0.022	0.220
White blood cell count	0.114	<0.001
Infectious burden factor score	0.090	0.165

Note: N=6,338. One regression, adjusted for age and sex

Table 5: OLS Regressions for ln(CRP): NHANES 1999-2004, Ages 3-16

	Model 1		Model 2		Model 3		Model 4	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
Male	-0.085	0.068	-0.010	0.772	-0.049	0.165	-0.013	0.714
Age	0.002	0.001	-0.005	<0.001	-0.006	<0.001	-0.005	<0.001
Social Variables								
Poverty income ratio	-0.060	0.002			-0.032	0.060	-0.016	0.379
Foreign born	-0.149	0.070			-0.008	0.912	-0.009	0.896
Household size	-0.039	0.042			0.014	0.362	0.021	0.208
Parental education: finished high school	0.051	0.497			0.085	0.173	0.093	0.106
Parental education: beyond high school	-0.084	0.360			0.013	0.881	0.038	0.618
Race								
Black	0.036	0.577			-0.051	0.379	0.089	0.111
Mexican American	0.393	<0.001			0.292	<0.001	0.307	<0.001
Other	0.207	0.041			0.120	0.195	0.111	0.229
Physical Risk Factors								
BMI			0.139	<0.001	0.149	<0.001	0.137	<0.001
Low birth weight			-0.056	0.533	-0.037	0.644	-0.066	0.462
Mother smoked			0.032	0.613				
Household smoker			0.008	0.877	0.109	0.040	0.027	0.646
Recently Sick			0.410	<0.001	0.478	<0.001	0.412	<0.001
Lab Measures								
ln(Cotinine)			0.022	0.220			0.024	0.174
White blood cell count			0.114	<0.001			0.113	<0.001
Infectious burden factor score			0.090	0.165			0.002	0.981

Note: N=6,338.