Early Origins of Inflammation: Long Term Effects of Birth Weight and Breastfeeding Duration on C-Reactive Protein in Young Adulthood

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Abstract

Chronic inflammation is a potentially important physiological mechanism linking social environments and health across the life course. Elevated concentrations of C-reactive protein (CRP)—a key biomarker of inflammation—predict increased cardiovascular and metabolic disease risk in adulthood, but the developmental factors that shape the regulation of inflammation are not known. Lower birth weight and shorter durations of breastfeeding in infancy are potentially important determinants of chronic inflammation. Using data from a large, nationally representative sample of young adults in the US (National Longitudinal Study of Adolescent Health), we estimated a series of weighted least squares regression and fixed-effects sibling comparison models to evaluate birth weight and breastfeeding duration as predictors of CRP in adulthood (24-32 years). Complete data were available for *N*=10,495 participants. Lower birth weight was associated with higher CRP in weighted least squares (β = -0.021, SE = 0.007, $p<0.01$) and sibling comparison models (β = -0.076, SE = 0.027, $p<0.01$). Breastfeeding duration was considered as a series of indicator variables. Compared with individuals not breastfed, CRP concentrations were 19.9% (β = -0.065, SE = 0.028, $p<0.05$), 27.3% (β = -0.108, SE = 0.029, $p<0.01$), 29.0% (β = -0.122, SE = 0.032, $p<0.01$) and 30.9% (β = -0.128, SE = 0.037, $p<0.01$) lower among individuals breastfed for <3 months, 3-6 months, 6-12 months, and >12 months, respectively. In sibling comparison models, breastfeeding >3 months was marginally associated with lower CRP (β = -0.239, SE = 0.136, $p<0.10$). Efforts to promote breastfeeding and improve birth outcomes may have clinically relevant effects on reducing levels of chronic inflammation and lowering risk for cardiovascular and metabolic diseases in adulthood. A focus on early environments may also reduce social disparities in these diseases in adulthood, which run parallel to, and perhaps derive in part from, social disparities in birth weight and breastfeeding behavior.

Introduction

Inflammation has become a major focus of population-based research as a potentially important mechanism linking social environments and health over the life course (Crimmins et al., 2006; Miller et al., 2009). High sensitivity C-reactive protein (CRP)—a prototypical acute phase protein and key biomarker of inflammation—has been positively associated with incident cardiovascular disease (Ridker et al., 1998), type 2 diabetes (Pradhan et al., 2001), late-life disability (Kuo et al., 2006), and all-cause mortality (Harris et al., 1999; Jenny et al., 2007). Several studies have demonstrated significant socioeconomic and race/ethnic differences in CRP concentration, with overweight/obesity, health behaviors (e.g., smoking, physical activity), and psychosocial stressors as contributing factors (Alley et al., 2006; Nazmi et al., 2007; Ranjit et al., 2007; McDade et al., 2011).

Although chronic inflammation is most often studied in relation to exposures in adulthood, there is growing evidence that early life environments have long-term, independent effects on immune regulation and inflammation. For example, low early life socioeconomic status has been associated with elevated CRP among adults in the CARDIA study (Taylor et al., 2006), and exaggerated inflammatory response to challenge (Miller et al., 2009; Miller et al., 2010). Low birth weight—used as a proxy for prenatal undernutrition—has been associated with higher CRP in several international studies (Sattar et al., 2004; Danese et al., 2007; Tzoulaki et al., 2008; McDade et al., 2010).

Early infancy feeding decisions, such as breast feeding, also have the potential for lasting effects on inflammation. Breast milk provides nutritional and immunological support to infants following delivery, and has sensitive period effects on immune development and on metabolic processes related to the development of obesity—two potential avenues of influence on adult

CRP production (Shanks et al., 2001; Metzger et al., 2010). Inflammation may therefore represent an important physiological pathway through which environments early in life condition risk for chronic degenerative diseases and mortality later in life (McDade, 2012). While there is tremendous interest in the developmental origins of health and disease (Bateson et al., 2004; Hayward et al., 2004), the early life predictors of inflammation among adults in the US are not known.

Breastfeeding is of particular interest since current American Academy of Pediatrics (AAP) guidelines recommend exclusive breastfeeding to 6 months of age, and continued breastfeeding to one year (American Academy of Pediatrics, 2012). A small proportion of infants in the US currently meet these recommendations (16.3% exclusively breastfeed for 6 months; 25.5% receiving any breast milk at one year)(Centers for Disease Control and Prevention, 2012), with lower uptake for some race/ethnic groups and mothers with lower levels of education (Li et al., 2005). Comparable race- and education-based disparities in birth outcomes further motivate attention to early environments as potential contributors to disparities in health later in life (Braveman et al., 2009; Blumenshine et al., 2010).

We investigate birth weight and breastfeeding duration in infancy as predictors of CRP in young adulthood, using data from the National Longitudinal Study of Adolescent Health (Add Health). The size, longitudinal scope, and national representation of the Add Health dataset provide an exceptional opportunity to investigate the determinants of inflammation and their relevance to population health. In addition, the study design enables us to estimate sibling comparison models that account for unmeasured characteristics of mothers that are common to siblings and simultaneously affect offspring birth weight, breastfeeding decisions, as well as child health. Sibling comparison models—a form of fixed effects modeling—use differences

between siblings as the independent and dependent variables to estimate regression model parameters (Wooldridge, 2006). As a consequence, any characteristics, observable or unobservable, that are shared by siblings are differenced out of the model. A sibling fixed-effects approach is particularly useful for our purposes since it implicitly controls for many of the factors that are typically shared by siblings and implicated in the complex processes that shape prenatal and postnatal environments, such as race and ethnicity, socioeconomic status, and maternal education.

Methods

Participants and study design Data come from the first and fourth waves of the National Longitudinal Study of Adolescent Health, a large, nationally representative study of the social, behavioral, and biological linkages defining health trajectories from adolescence through adulthood (Harris, 2011). The Wave 1 in-home interview was conducted in 1994-95 with a stratified random sample of 20,745 seventh through twelfth graders attending a nationally-representative sample of 80 middle and high schools. Of this initial sample, 17,670 parents were also interviewed at Wave 1. Conducted in 2007-8, Wave 4 provided both interview and biomarker data on 15,701 of the original study participants when they were 24 to 32 years old. Procedures for data access and analysis were implemented as approved by the Institutional Review Board at Northwestern University, and in agreement with the sensitive data security plan approved by Add Health data managers.

Measurement of CRP Dried blood spot (DBS) samples—drops of capillary whole blood collected on filter paper (Whatman #903) following simple finger stick—were collected from 94% of participants as part of the Wave 4 in-home interview (Entzel et al., 2009). Dried blood

spot sampling has recently been incorporated into several population-based surveys like Add Health, building on its longstanding application in routine neonatal screening programs (McDade et al., 2007). CRP was quantified based on modifications to a high sensitivity protocol previously validated for use with DBS samples (McDade et al., 2004). Results are reported as serum equivalent values, calculated from a conversion factor derived from the analysis of 80 matched serum and DBS samples. Prior validation of assay performance indicates that the DBS CRP method produces results that are comparable to gold standard serum-based clinical methods (McDade et al., 2004).

Independent variables Information on participant birth weight and duration of breastfeeding was based on maternal recall in the Wave 1 parental interview. For breastfeeding duration, parents were asked, "For how long was [child's name] breastfed?" and chose from seven categories: less than 3 months, 3-6 months, 6-9 months, 9-12 months,12-24 months, greater than 24 months, or never breastfed. Due to small sample sizes for the categories above 6 months, for our analyses we consolidated responses of 6 months or more into "6-12 months" and "greater than 12 months." Breastfeeding duration was entered into regression models as a series of indicator variables, with no breastfeeding serving as the omitted reference group. Birth weight was entered as a continuous variable after preliminary analyses revealed no evidence of non-linear associations of birth weight with CRP. In addition to these primary independent variables, non-fixed-effects models included a comprehensive set of sociodemographic and contextual variables collected during Wave 1 (e.g., gender, race/ethnicity, parental education), and health behavior variables at Wave 4 known to influence inflammation (e.g., smoking, oral contraceptive use). Waist circumference at Wave 4 was measured to the nearest 0.5 cm at the superior border of the iliac crest (Entzel et al., 2009).

Data analysis Complete data were available for *N*=10,495 participants. The majority of cases with incomplete data were missing information concerning the key independent variables of breastfeeding duration (missing for *N*=2,352) and birth weight (missing for *N*=2,592). Studies measuring CRP as a biomarker of chronic, low-grade inflammation typically remove from the analysis individuals with acute elevations in CRP due to infection around the time of blood collection since these values do not represent baseline levels of inflammatory activity that are predictive of subsequent risk for chronic disease (Pearson et al., 2003). For this analysis we excluded individuals reporting symptoms of infection in the two weeks preceding blood collection (*N*=3,337), as well as pregnant women (*N*=363), resulting in a final sample of *N*=6,990. Analyses were implemented with Add Health longitudinal sampling weights, which adjust for complex sample design, selection, and non-response.

Analyses proceeded in three stages, and were implemented in Stata (Version 12, StataCorp, College Station, TX). First, we estimated bivariate associations between birth weight and log-transformed CRP (base 10), and between breastfeeding and log CRP, using weighted least squares regression. We then added a series of Wave 1 control variables, representing factors that may confound associations between early environments and adult CRP. In a final model we added waist circumference at Wave 4 to evaluate central adiposity as a potential mediator of early environment effects on inflammation.

This series of models was then repeated using sibling fixed effects regression for the subset of full biological siblings in the dataset (*N*=714, with 354 sibling groups comprised of 348 pairs and 6 sibling trios). These models included only those Wave 1 control variables that differed across siblings. All analyses were repeated to evaluate the sensitivity of results to alternative strategies for handling acute elevations in CRP. In particular, we implemented

models including covariates for infectious symptoms to adjust for acute inflammation, rather than excluding these observations from the analytic sample.

Results

Tables 1 and 2 describe the distribution of birth weight, breastfeeding, and control variables in the analytic sample. Mean birth weight was 7.45 pounds, with significant differences across race/ethnic and education groups (Table 2). Overall, 44.9% of participants were breastfed as infants for some amount of time, with large differences in initiation and duration across race/ethnic and education groups. Median CRP concentration was 2.1 mg/L for the entire sample and 1.7 mg/L for the analytic sample, which excluded participants with infectious symptoms at the time of blood collection.

Table 3 presents results from the weighted least squares regression models. The bivariate association between birth weight and CRP in adulthood is negative (model 1). This association is attenuated when breastfeeding duration (model 3) and other control variables (model 4) are considered, but strengthens when waist circumference at Wave IV is added to the model (model 5). Birth weight is positively associated with waist circumference in this sample, which appears to suppress the negative association with CRP that strengthens after adjustment for current waist circumference. In other words, larger waist circumference is associated with both higher birth weight and higher CRP, but at a given level of waist circumference higher birth weight predicts lower CRP. Based on the fully adjusted model, each pound of birth weight is associated with 4.8% lower CRP in young adulthood.

In unadjusted models, and after accounting for birth weight (Models 2-3), breastfeeding duration is a significant predictor of lower CRP in young adulthood. The pattern of coefficients

suggests a threshold association between breastfeeding duration and CRP, with substantially lower concentrations of CRP for individuals breastfed for 3 months or longer. Associations were attenuated, but remained statistically significant, with the addition of baseline covariates representing potentially confounding influences (Model 4). When waist circumference at Wave 4 was added to the model, associations between breastfeeding duration and CRP were attenuated further but remained statistically significant (Model 5).

Waist circumference is a well-established predictor of chronic inflammation (Schaffler et al., 2006), and prior research has documented protective effects of breastfeeding in preventing overweight and obesity in adulthood (Harder et al., 2005). These associations suggest that waist circumference represents a plausible mediator of the effects of breastfeeding on inflammation. Accordingly, we conducted Sobel-Goodman tests of statistical mediation(MacKinnon et al., 2002). Results indicate that waist circumference accounted for 40.2% (p=.06), 52.7% (p<.001), 44.1% (p<.001), and 41.7% (p<.01) of the association between adult CRP and breastfeeding durations of <3 months, 3-6 months, 6-12 months, and >12 months, respectively, relative to non-breastfed individuals.

Figure 1 presents the association between breastfeeding duration and CRP, without adjustment for waist circumference. Compared with individuals not breastfed, CRP concentrations were 19.9, 27.3, 29.0 and 30.9% lower among individuals breastfeed for <3 months, 3-6 months, 6-12 months, and >12 months, respectively.

Table 4 presents results from fixed-effects sibling models. As might be expected from the smaller sample size and more limited variation in dependent and independent variables, standard errors are considerably larger than in Table 3. Differences in birth weight across siblings negatively predicted differences in adult CRP concentration, although the coefficient was

statistically significant only in Models 1 and 5. Due to the more limited variation in breastfeeding duration between siblings than in the full population, we chose three months as a single cut-point based on results in Table 3 (25 sibling pairs and 1 sibling trio contained siblings on both sides of the three month breastfeeding cut-point, for a subsample of N=53 "discordantly fed" participants). The estimated magnitude of the associations between breastfeeding duration and CRP are larger than in Table 3 and reasonably invariant across models, but not statistically significant at $p<0.05$.

Finally, we evaluated the robustness of these results to alternative strategies for controlling for infectious symptoms around the time of blood collection. Specifically, we repeated our analyses using an indicator variable to control for the presence of infectious symptoms, rather than excluding individuals with infectious symptoms from the analytic sample. Results from least squares regression models were very similar, both in terms of magnitude and significance of the associations between birth weight, breastfeeding duration, and CRP. Results from sibling comparison models were also similar, although the coefficients for the association between CRP and birth weight (β = -0.034, SE = 0.020) and breastfeeding greater than 3 months (β = -0.076, SE = 0.087) were substantially smaller in magnitude in the fully adjusted model.

Discussion

Clinicians, researchers, and policy makers increasingly emphasize the importance of prenatal and early postnatal environments in influencing physiological function and health over the life course (Halfon et al., 2002; Gluckman et al., 2008). In this analysis we document large disparities in birth weight and rates of breastfeeding associated with race/ethnicity and education level. We present evidence that lower birth weight and shorter durations of breastfeeding both

predict elevated concentrations of CRP in young adulthood, indicating increased risk for cardiovascular and metabolic diseases that are major health burdens in the US. Clinical trials have demonstrated that statin therapy reduces CRP in healthy adults by 14.8 to 17.4% (Ridker et al., 1999; Albert et al., 2001; Ridker et al., 2001). Our results suggest that the effects of breastfeeding on adult CRP are comparable, or larger, in magnitude.

Advantages of our study include the use of a large, nationally representative sample, and the application of sibling fixed-effects models that account for hard-to-measure attributes that may otherwise confound associations between early environments and adult health. A limitation of our study is the application of maternal recall to collect information on birth weight and breastfeeding duration. However, prior validation studies indicate that maternal reports of birth weight correlate highly with birth records, and that breastfeeding initiation and duration are also reported with high validity and reliability (Tomeo et al., 1999; Li et al., 2008). In addition, similar to other epidemiological studies of inflammation (Ridker et al., 2000; Pradhan et al., 2001; Albert et al., 2004), the Add Health study uses a single CRP measure to assess baseline levels of inflammation, which makes it more difficult to differentiate acute from chronic, low-grade inflammatory activity. Multiple CRP values would be preferable, but we use infectious symptoms to control for a major source of acute activation, and our results are robust to alternative control strategies.

To the best of our knowledge, this study is the first to document a negative association between birth weight and CRP in sibling comparison models, which eliminate a wide range of potentially confounding influences on adult CRP and increase our confidence in concluding that aspects of the prenatal environment have effects on the regulation of inflammation that last into adulthood. We find a similar association between lower birth weight and elevated CRP in the

full sample of young adults, consistent with prior international findings and a smaller study in the US (Sattar et al., 2004; Danese et al., 2007; Tzoulaki et al., 2008; McDade et al., 2010; Bhuiyan et al., 2011). A large body of epidemiological research has documented associations between lower birth weight and increased risk for cardiovascular and metabolic diseases later in life (Barker, 1994; Gluckman et al., 2008), and our results point toward chronic inflammation as a potentially important intervening mechanism.

While the prenatal environment has been the primary focus of research into the developmental origins of disease, postnatal feeding decisions may provide additional opportunities for intervention, particularly given low rates of extended breastfeeding in the US. Our findings are consistent with prior studies in New Zealand and Scotland (Williams et al., 2006; Rudnicka et al., 2007), and are important in demonstrating negative associations between breastfeeding duration and CRP concentration in a large representative sample of adults in the US. Results from sibling comparison models indicate a similar pattern of association, but are constrained by low statistical power due to the relatively small number of discordant siblings. Consumption of breast milk in infancy may have lasting effects on inflammation by shaping regulatory pathways during sensitive periods of immune development (Field, 2005; McDade, 2012). Effects of breastfeeding may also be indirect, through programming of metabolic pathways that reduce the accumulation of body fat and the production of pro-inflammatory cytokines (Harder et al., 2005; Schaffler et al., 2006).

Our results suggest that efforts to increase the initiation and duration of breastfeeding in accordance with current AAP recommendations, and to improve birth outcomes, may have clinically relevant effects on reducing levels of chronic inflammation in adulthood that lower risk for chronic degenerative diseases of aging. A focus on environments early in development may

also help address social disparities in population health outcomes in adulthood, which run parallel to, and perhaps derive in part from, social disparities in birth weight and breastfeeding behavior (Braveman et al., 2009; Kuzawa et al., 2009).

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Figure 1. Predicted CRP values by breastfeeding duration. Note: Values are based on coefficients from Table 3, Model 4. Error bars represent 95% confidence intervals.

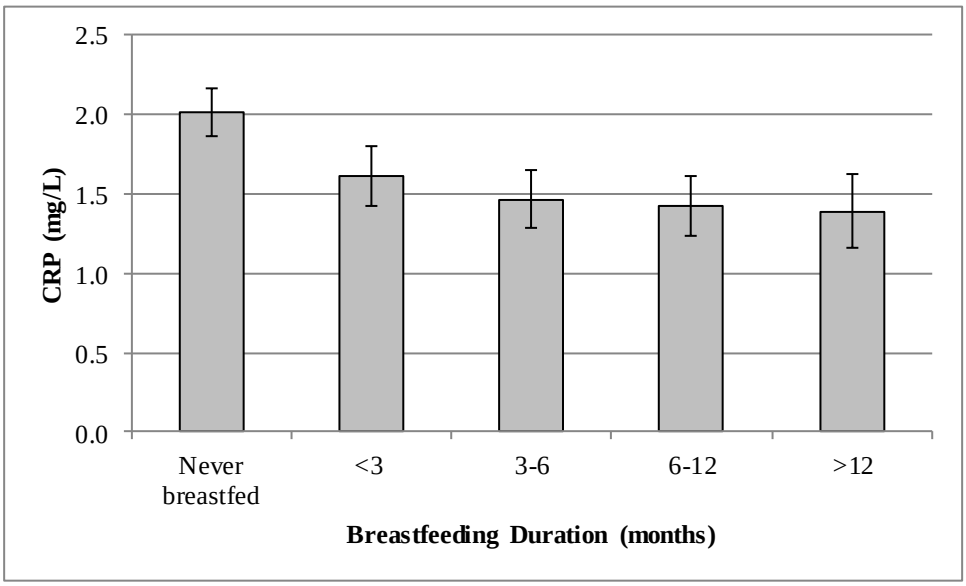

Table 1. Demographic composition of the analytic sample

	Percent	[95% Confidence Interval]
Sex		
Male	54.1	[52.3, 56.0]
Female	45.9	[44.0, 47.7]
Race/Ethnicity		
Latino/a	11.1	[7.8, 14.5]
White	71.9	[66.4, 77.3]
Black	13.1	[9.4, 16.8]
Asian	2.5	[1.2, 3.8]
Native American	0.7	[0.2, 1.1]
Other	0.01	[0.003, 0.010]
Parent education		
Less than high school	13.2	[10.9, 15.4]
High school diploma/GED	31.3	[28.8, 33.8]
Some college	21.2	[19.6, 22.9]
College degree	23.3	[21.2, 25.5]
Advanced degree	11.0	[9.1, 12.9]
Breastfeeding Duration		
Never	55.1	[51.9, 58.2]
<3 months	14.0	[12.6, 15.5]
3-6 months	10.4	[9.2, 11.6]
6-12 months	13.4	[11.8, 15.0]
>12 months	7.1	[6.0, 8.2]
Birth control pill	14.7	[13.5, 15.9]
Daily smoker	24.9	[22.8, 27.0]
First born child	63.2	[60.9, 65.5]

N =6,990. All estimates utilize sampling weights.

Table 2. Subgroup differences in birth weight and breastfeeding

	Birthweight		Never Breastfed		Breastfed for <3 Months		Breastfed for >3 Months	
	Mean (SE)	*p* [a]	% (SE)	*p* [b]	% (SE)	*p* [b]	% (SE)	*p* [b]
Sex								
Male	7.57 (.03)		54.0 (1.7)		14.9 (1.0)		31.1 (1.6)	
Female	7.30 (.04)		56.3 (1.8)		13.0 (0.8)		30.6 (1.6)	
Difference		<.001		.12		.12		.70
Race/Ethnicity								
Latino/a	7.45 (.09)		47.3 (2.7)		18.1 (2.0)		34.5 (2.4)	
White (non-Latino)	7.54 (.03)		53.0 (1.8)		14.4 (0.9)		32.6 (1.7)	
Black (non-Latino)	7.03 (.05)		79.2 (2.2)		7.8 (1.2)		13.0 (1.6)	
Asian (non-Latino)	6.96 (.15)		30.0 (4.8)		11.1 (3.1)		58.8 (5.5)	
Native American (non-Latino)	7.57 (.32)		55.7 (10.3)		17.7 (9.2)		26.6 (7.6)	
Other (non-Latino)	7.56 (.24)		27.1 (8.1)		38.4 (10.5)		34.5 (9.0)	
Difference		<.001		<.001		<.001		<.001
Birth order								
First Born	7.40 (.03)		55.2 (1.7)		15.0 (0.9)		29.8 (1.5)	
Not first born	7.53 (.05)		54.9 (1.8)		12.4 (1.1)		32.8 (1.8)	
Difference		.006		.84		.05		.07
Parent education								
Less than high school	7.29 (.09)		71.1 (2.8)		10.4 (1.5)		18.5 (2.2)	
High school diploma/GED	7.39 (.04)		67.7 (1.8)		11.4 (1.0)		20.9 (1.4)	
Some college	7.46 (.04)		53.9 (2.1)		18.1 (1.5)		27.9 (1.7)	
College degree	7.52 (.05)		43.0 (2.0)		15.5 (1.4)		41.4 (2.1)	
More than college	7.60 (.05)		27.6 (2.6)		14.9 (1.5)		57.6 (2.8)	
Difference		.002		<.001		<.001		<.001
Total	7.45		55.1		14.0		30.9	

N=6,990.

[a]Birthweight *p* values are based on *t* tests for sex and birth order, ANOVA for race/ethnicity and parent education.

[b]Breastfeeding *p* values are based on χ^2 tests.

Table 3. Coefficients and standard errors from weighted least squares regression models predicting log CRP

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	SE	β	SE	β	SE	β	SE	β	SE
Birth weight (lbs)	-.017*	(.007)			-.011	(.007)	-.004	(.007)	-.021**	(.007)
Never breastfed			reference		reference		reference		reference	
Breastfed <3 months			-.085**	(.027)	-.083**	(.027)	-.065*	(.028)	-.039	(.026)
3-6 months			-.134**	(.030)	-.131**	(.030)	-.108**	(.029)	-.051*	(.025)
6-12 months			-.169**	(.032)	-.164**	(.031)	-.122**	(.032)	-.068**	(.024)
>12 months			-.161**	(.040)	-.158**	(.040)	-.128**	(.037)	-.074*	(.034)
Male							-.164**	(.020)	-.194**	(.016)
White (non-Latino)							reference		reference	
Latino/a							.070*	(.029)	.053*	(.024)
Black (non-Latino)							.043	(.029)	.036	(.025)
Asian (non-Latino)							-.224**	(.057)	-.133**	(.041)
Native American (non-Latino)							.209	(.160)	.032	(.092)
Other (non-Latino)							-.016	(.091)	.014	(.075)
Birth control pill							.147**	(.025)	.243**	(.022)
Daily smoker							.028	(.024)	.054**	(.020)
First born child							.009	(.021)	.002	(.017)
Parent's education: Less than high school							reference		reference	
Parent's education: High school							.017	(.029)	.028	(.026)
Parent's education: Some college							-.006	(.0335)	.016	(.031)
Parent's education: College graduate							-.061†	(.034)	-.006	(.027)
Parent's education: More than college							-.087*	(.039)	-.033	(.031)
Waist circumference at Wave 4 (cm)									.016**	(.001)
R^2	.002		.015		.016		.068		.298	

N = 6,990

†*p* <.10; **p* <.05; ***p* <.01

Table 4. Coefficients and standard errors from fixed-effects sibling comparison models predicting log CRP.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	SE	β	SE	β	SE	β	SE	β	SE
Birth weight (lbs)	-.096**	(.029)			-.094**	(.029)	-.078**	(.029)	-.076**	(.027)
Breastfed >3 months			-.222	(.139)	-.202	(.137)	-.239†	(.136)	-.182	(.125)
Male							-.176**	(.065)	-.230**	(.060)
Birth control pill							.082	(.086)	.092	(.079)
Daily smoker							-.140†	(.074)	-.110	(.068)
First born child							-.004	(.055)	-.011	(.051)
Waist circumference at Wave 4 (cm)									.014**	(.002)
R^2, Within sibling groups	.029		.007		.035		.075		.218	
R^2, Between sibling groups	.000		.021		.005		.018		.302	
R^2, Overall	.002		.015		.008		.028		.275	

N = 714
†*p* <.10; **p* <.05; ***p* <.01