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Early Origins of Socioeconomic Inequalities in Chronic Inflammation: Evaluating the Contributions of Low Birth Weight and Short Breastfeeding

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ABSTRACT

The United States is characterized by persistent and widening social inequities in a wide range of adult health outcomes. A life course approach challenges us to consider if, and how, these inequities trace back to early life conditions, and chronic inflammation represents a potentially important mechanism through which early environments may have lasting effects on health in adulthood. Low birth weight (LBW) and shorter durations of breastfeeding both predict increased inflammation in adulthood, which is associated with increased risk for cardiovascular disease, metabolic syndrome, and all-cause mortality. Using data from a large representative sample of young adults in the U.S. (National Longitudinal Study of Adolescent to Adult Health (Add Health)), the researchers document the socioeconomic status (SES) gradient in chronic inflammation, as indicated by concentrations of C-reactive protein (CRP). Using a nested set of structural equation models and marginal standardization techniques, they investigate the extent to which this gradient is explained by patterns of LBW and breastfeeding in infancy. Findings reveal a particularly important role for breastfeeding duration: Based on model predictive margins, increasing breastfeeding duration to three or more months corresponds to a flattening of the SES gradient by 78%, and 81% when LBW is eliminated. This study expands current understandings of the consequential role of developmental environments for population health and for addressing health inequities in future generations.

1. Introduction

Wide socioeconomic gaps in morbidity and mortality in the US are well-established, but their origins are not. Lifestyle factors and health behaviors in adulthood, as well as access to health care services, explain only a portion of social gradients in health (Woolf et al. 2007, Berkman et al. 2014). Psychosocial stressors in adulthood are also important (Adler and Snibbe 2003, Jackson et al. 2010, Goosby et al. 2018), but it has become increasingly apparent that contexts and experiences earlier in development have direct, as well as indirect, effects on physiological systems and later life morbidity (Hayward and Gorman 2004, Gluckman et al. 2008, Goosby et al. 2016). We are therefore challenged to consider the extent to which socioeconomic inequalities in adult health trace back—at least in part—to socially patterned exposures earlier in the life course.

In this analysis we focus on chronic inflammation as a plausible physiological pathway through which environments early in life shape trajectories of health in adulthood. Higher levels of chronic inflammation—indicated here by C-reactive protein (CRP)—predict increased risk for all-cause mortality, as well as risk for cardiometabolic diseases that are major public health burdens in the US (Harris et al. 1999, Pradhan et al. 2001, Pearson et al. 2003, Kuo et al. 2005, Kuo et al. 2006). We use data from a large, nationally representative sample of young adults with contextual, behavioral, and physiological measures collected at multiple time points. While rates of clinical disease are low in young adulthood, trajectories of later life health are well established and can be revealed by biological measures such as CRP.

After briefly outlining the rationale for considering the developmental origins of social inequalities in adult health, we discuss the life course determinants of chronic inflammation and highlight birth weight and breastfeeding duration as particularly important aspects of the prenatal

and postnatal environment. We describe the socioeconomic distribution of breastfeeding duration and birth weight, and note that shorter durations of breastfeeding and lower birth weight deliveries are strongly associated with lower socioeconomic status (SES) in the US. We therefore hypothesize that SES gradients in chronic inflammation are a partial product of breastfeeding duration and birth weight, and we outline a structural equation modeling framework for testing this hypothesis.

1.2. Developmental origins of social inequalities in health

Developmental, life course approaches highlight the importance of contexts and experiences early in life as potential determinants of later life health, independent of circumstances in adulthood (Barker et al. 2002, Hayward and Gorman 2004, Kittleson et al. 2006, Gluckman et al. 2008, Shonkoff et al. 2009, Halfon et al. 2014). For example, the onset of coronary heart disease (CHD) has been investigated among graduates of the Johns Hopkins medical school, and even for this group of highly educated, affluent physicians, low SES in childhood more than doubles the risk of CHD by age 50 (Kittleson et al. 2006). More broadly, a growing body of research in biodemography and life course epidemiology has established the "long arm of childhood," with early life circumstances shaping health outcomes decades later through several direct and indirect pathways (Preston et al. 1998, Blackwell et al. 2001, Hayward and Gorman 2004, Case and Paxson 2010).

The biological processes that link environments in infancy with health in adulthood are the primary focus of research on the developmental origins of health and disease (DOHaD). Building on early observations linking socioeconomic conditions around the time of birth and life expectancy within birth cohorts (Kermack et al. 1934, Forsdahl 1977), scholars across a wide range of disciplines have applied observational, quasi-experimental, and experimental animal

models to illuminate the mechanisms through which early environments can have disproportionate and lasting effects on the function of key physiological systems (Barker et al. 2002, Gluckman et al. 2008, Gluckman et al. 2016). Initial analyses, led primarily by Barker and colleagues, focused on birthweight as an indicator of nutrient transfer to the fetus during gestation, with lower birth weight predicting increased cardiovascular disease risk (Barker et al. 1989, Barker 1998, Barker et al. 2006). Subsequent research has considered a wider range of prenatal and postnatal factors that predict increased risk for morbidity and mortality through modifications to physiological systems, organ growth, and metabolism during sensitive periods of development (Cameron and Demerath 2002, Gluckman et al. 2008, Bengtsson and Broström 2009, Smith and Ryckman 2015).

While the DOHaD framework emphasizes the biological mechanisms through which developmental contexts shape risk for disease later in life, it generally does not attend to the unequal distribution of these contexts and how they may, in turn, contribute to social inequalities in morbidity and mortality in adulthood. The concepts of "embodiment" and "biological embedding" have provided opportunities for synthesis: Both underscore environmental sensitivity and developmental plasticity as defining features of human biology, and both emphasize that socially patterned contexts and experiences have enduring effects on the phenotype that shape risk for a wide range of health outcomes (Gravlee 2009, Kuzawa and Sweet 2009, Hertzman and Boyce 2010, Thayer and Kuzawa 2013, Hoke and McDade 2014). In the analyses below we focus on birth weight and breastfeeding as important aspects of the developmental environment that influence chronic inflammation and trajectories of cardiometabolic disease risk. However, we go beyond a typical DOHaD approach in considering

how these environments are patterned by SES and their potential role as drivers of social inequalities in chronic inflammation in adulthood.

1.3. Life course determinants of chronic inflammation

When the immune system detects injury or an invading pathogen, an inflammatory response mobilizes cellular and biochemical defenses that repair damaged tissue and eliminate the pathogen. This process is coordinated by pro- (e.g., IL1b, IL6, TNFa) and anti-inflammatory (e.g., IL10) cytokines, which—along with CRP, an acute phase reactant produced by the liver—are frequently measured in circulation as indicators of ongoing inflammatory activity (Pearson et al. 2003, Black et al. 2004). Effective regulation of inflammation is essential since excessive or chronic activation can cause tissue damage and contribute to the development of a wide range of negative health outcomes, including CHD, type 2 diabetes, metabolic syndrome, late-life disability, and mortality (Pradhan et al. 2001, Ridker et al. 2003, Kuo et al. 2006, Jenny et al. 2007). Similarly, there is growing awareness that inflammatory processes during pregnancy play important roles in adverse birth outcomes, including preterm delivery and intra-uterine growth restriction (Romero et al. 2007, Challis et al. 2009).

Socioeconomic inequalities in these health outcomes are widely recognized (Adler et al. 1994, Mackenbach and Kunst 1997, Marmot et al. 1997, Keppel et al. 2002, Cohen et al. 2003), and inflammation has become a major focus of research as a potentially important mechanism linking social environments and health (Alley et al. 2006, Crimmins and Finch 2006, Nazmi and Victora 2007, Ranjit et al. 2007). Several studies have demonstrated socioeconomic gradients in CRP, with higher concentrations of CRP found in groups with lower levels of education and income (Alley et al. 2006, Nazmi and Victora 2007, Ranjit et al. 2007). Complementary lines of inquiry consider whether inflammation mediates the impact of intermediate psychosocial factors

(e.g., stress, depression, social isolation) on morbidity and mortality (Miller et al. 2002, Miller et al. 2003, McDade et al. 2006, Cole et al. 2007, Ranjit et al. 2007). Prior research has suggested that these factors, as well as obesity/overweight and infectious exposures, represent more proximate factors that explain part—but not all—of the established link between SES and inflammation (Ford et al. 2004, Aiello and Kaplan 2009, McDade et al. 2010).

Although inflammation is most often studied in relation to environments in adulthood, there is growing evidence that early life environments have long-term, independent effects on immune regulation and inflammation (Shanks and Lightman 2001, McDade 2006, Taylor 2010). For example, low early life SES is associated with elevated CRP among adults in the CARDIA study (Taylor et al. 2006), and it predicts increased pro-inflammatory and decreased anti-inflammatory gene expression in otherwise healthy adults (Miller et al. 2009). Low birth weight has also been associated with elevated inflammation in adulthood in several cohorts (Sattar et al. 2004, Danese et al. 2007, Tzoulaki et al. 2008, McDade et al. 2010).

In a recent analysis of Add Health data, Goosby and colleagues (Goosby et al. 2016) document "chains of risk" in which birthweight and body mass early in life predict body mass in adolescence and young adulthood, which in turn predict chronic inflammation. McDade and colleagues have also reported significant associations between birth weight and CRP in young adulthood in Add Health (McDade et al. 2014). Of note, a one kilogram increase in birth weight predicted a 9.2% reduction in adult CRP across the cohort, whereas sibling comparison models reported stronger associations, with a 24% reduction in CRP for each kilogram. Results from sibling comparisons are significant in that they control for many hard-to-measure attributes of families and communities that might otherwise confound associations between early

environments and later life health, and they increase confidence in concluding that aspects of the prenatal environment have causal effects on the regulation of inflammation in adulthood.

While birth weight has been the primary focus in DOHaD, the postnatal nutritional environment can also have lasting effects on inflammation. Breastfeeding, in particular, provides nutritional and immunological support to infants, and studies in New Zealand, Scotland, and the US have documented lower CRP in adults who were breastfed as infants (Williams et al. 2006, Rudnicka et al. 2007, McDade et al. 2014, Olson and Hayward 2017). The effects of breastfeeding on inflammation can be direct, through the shaping of regulatory pathways during sensitive periods of immune development in infancy (Field 2005, McDade 2012), and they can be indirect, through programming of metabolic pathways that contribute to the accumulation of body fat and the emergence of overweight/obesity (Harder et al. 2005, Schaffler et al. 2006). Emerging evidence also points to obesogenic effects of formula feeding on the gut microbiota in infancy (Forbes et al. 2018).

In Add Health, we previously documented a negative association between breastfeeding duration and adult CRP, with an important inflection point at 3 months: CRP concentrations in young adulthood were almost 30% higher among individuals who were not breastfed as infants in comparison with those breastfed for 3 months or longer (McDade et al. 2014). Sibling comparisons suggested the possibility of stronger effects, with 46% higher CRP in siblings breastfed for less than three months (or not at all), in comparison with a sister for brother who was breastfed for longer than three months. Mediation analyses suggested that approximately 40% of the association between breastfeeding duration and adult CRP in Add Health was accounted for by waist circumference, consistent with the established associations between

breastfeeding and adiposity (Harder et al. 2005, Metzger and McDade 2010, Olson and Hayward 2017), and between adiposity and chronic inflammation (Schaffler et al. 2006).

1.4. Social inequalities in birth outcomes and breastfeeding duration

Race- and class-based inequalities in birth outcomes in the US are large and growing: Infants born to Black women are almost twice as likely as White infants to be born preterm or low birth weight, and more than twice as likely to die in infancy (Mathews and MacDorman 2013, Martin et al. 2015). Similar trends are seen when comparing low income or poorly educated women with high SES women: Risk of infant mortality is more than double for a high school drop out compared with a college graduate (Blumenshine et al. 2010, Green and Hamilton 2019). And after decades of overall improvement, average birth weights in the US may now be on the decline, with steeper drops for low SES and Black women that are widening birth weight inequalities (Morisaki et al. 2013, Catov et al. 2015). This is a significant, and costly, public health problem: Preterm deliveries alone cost more than $26 billion annually (National Center for Health Statistics 2012).

Patterns of breastfeeding initiation and duration follow similar social gradients in the US, with overall low levels of breastfeeding in comparison with current guidelines. The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding—defined as feeding an infant only breast milk, with no other liquids or solids other than vitamins or medicines—for six months, with continued breastfeeding for one year or longer as complementary foods are introduced (AAP 2012). As of 2016, 83.8% of infants born in the US were breastfed in some form, but only 25.4% were exclusively breastfed for six months, and 36.2% were breastfed at one year (Centers for Disease Control and Prevention 2020). While these rates fall short of current guidelines, they are much better than the late 70s and early 80s, when breastfeeding was

initiated for only one in two infants in the US, and when fewer than one in four were still receiving any breastmilk at six months (Institute of Medicine et al. 1991, Ryan 1997).

As with birth weight, social inequalities in breastfeeding are evident. Babies born to college graduates are approximately twice as likely to meet AAP recommendations as high school graduates (32.9 vs. 18.7% exclusive breastfeeding to 6 months; 48.6 vs. 24.0% breastfeeding at 12 months). Similarly, poverty-income-ratio predicts breastfeeding, with 31.0% of the most affluent households (PIR > 600) breastfeeding exclusively at 6 months and 46.0% continuing at one year, in comparison with prevalences of 17.1% and 24.3%, respectively, for households with PIR less than 100. Race/ethnic differences in breastfeeding are also present, although differences across self-identified race/ethnic groups are smaller than those associated with SES (Centers for Disease Control and Prevention 2020).

It is important to note that social inequalities in breastfeeding initiation are much smaller than the inequalities in duration: The vast majority of mothers in the US start to breastfeed their babies soon after delivery, but only more educated and affluent women are able to continue breastfeeding for longer periods of time. And even the majority of these women fall short of current AAP recommendations, attesting to the challenges that mothers face in the absence of social policies and cultural norms that support and promote extended breastfeeding in the US (Johnston and Esposito 2007, Hausman 2014).

1.5. Objectives

In the current study, we aim to elucidate the developmental origins of the socioeconomic gradient in chronic inflammation in young adulthood, with a specific focus on LBW and BF duration. We unpack the SES-based gradient in CRP observed in the Add Health cohort with staged structural equation models that introduce both proximate (adult) and distal (early life)

contributors to inflammation and its uneven socioeconomic distribution. Our models also highlight the roles of BMI and parent education in understanding these relationships of interest.

2. Methods

2.1. Data

We used data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), a nationally representative cohort of adolescents in the United States in 1994-95 (Harris et al. 2019). The core sample included 20,745 adolescents, 12-19 years old, at Wave 1 (W1). Participants and their parents were recruited with informed consent and interviewed regarding a wide range of social, economic, behavioral, and health measures. For the current study, W1 data were linked to Wave 4 (W4) follow-up data, collected in 2007-8 when participants were 24-32 years old. This dataset includes W4 data from in-home interviews and biomarker data (n=15,701) (Whitsel et al. 2012).

2.2. Inflammation

Inflammation was measured using a high sensitivity immunoassay quantifying CRP in dried blood spot (DBS) samples, with values converted to plasma-equivalents (Whitsel et al. 2012) and log-transformed. A single CRP measure provides information on stable, between-individual differences in levels of chronic inflammation that predict future disease risk (Pearson et al. 2003). The DBS samples were collected as part of the W4 in-home interview from 94% of Add Health participants. Among participants that completed both W4 components, 13,166 DBS samples were successfully assayed for CRP. In order to control for acute elevations in inflammation that obscure our ability to determine stable levels of systemic inflammation, we excluded individuals with CRP>10 mg/L, individuals experiencing infectious disease symptoms

(cold or flu-like symptoms such as sore throat, runny nose, or cough; fever; night sweats; nausea, vomiting, or diarrhea; bloody stool or urine; frequent urination; or skin rash or abscess) in the two weeks preceding blood collection, and women who reported being pregnant (Pearson et al. 2003, McDade et al. 2014). The remaining sample with complete data included 7,610 participants.

2.3. Independent variables

Socioeconomic status was measured using an index based on household income, college completion, tract level poverty (proportion of population below poverty level in past year), and self-assessed SES (10-point scale). The index was calculated from optimally weighted factor scores in Stata using the regression method and a polychoric correlation matrix to account for categorical input variables. Rounded to the nearest integer, values for the sample on the constructed index range from 0 to 7.

Birth weight and breastfeeding were measured based on parent interviews at W1. Low birth weight (LBW; ≤ 2,500 grams) was constructed as a dichotomous variable (LBW=1). Breastfeeding duration was constructed as a categorical variable, based on prior research and response options in the W1 survey: none, less than three months, and three months or more (McDade et al. 2014). Body mass in early adulthood was measured as body mass index (BMI), calculated from measured height and weight at W4 and modeled as a continuous variable (kg/m^2). Additional covariates included sex, contraceptive use in the past 12 months (reported use of birth control pills, Depo-Provera, Norplant, or an intrauterine device, coil, or loop), anti-inflammatory medication use in the past four weeks (salicylates or nonsteroidal anti-inflammatory, cox-2 inhibitor, inhaled corticosteroid, corticotropin/glucocorticoid, antirheumatic/antipsoriatic, or immunosuppressive medication), smoking regularly in last 30

days (≥ 1 cigarette per day), and parent college completion (graduated from a 4-year college or university, or professional training equivalent).

2.4. Analysis

We first determined the unadjusted SES gradient in chronic inflammation at W4. Based on the distribution of CRP (mg/L), we calculated the gradient as the slope in mean $\log_{10}$CRP over the 8-point SES index using survey weighting to account for the study design (Chen and Harris 2020). Our constructed SES index is scaled so that the survey-weighted interquartile range is 2 points. Preliminary analyses also included consideration of bivariate associations between adult SES, parental SES, BMI, birth weight, and breastfeeding.

To assess the relative contributions of LBW and BF to the SES gradient in CRP, we employed generalized linear models of $\log_{10}$CRP in nested stages. First, we adjusted for proximate risk factors not considered to be on the causal pathway linking LBW and BF to CRP (contraceptive use, anti-inflammatory medications, smoking). Next, we added parent education as a potential contributor to both early-life environment and adult inflammation. This model served as our baseline for evaluating the contributions of LBW and BF in the final model set.

Our final set of models added terms to the baseline model that considered the contributions of LBW and BF, separately and then jointly. This final model set comprised generalized structural equation models (SEM) within which the baseline models were still nested. Each measure was included as a predictor of $\log_{10}$CRP directly and through pathways mediated by BMI (including a quadratic term for nonlinearity). Two-way interaction terms were included between adult SES and both LBW and BF. These interactions allowed for associations to vary by SES, thereby enabling us to assess whether and how improvements to LBW, BF, or both attenuated the SES gradient. To estimate the degree to which specified improvements in

these measures would potentially diminish the SES gradient, we estimated predictive margins from each model for comparison. These models produce predicted $\log_{10}$CRP values based on the weighted covariate distributions in the study cohort. For the second stage, or set of models, adjusting for LBW, BF, or both, we focused on conditional predictive margins fixed at advantageous values for breastfeeding duration (≥ three months [BF=3+]) and birth weight (birth weight ≥ 2,500 grams [LBW=0]).

All statistical analyses were performed in Stata 15 (StataCorp, College Station, TX), using gsem, margins, and svy commands. Survey weights were provided by the Add Health study team to account for the study design and missingness (Harris 2013). Characteristics of the analytical subsample were compared with the entire W4 sample with completed interviews, with few differences detected (supplementary Table S1).

We performed multiple sensitivity analyses to assess the robustness of our findings, including replicating our analyses with the inclusion of CRP values above 10 mg/L and respondents reporting recent infectious disease symptoms, alternative specifications of BMI, and adjustments for additional factors potentially underlying inequalities in early life environments and adult inflammation. This included additionally adjusting for maternal education alone, maternal age at birth, birth order, and number of siblings.

3. Results

Sample characteristics are summarized in Table 1, including the measures that inform the SES index. Initial bivariate analysis confirmed a strong negative association between adult SES and CRP at ages 24-32 years. This pattern was consistent across transformations of CRP, including a strong linear fit with $\log_{10}$CRP (supplementary Figure S1). Along the fitted line

(Figure 1), mean $\log_{10}$CRP equals 0.293 at the lowest SES level, which is equivalent to a geometric mean CRP concentration of 1.97 mg/L. At the highest level of SES, mean $\log_{10}$CRP is -0.009, or 0.98 mg/L. The unadjusted SES gradient—the difference in $\log_{10}$CRP associated with a one-unit higher SES index value—is -0.043 (95% CI: -0.056, -0.030).

Bivariate analyses also confirmed associations between CRP and the early environment (supplementary Figure S2). Individuals who were breastfed for ≥ 3 months had 18% lower CRP. Unadjusted, there was not a clear association between CRP and LBW. Breastfeeding duration and birth weight, along with adult SES, are also patterned by parental education (supplementary Table S2). Having a parent who completed college was associated with a 63% higher probability of breastfeeding for three or more months, an increase in birth weight of 181 g, a 11% higher CRP concentration, and a one-point higher position on the SES index, relative to having a parent who did not complete high school.

Next, we assessed the relative contributions of these variables, along with proximate risk factors, to the observed SES gradient in CRP. The gradient, or slope, estimated from each model using adjusted predictive margins is plotted alongside the unadjusted slope in Figure 1. The model including parent education is the baseline for evaluating how LBW and BF duration account for shifts in the SES gradient in CRP.

Results indicate a strong attenuation of the SES gradient in CRP when BF, LBW, and BMI are added to the models. This attenuation is summarized in Table 2. Relative to the baseline, accounting for LBW and setting LBW at 0 was associated with a 47% reduction in the slope associating SES and CRP. Breastfeeding plays an even stronger role: When BF duration is 3 months or greater, the SES gradient in CRP is reduced 78%. Adjusting for both LBW and BF was associated with an 81% reduction.

Using the same fully adjusted SEM from above, we examined the patterns of association among key variables, with specific attention to BMI as a potential mediator linking LBW and BF to adult CRP (Figure 2). To aid the interpretation of non-linear terms, measures of association are presented as predictive marginal differences (derivatives of mean predicted CRP based on the predictor values of each individual). Thus, these estimates can be interpreted similarly to coefficient values, but are standardized by cohort member characteristics to incorporate non-linear patterns. For example, the numerical derivative of $\log_{10}$CRP with respect to BMI is 0.04. This represents the adjusted difference in $\log_{10}$CRP associated with a 1 kg/m^2 difference in BMI, averaged across individual predicted values. Breastfeeding for three or more months is associated with a lower BMI by 0.70 kg/m^2, relative to not breastfeeding; and LBW is associated a lower BMI by 0.96 kg/m^2. The summary estimates linking LBW and BF directly to CRP are calculated similarly, as marginal differences independent of BMI. All SEM coefficient coefficients are listed in supplementary Table S3.

Overall, SEM results indicate that links between LBW, BF duration, and CRP are largely mediated through their associations with BMI, which was positively associated with CRP in both unadjusted (supplementary Figure S3) and adjusted analyses (supplementary Table S3). Comparisons with models omitting BMI (supplementary Table S4) reveal that BMI accounts for 52% of the marginal difference in $\log_{10}$CRP associated with breastfeeding $\geq$ 3 months. The direct association between LBW and higher CRP is only revealed after taking into account BMI as a mediator, which is explained jointly by the negative association between LBW and BMI and the positive association between BMI and CRP. Additionally, when BMI is not taken into account LBW and BF $\geq$ 3 months are associated with smaller reductions in the SES gradient in CRP (supplementary Table S5).

Finally, as expected, parent education is additionally important for adult inflammation in multiple ways. Beyond patterning birth weight, breastfeeding, adult SES, and BMI, it also maintains an independent association with adult CRP. After adjusting for other independent and mediating variables in our model, individuals with a parent who completed college still experience a -0.04 (95% CI: -0.07, 0.00) lower $\log_{10}$CRP than individuals with a parent who did not complete high school.

Sensitivity analyses suggest that findings and their interpretation are robust to modeling choices related to our exclusion criteria and additional adjustments (Table S5). Replicating our analyses with the inclusion of CRP values above 10 mg/L resulted in a steeper SES slope in $\log_{10}$CRP, with more of the slope accounted for by LBW and BF duration. Associations were attenuated when individuals with infectious symptoms at the time of blood collection were included. Additional baseline adjustments for maternal education, age at birth, number of siblings, and birth order, all resulted in SES slopes and attenuation similar to the main analysis. Adjusting for BMI at baseline led to smaller estimates of the slope and attenuation, as expected. Not adjusting for BMI at all led to the least amount of attenuation across adjustments, as discussed above.

4. Discussion

Social inequalities in cardiometabolic diseases in the US are large and growing. Environments early in life shape the development of physiological systems and have lasting effects on health in adulthood. In this analysis we weave these threads together to investigate the extent to which the SES gradient in chronic inflammation in adulthood can be explained by patterns of birth weight and breastfeeding in infancy. Results indicate that environments early in

infancy are important determinants of chronic inflammation in adulthood, and that breastfeeding in particular plays an important role in shaping the SES gradient in CRP.

First, our study documents substantial inequalities in chronic inflammation in a large, representative cohort of young adults in the US, with lower SES associated with significantly higher concentrations of CRP. This observation is consistent with prior studies of older adults (Alley et al. 2006, Nazmi and Victora 2007, Ranjit et al. 2007, McDade et al. 2010), but the magnitude of the SES gradient in CRP is particularly striking given that the sample is comprised of young adults. CRP is a strong, preclinical predictor of cardiometabolic disease and overall health, and it is clear that processes contributing to health inequalities are in motion in young adulthood despite the fact that the prevalence of clinical disease is relatively low compared with later stages of the life course.

Second, we uncover important contributions of the environment in infancy to the SES gradient in CRP in adulthood. In particular, our models point toward breastfeeding as playing a central role in the developmental origins of social inequities in chronic inflammation. Members of the Add Health cohort were born in the late 1970s and early 1980s, during a time when rates of breastfeeding in the US were on the rise after falling to historic lows (Institute of Medicine et al. 1991, Ryan 1997). In our sample, more than half the participants were not breastfed at all, and less than one in three was breastfed for three months or longer. However, if all of the members of the cohort had been breastfed for ≥3 months, our estimates suggest that the SES gradient in chronic inflammation in young adulthood would be reduced by 78%. By contrast, low birth weight—a widely studied marker of the prenatal environment—accounts for only 47% of the SES gradient in CRP.

It is important to keep in mind that our estimates are based on observational data, and while we control for a wide range of potentially confounding influences it is possible that the associations among breastfeeding, birthweight, BMI, and CRP are not causal. However, our findings build upon, and are consistent with, prior studies that document significant long term effects of breastfeeding and birth weight with quasi-experimental research designs (Metzger and McDade 2010, McDade et al. 2014).

Furthermore, biological mechanisms through which breastfeeding can exert lasting effects on immune development are well-established (Field 2005, Cacho and Lawrence 2017, Vieira Borba et al. 2018). Breastmilk is comprised of bioactive proteins and cells that not only protect against infection, but also promote the maturation and regulation of the infant's immune defenses. In addition, human milk oligosaccharides serve as prebiotics that, along with the microbiota in milk, promote the establishment of a healthy intestinal microbiota in infancy, which in turn modulates intestinal barrier function and regulates local and systemic inflammatory responses (Stiemsma and Michels 2018). Lastly, breastfeeding can also have indirect effects on inflammation through the programming of metabolic pathways that contribute to the development of overweight/obesity and the production of pro-inflammatory cytokines in adipose tissue (Harder et al. 2005, Schaffler et al. 2006). Our results underscore the importance of this latter pathway: Approximately half of the association between breastfeeding and CRP is explained by adult BMI.

This study makes an important contribution in evaluating the developmental origins of social inequities in health in adulthood. Using a consequentialist epidemiological approach, we go beyond the focus on individual risk factors to illuminate the processes that lead to inequities in population-based risk (Keyes and Galea 2015). While prior research has documented how

exposures in infancy shape individual trajectories of later life health, we consider the implications for population health by demonstrating how shifts in breastfeeding and birthweight can modify distributions of chronic inflammation in adulthood. By focusing on the SES gradient in inflammation as our primary outcome, we prioritize actionable goals that would have the greatest impact on reducing social inequities in health.

In particular, our models suggest that extending the duration of breastfeeding to three months or longer—a modest goal in relation to current AAP guidelines—could dramatically shift the population distribution of chronic inflammation and reduce SES-based inequities in cardio-metabolic disease risk. Barriers to extended breastfeeding in the US are substantial, but there is clear evidence for policies that effectively promote the initiation and continuation of breastfeeding (Baker and Milligan 2008, Pérez-Escamilla et al. 2016, Hamad et al. 2019). While many programs focus on attitudes and knowledge of mothers, fathers, and healthcare providers, social policies that address structural barriers to extended breastfeeding (e.g., paid family leave) will likely have greater impact on reducing social inequities in breastfeeding.

Our study additionally highlights the importance of parental SES and the role of intergenerational social advantage and disadvantage that continue to shape population health inequities. In our analyses, parental education predicts birthweight and breastfeeding, but remains independently and significantly associated with lower CRP. Any successful intervention on early life environments must jointly address socioeconomic barriers faced by parents of young children in ways that structurally break intergenerational chains of poverty and disadvantage.

Our conclusions are based the analysis of data from a large, nationally representative cohort of young adults. However, the study is observational and while we apply an adjusted

structural modeling approach with multiple robustness tests, we cannot completely rule out the possibility that omitted variables may bias associations of interest. Additional limitations include our use of a single measure of CRP to index chronic inflammation, and our reliance on maternal recall to provide information on birth weight and breastfeeding duration. However, maternal reports of birth weight correlate highly with birth records, and recalls of breastfeeding initiation and duration have been shown to be reported with high validity and reliability (Tomeo et al. 1999, Li et al. 2008). Lastly, the Add Health study did not collect information on gestational age, so it is not possible for us to determine whether associations between LBW and CRP are due to pre-term vs. small-for-gestational age deliveries.

This study contributes to existing research that has revealed how early-life development and nutrition affect health over the life course by examining more closely how these processes underlie socioeconomic inequities in U.S. adult health. In doing so, it builds beyond an understanding of development as a risk factor for adult health and toward a more consequential epidemiological understanding of its critical role in eliminating persistent health inequities affecting the U.S. population.

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Table 1. Descriptive statistics for analytic sample (N=7,610).

	Summary statistic	Standard Deviation
Inflammation		
Median CRP	1.47	
Mean $\log_{10}$CRP	0.15	0.47
Socioeconomic Status		
Mean constructed SES index	3.39	1.15
Education		
< High school	9%	
High school	18%	
Some college	43%	
College (4 year)	19%	
More than college	11%	
Household income (thousands)		
< $20	12%	
$20-49.9	32%	
$50-74.9	25%	
$75+	31%	
Census track percent population <PL	15%	
Mean self-assessed SES (1-10)	5.05	1.72
Parent education		
< High school	16%	
HS equivalent	44%	
Some college	18%	
College (≥4 year)	23%	
Early environment		
Mean birth weight (grams)	3,366	605
Low birth weight (<2,500 g)	7%	
Breastfeeding		
None	55%	
< 3 months	14%	
≥ 3 months	31%	
Other adult risk factors		
Mean BMI (kg/m^2)	28.3	6.8
Female sex	43%	
Contraceptive use	38%	
Regular smoker	25%	

	Summary statistic	Standard Deviation
Anti-inflammatory medication use	26%	

Table 2. SES gradient in $\log_{10}$CRP estimated using conditional predictive marginal differences with four different models and specifications for LBW and BF. The baseline (top left) adjusted for parent education, sex, contraceptive use, smoking, and anti-inflammatory medication.

	Without LBW	**LBW- and BMI-adjusted & Conditioned on LBW=0**
Without BF *Percent reduction*	-0.032 (-0.047, -0.012)	-0.017 (-0.031, -0.005) *47%*
BF- and BMI-adjusted & Conditioned on BF= 3+ months *Percent reduction*	-0.007 (-0.029, 0.014) *78%*	-0.006 (-0.027, 0.015) *81%*

Figure 1. Conditional predictive margins for log_{10}CRP by SES based on nested model stages adjusting for proximate risk factors, parental education, and, finally, adjusting and conditioning on LBW and BF, separately and jointly.

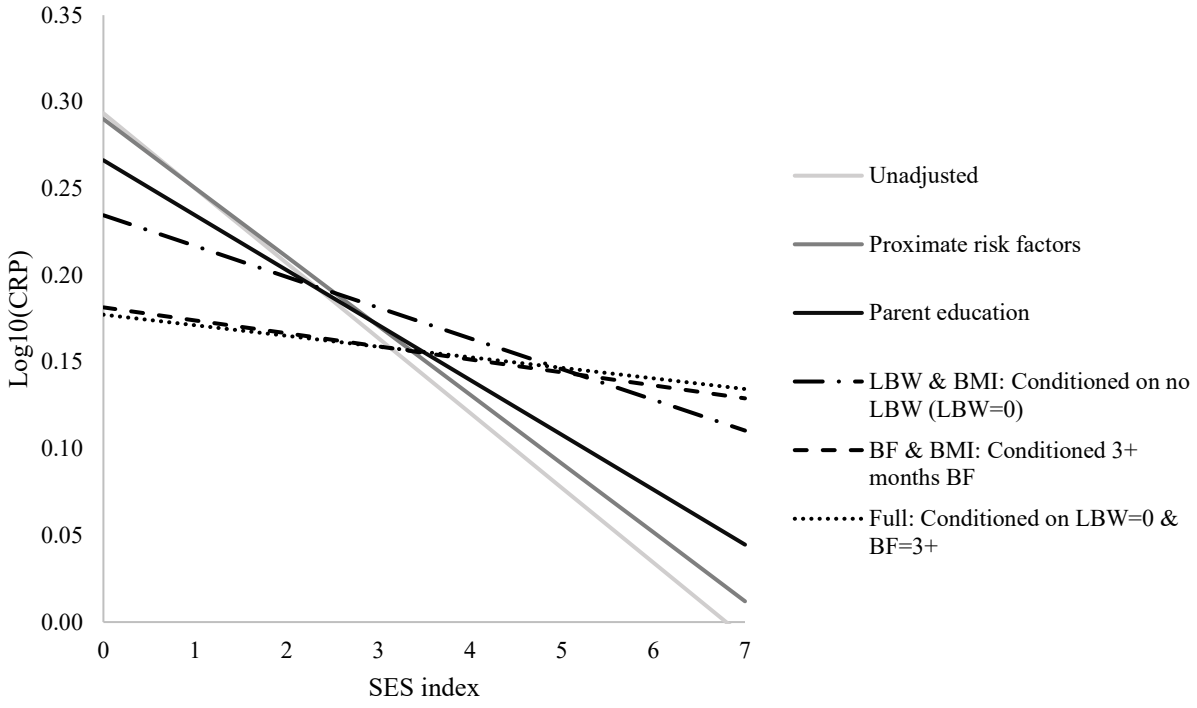
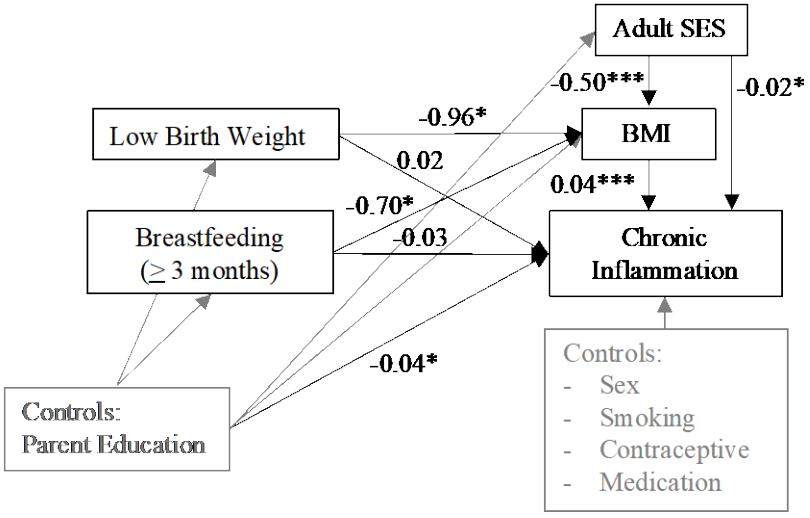


Figure 2. Summary of full SEM results using predictive marginal differences with the Add Health cohort at W4 (survey-weighted). The summary measures referencing categorical variables compare the highest and lowest value groups. Statistical test results indicated as: *p<0.05, **p<0.01, ***p<0.001.



SUPPLEMENTARY MATERIALS

Table S1. Analytical and full W4 sample characteristics. Variable means and standard deviations, or percentages, are presented. Separate columns include missingness counts for the full and analytical samples.

	Analytical sample	Missing (n)	Missing (%)	W4 sample	Missing (n)	Missing (%)
Count	7,610			14,800		
Inflammation						
Log(CRP)	0.15 (0.47)	0	0%	0.32 (0.57)	1634	11%
Socioeconomic Status						
Constructed Index	3.39 (1.15)	485	6%	3.34 (1.17)	1005	7%
Education		0	0%		4	0%
< High school	9%			9%		
High school	18%			18%		
Some college	43%			43%		
College (4 year)	19%			19%		
More than college	11%			11%		
Household income (thousands)		474	6%		976	7%
< $20	12%			13%		
$20-49.9	32%			33%		
$50-74.9	25%			24%		
$75+	31%			30%		
Census track percent population <PL	15%	2	0%	15%	6	0%
Self-assessed SES (1-10)	5.0 (1.7)	14	0%	5.0 (1.8)	39	0%
Parent education		1035	14%		2098	14%
< High school	16%			16%		
HS equivalent	44%			44%		
Some college	18%			19%		
College (≥4 year)	23%			22%		
Early environment						
Birth weight (grams)	3366 (605)	1296	17%	3346 (606)	2592	18%
Low birth weight (<2,500 g)	7%			8%		
Breastfeeding		1184	16%		2352	16%
None	55%			56%		
< 3 months	14%			14%		
≥ 3 months	31%			30%		
Other adult risk factors						
BMI (kg/m^2)	28.3 (6.8)	73	1%	29.1 (7.5)	233	2%
Female sex	43%	0	0%	49%	0	0%
Contraceptive use	38%	32	0%	37%	63	0%
Cigarettes in last 30 days	25%	58	1%	25%	125	1%
Anti-inflammatory medication use	26%	0	0%	30%	0	0%

Figure S1. Inflammation by socioeconomic status (SES). Survey-weighted, unadjusted SES gradients in inflammation across transformations of CRP (mg/L). A strongly negative linear pattern between SES index and $\log_{10}$CRP was confirmed, based on no observed differences in the linear fitted and lowess smoothing predicted values.

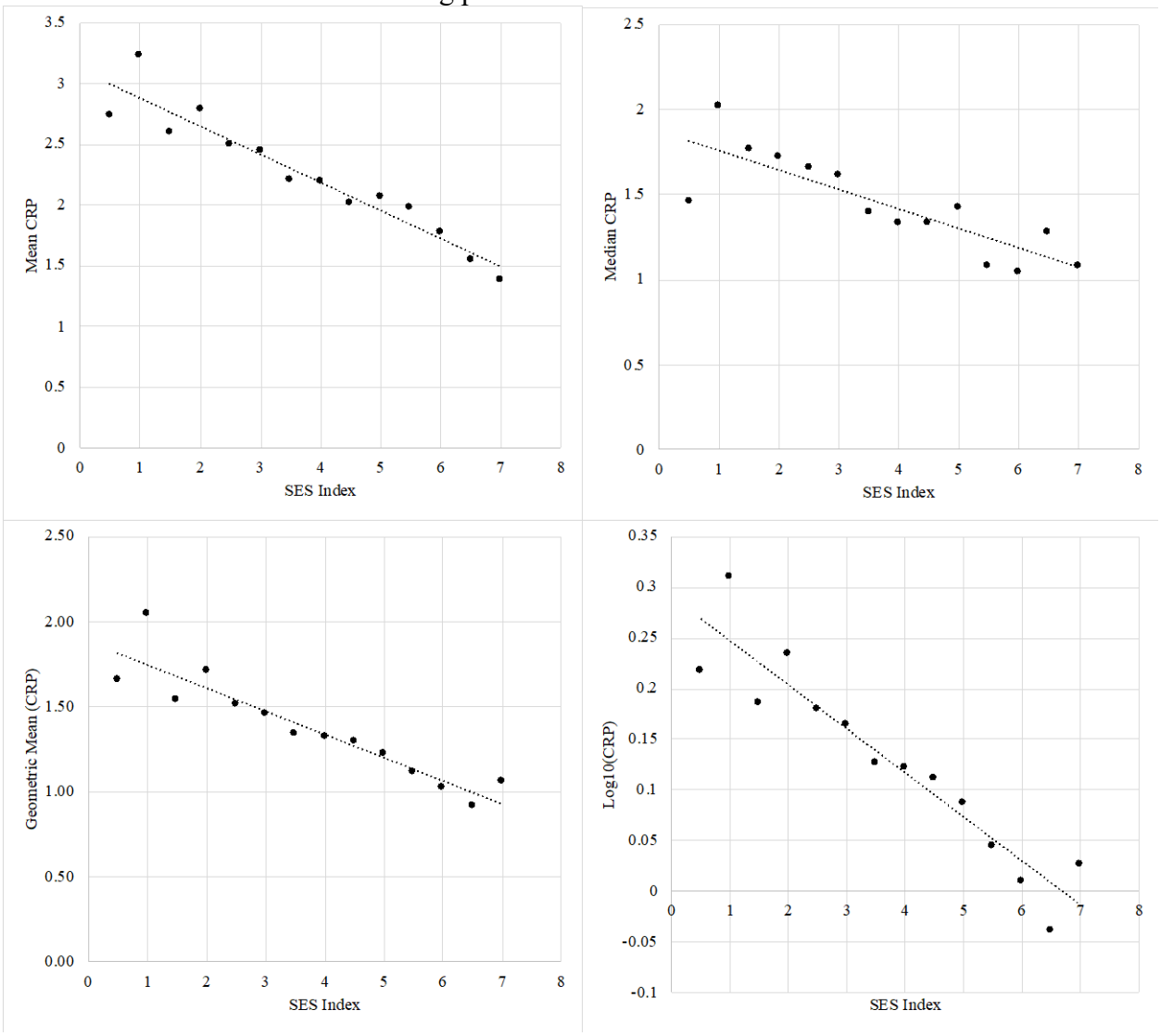
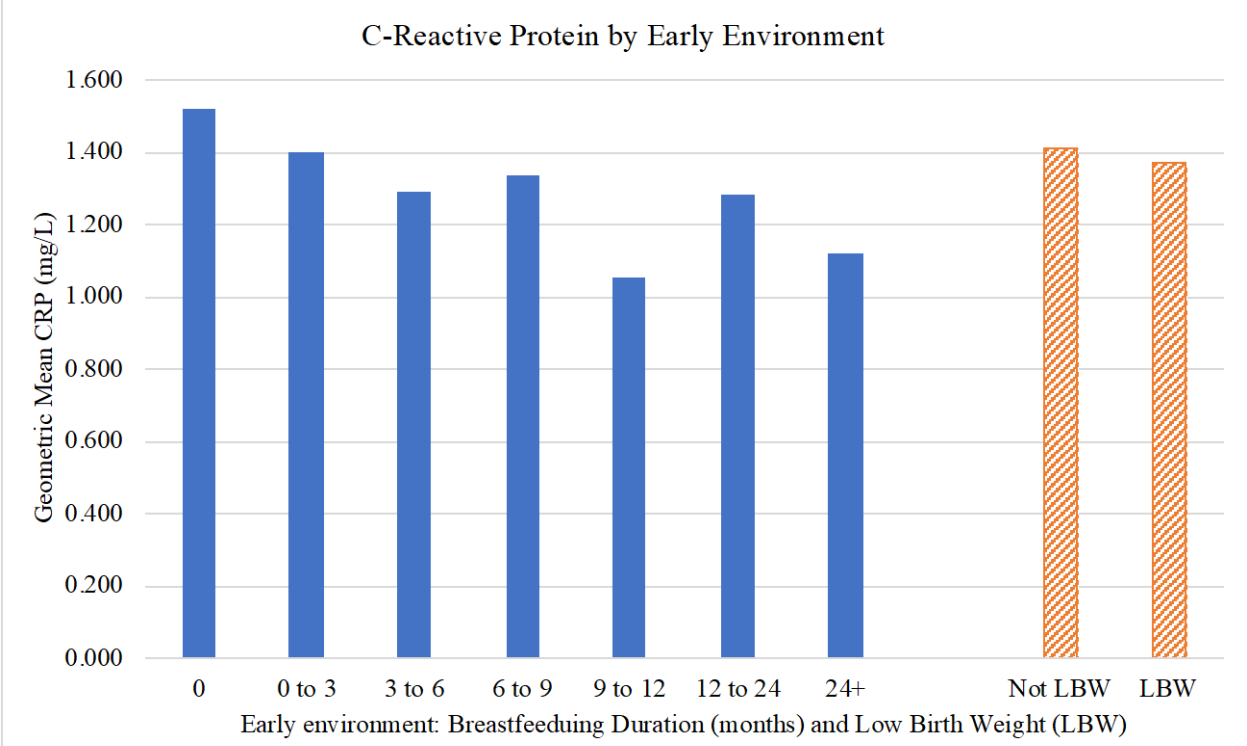


Figure S2. Inflammation by early environment factors. Survey-weighted distributions of CRP by breastfeeding duration in months (left) and low birth weight (LBW; right).



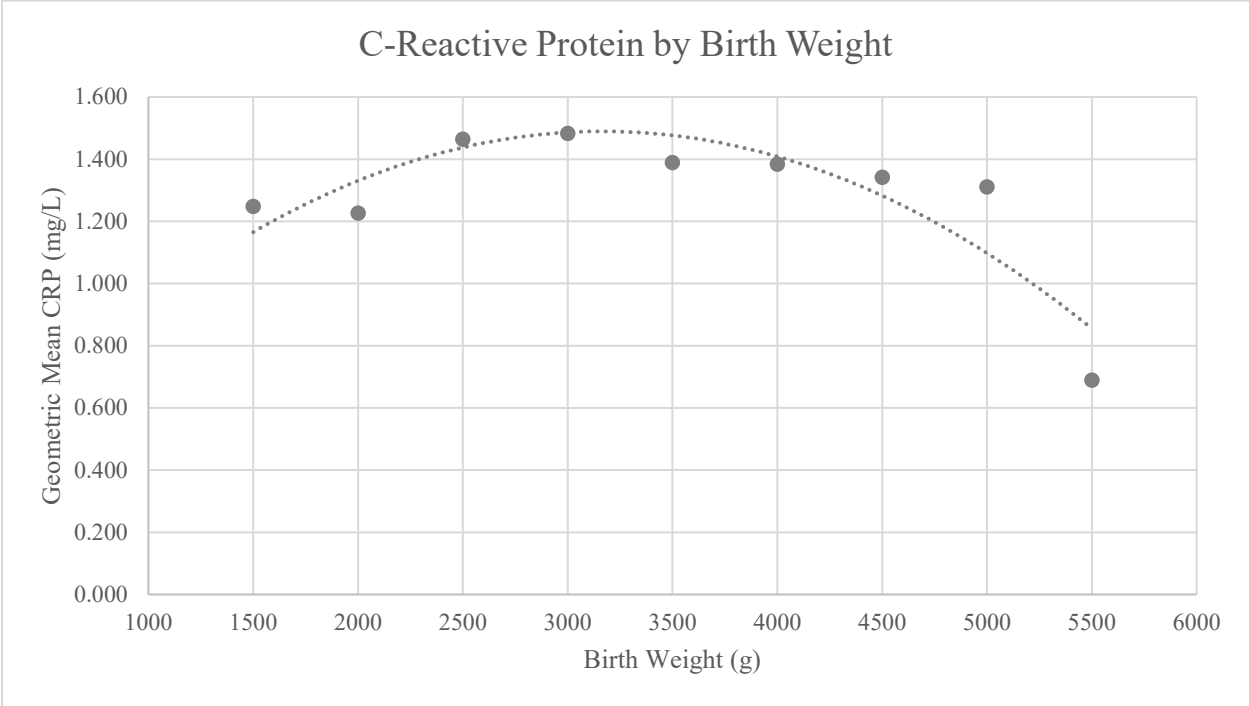


Table S2. Associations between parental education and breastfeeding, birth weight, and CRP in young adulthood. Survey-weighted, descriptive statistics (mean and standard deviation, or percent) for analytical variables of interest, disaggregated by parent education.

	Parent Education			
	< High school	**HS equivalent**	**Some college**	**College (≥4 year)**
$\log_{10}$CRP	0.21 (0.4)	0.18 (0.5)	0.14 (0.4)	0.07 (0.5)
Birth weight (g)	3234 (705)	3374 (582)	3390 (602)	3415 (562)
Breastfeeding (%)				
None	70%	64%	47%	34%
< 3 months	12%	13%	18%	14%
≥ 3 months	19%	22%	35%	52%
BMI (kg/m^2)	29 (7)	29 (7)	28 (6)	27 (6)
Adult SES	2.9 (1.1)	3.2 (1.0)	3.5 (1.1)	3.9 (1.2)

Figure S3. Body mass: Associations with CRP and early environment. Survey-weighted distributions of C-reactive protein by body mass (above) and BMI by early environment factors (below).

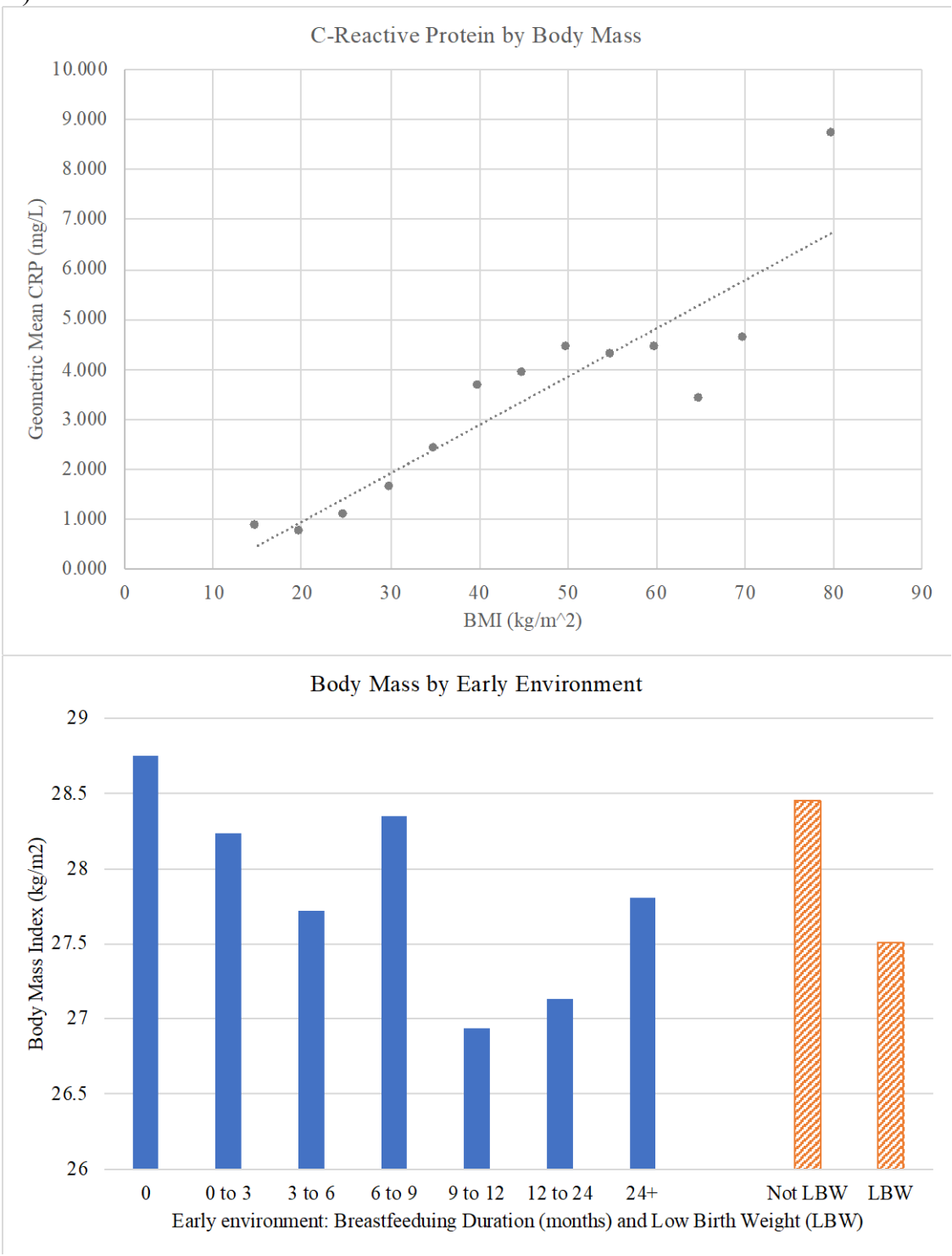


Table S3. Structural Equation Model Results. Coefficient and intercept point estimates (PE) and confidence intervals (CI) for nested stages of generalized linear regression on Log_{10}CRP. Results for BMI outcome are also included for second set of models, which utilize generalized structural equation modeling to account for mediation.

	PE	95% CI		PE	95% CI		PE	95% CI	
Log10(hsCRP)									
SES	-0.043	-0.056	-0.030	-0.040	(-0.053,	-0.026)	-0.032	(-0.048,	-0.016)
LBW (=1)									
*LBW*SES*									
Breastfeeding									
None									
< 3 months									
*< 3 months*SES*									
≥ 3 months									
*≥ 3 months*SES*									
BMI									
BMI^2									
Parent college completion							-0.082	(-0.121,	-0.044)
Female sex				0.115	(0.087,	0.143)	0.108	(0.079,	0.137)
Contraceptive use				-0.008	(-0.037,	0.021)	-0.015	(-0.046,	0.016)
Regular smoking				0.008	(-0.027,	0.043)	0.146	(0.105,	0.187)
Medication				0.046	(0.015,	0.077)	0.053	(0.019,	0.087)
Intercept	0.293	(0.248,	0.339)	0.101	(0.072,	0.130)	0.124	(0.089,	0.159)

Table S3, continued

	PE	95% CI		PE	95% CI		PE	95% CI	
Log10(hsCRP)									
SES	-0.018	(-0.030,	-0.005)	-0.015	(-0.033,	0.002)	-0.016	(-0.034,	0.002)
LBW	0.023	(-0.189,	0.235)				0.020	(-0.195,	0.236)
*LBW*SES*	-0.002	(-0.060,	0.056)				-0.001	(-0.060,	0.057)
Breastfeeding									
None				*(Ref.)*			*(Ref.)*		
< 3 months				0.094	(-0.034,	0.223)	0.101	(-0.029,	0.232)
*< 3 months*SES*				-0.028	(-0.062,	0.007)	-0.030	(-0.065,	0.006)
≥ 3 months				-0.055	(-0.153,	0.043)	-0.059	(-0.160,	0.042)
*≥ 3 months*SES*				0.008	(-0.019,	0.034)	0.010	(-0.017,	0.037)
BMI	0.070	(0.058,	0.083)	0.070	(0.058,	0.082)	0.070	(0.058,	0.082)
BMI^2	-0.001	(-0.001,	0.000)	-0.001	(-0.001,	0.000)	-0.001	(-0.001,	0.000)
Parent college completion	-0.041	(-0.075,	-0.008)	-0.038	(-0.072,	-0.003)	-0.037	(-0.072,	-0.003)
Female sex	0.171	(0.144,	0.197)	0.171	(0.144,	0.198)	0.175	(0.148,	0.201)
Contraceptive use	0.029	(0.000,	0.059)	0.027	(-0.002,	0.057)	0.029	(0.000,	0.059)
Regular smoking	0.060	(0.024,	0.096)	0.056	(0.021,	0.092)	0.060	(0.023,	0.096)
Medication	0.040	(0.008,	0.072)	0.039	(0.007,	0.070)	0.039	(0.007,	0.071)
Intercept	-1.392	(-1.599,	-1.184)	-1.380	(-1.584,	-1.177)	-1.392	(-1.597,	-1.186)
BMI									
SES	-0.566	(-0.837,	-0.294)	-0.275	(-0.618,	0.068)	-0.392	(-0.749,	-0.035)
LBW	-2.388	(-5.336,	0.560)				-1.904	(-4.841,	1.034)
*LBW*SES*	0.418	(-0.391,	1.226)				0.280	(-0.529,	1.090)
Breastfeeding									
None				*(Ref.)*			*(Ref.)*		
< 3 months				-0.003	(-2.128,	2.122)	-0.353	(-2.509,	1.803)
*< 3 months*SES*				-0.084	(-0.636,	0.469)	0.006	(-0.554,	0.565)
≥ 3 months				0.820	(-0.965,	2.605)	0.479	(-1.310,	2.268)
*≥ 3 months*SES*				-0.437	(-0.933,	0.058)	-0.350	(-0.847,	0.147)
Parent college completion	-1.085	(-1.740,	-0.431)	-0.804	(-1.435,	-0.173)	-0.844	(-1.484,	-0.203)
Female sex	-1.408	(-1.851,	-0.966)	-1.566	(-1.995,	-1.137)	-1.525	(-1.956,	-1.095)
Contraceptive use	-1.419	(-1.872,	-0.966)	-1.285	(-1.731,	-0.839)	-1.345	(-1.787,	-0.902)
Regular smoking	-1.212	(-1.858,	-0.565)	-1.176	(-1.813,	-0.539)	-1.211	(-1.845,	-0.577)
Medication	0.410	(-0.180,	1.000)	0.428	(-0.145,	1.002)	0.454	(-0.127,	1.035)
Intercept	32.046	(30.969,	33.124)	31.136	(29.969,	32.302)	31.679	(30.443,	32.915)

Table S4. Mediating role of body mass. Point estimates (PE) and confidence intervals (CI) from additional nested stages of generalized linear regressions on Log_{10}CRP highlight the intermediate role of body mass (BMI). PE's are predictive margins attributable to LBW and BF, respectively, net of differences mediated through BMI.

	Without BMI adjustment			**Full adjustment**		
	PE	**95% CI**		**PE**	**95% CI**	
LBW predictive marginal difference	-0.01	(-0.07,	0.05)	0.02	(-0.02,	0.05)
BF predictive marginal difference	-0.05	(-0.10,	-0.01)	-0.03	(-0.06,	0.01)

Table S5. Sensitivity Analysis Results. Sensitivity analysis (SA) results are listed for the seven alternative specifications, specifically the SES slope estimated from each model and its percent reduction under the staged model sets.

	SA 1			**SA 2**			**SA 3**			**SA 4**		
n	7,914			11,877			7,125			7,125		
	SES slope			SES slope			SES slope			SES slope		
Unadjusted	-0.06	***		-0.06	***		-0.04	***		-0.04	***	
Adjusted at baseline	-0.04	***	(Ref.)	-0.05	***	(Ref.)	-0.03	***	(Ref.)	-0.03	***	(Ref.)
LBW=0	-0.02	**	47%	-0.02	**	59%	-0.02	*	53%	-0.02	*	50%
BF= 3+ months	0.00		91%	-0.01		71%	-0.01		76%	-0.01		71%
LBW=0 & BF=3+	0.00		92%	-0.01		73%	-0.01		76%	-0.01		74%
	SA 5			**SA 6**			**SA 7**			**SA 8**		
n	7,125			7,125			7,125			7,125		
	SES slope			SES slope			SES slope			SES slope		
Unadjusted	-0.04	***		-0.04	***		-0.04	***		-0.04	***	
Adjusted at baseline	-0.03	***	(Ref.)	-0.04	***	(Ref.)	-0.02	*	(Ref.)	-0.03	***	(Ref.)
LBW=0	-0.02	**	41%	-0.02	**	47%	-0.02	**	-13%	-0.04	***	-16%
BF= 3+ months	-0.01		74%	-0.01		69%	-0.01		56%	-0.03	**	3%
LBW=0 & BF=3+	-0.01		76%	-0.01		69%	-0.01		63%	-0.03	**	6%

*** p< 0.001, ** p< 0.01, * p<0.05

SA 1:	Include CRP>10 mg/L; ID symptoms (still) excluded
SA 2:	Include CRP>10 mg/L; ID symptoms included and adjusted for
SA 3:	Adjust for maternal education
SA 4:	Adjust for maternal age at birth (with quadratic term)
SA 5:	Adjust for sibship and birth order
SA 6:	Adjust for all variables listed in SA 4-6
SA 7:	BMI adjusted for at baseline
SA 8:	BMI not adjusted for across models