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Breastfeeding, Overweight Status, and Inflammation

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Abstract

An array of research documents a host of health benefits of breastfeeding for infants and children, including long-term health conditions arising from inflammation. Here, we provide new evidence about this association, focusing on the link between breastfeeding in infancy and inflammation in early adulthood. Our study is based on the National Longitudinal Study of Adolescent to Adult Health (Add Health) which allows us investigate a potentially important mediating pathway – overweight status from early adolescence into young adulthood. Results from pathway analyses in a structural equation modeling framework indicate that, in addition to a direct pathway linking breastfeeding and inflammation, an indirect pathway through overweight status across adolescence into young adulthood partially explains the association between breastfeeding and inflammation. Overweight status, moreover, links breastfeeding to inflammation not only through proximal timing of overweight status, but also through an indirect cascading process of overweight status over the life course that is evident in adolescence. Overall, this study highlights the importance of considering breastfeeding, overweight status and inflammation as dynamic life course processes that contribute to development of health inequalities.

Keywords

breastfeeding; inflammation; overweight status; life course

Inflammation is an important biological process that connects early life experiences with a range of health outcomes later in life. For example, harmful childhood exposures to infections and stress contribute to higher inflammation levels in children (Dowd, Zajacova, and Aiello 2009; Broyles et al. 2012; McDade et al. 2013; Slopen et al. 2013), promoting biological processes that culminate in disease and poor health in later life (Crimmins and Finch 2006). Low-grade inflammation across adolescence and into young adulthood is not only associated with poorer health (Shanahan et al. 2014a), but it also represents higher risk of chronic disease later in life, with strong implications for cardiovascular disease (Pearson et al. 2003; Shanahan, Freeman, and Bauldry 2014b). The pathways through which childhood exposures promote inflammation thus contribute to the development of disadvantage and health disparities over the life course. In the present study, we examine an important parental practice that influences social and biological processes and can potentially reduce children's development of inflammation and ultimately reverberate into adulthood – duration of being breastfed as an infant. Being breastfed during infancy not only

protects against infections (Jackson and Nazar 2006), but a longer duration of being breastfed as infants is also associated with lower levels of C-reactive protein (CRP), a key biomarker of inflammation, in early adulthood (Shanks and Lightman 2001; Williams, Williams, and Poulton 2006; Rudnicka, Owen, and Strachan 2007; McDade et al. 2014). Understanding early-life origins of inflammation, therefore, is a critical component of the life course origins of adult health.

In this study, we revisit this association between the duration of breastfeeding for individuals in infancy and their inflammation in early adulthood among a nationally representative sample of young adults using the National Longitudinal Study of Adolescent to Adult Health (Add Health). We add to current understanding of this association by examining a potentially important biosocial pathway – weight status in adolescence and young adulthood. Our life course framework pushes forward understanding of weight status to consider weight not just as a point-in-time measurement, but rather as a process that can unfold across development in important ways. Longer duration of being breastfed in infancy is related to a lower risk of being overweight across the life course (McCrory and Layte 2012; Metzger and McDade 2010; Owen et al. 2005). Being overweight, additionally, is associated with heightened CRP levels in adulthood (Hak et al. 1999; Visser et al. 1999). The role of breastfeeding duration in protecting individuals against inflammation across the life course, coupled with the contribution of weight status to later life inflammation, suggests overweight status may thus be an especially important pathway through which breastfeeding duration gets under the skin and is associated with inflammation after infancy. Thus, in examining the role of overweight status, we pay special attention to the overweight status across adolescence into young adulthood to capture how overweight status at different points in the life course may serve as pathways through which breastfeeding duration in infancy influences inflammation in young adulthood. By conceptualizing weight in this way, we are able to identify potential sensitive periods and possible chains of risk, given that weight in early life is associated with inflammation through weight in later periods (Goosby, Cheadle, and McDade 2016). Sensitive periods (or timing of being overweight) highlight particular moments across development that matter for long-term health. Chains of risk (or cumulative pathways of weight in one developmental moment being associated with weight across the life course) refer to how weight over time influences health outcomes, including inflammation. We apply a structural equation framework that allows us to simultaneously examine timing and cumulative pathways by statistically testing which indirect pathways contribute to the effect between breastfeeding duration and inflammation. Although prior research makes clear that breastfeeding has long-term consequences for overweight status over the life, prior research is largely silent regarding whether overweight status at later stages of the life course operate as pathways linking breastfeeding duration in infancy to inflammation in young adulthood.

Given the multifaceted benefits of breastfeeding for infants, not only for short-term nutrition promotion and infection protection but also for long-term weight and inflammatory processes, a more comprehensive understanding of the pathways through which breastfeeding duration impacts later life health will better inform policymakers and health care providers. Additionally, gaining a deeper understanding of overweight experiences as life course processes allows for more careful evaluation of intervention and the timing of

intervention. Explicating how breastfeeding duration in infancy may indirectly impact inflammation in early adulthood through overweight status across adolescence into young adulthood therefore sheds light on crucial links that contribute to the development of health disparities in the short- and long-term.

Breastfeeding, Weight Status, and Inflammation

Breastfeeding is touted as the gold standard for feeding infants, with a host of advantages conferred in the short- and long-term (The American Academy of Family Physicians 2014; Horta and Victora 2013; U.S. Department of Health and Human Services 2011; Eglash, Montgomery, and Wood 2008). In the short-term, breastfeeding helps protect against infection and disease; and, in the long-term, being breastfed as an infant is associated with benefits to blood pressure, asthma, type-2 diabetes, cholesterol, and overweight and obesity (Horta and Victoria 2013; U.S. Department of Health and Human Services 2011). The advantages of being breastfed that persist across the life course, however, are subject to initiation and duration of breastfeeding --- decisions conditioned by socioeconomic status (Heck et al. 2006; Beck et al. 1999; Hirschman and Butler 1981). As such, breastfeeding—and its duration—represents a process that is both social and biological, occurring during infancy, but having serious implications for health and well-being across the life course.

Unpacking the association between breastfeeding duration and inflammation and identifying mechanisms that relate these processes across the life course is important to elucidate ways in which breastfeeding gets under the skin and inflammation is promoted across different life course stages, thereby impacting inequalities in health. Given the metabolic implications of breastfeeding and inflammation, overweight status is a potential mechanism linking breastfeeding to inflammation. Indeed, weight status later in life is connected to early life factors, including breastfeeding (Salsberry and Reagan 2007). Further, weight status is dynamic across the life course such that, although weight trajectories are anchored in early life, disparities magnify with age across adolescence and into young adulthood (Harris, Perreira, and Lee 2009).

The protective nature of breastfeeding against overweight status, however, extends across the life course (Horta and Victoria 2013; Owen et al. 2005; Gillman 2002), and is often attributed to the higher protein intake and increased insulin response associated with breast milk (Horta and Victoria 2013). Individuals who are breastfed thereby develop heightened metabolic and hormonal responses to feeding, which do not diminish later in life. The association between breastfeeding and overweight status is a dose-response relationship, such that individuals who are breastfed for longer periods of time enjoy decreased risk of being overweight as compared to individuals who were not breastfed, and individuals who were breastfed for shorter durations (Harder et al. 2005). During adolescence and the transition to adulthood, therefore, when differences in weight status become more apparent across sub-groups of the population, the under-the-skin protection afforded to individuals who were breastfed for longer durations in infancy may be particularly salient.

At the same time, being overweight is associated with higher levels of inflammation across the life course (Visser et al. 2001; Visser et al. 1999). Researchers speculate that this

association could be related to proteins released by adipose tissue that promote the production of CRP (Visser et al. 2001). Indeed, a link between increased adiposity and higher CRP concentrations emerges as early as childhood (Dowd, Zajacova, and Aiello 2010). Overweight individuals, therefore, experience elevated inflammation as a function of their excess body fat.

In sum, an individual's duration of being breastfed as an infant and inflammatory processes are both linked to weight status. The protection against being overweight that is conferred to breastfed individuals may therefore be the same protection these individuals enjoy against inflammation in later life. The primary aim of this study is to test overweight status as a mediating pathway through which breastfeeding in infancy impacts inflammation in early adulthood. We ask – does being overweight during early adolescence, later adolescence, or during the transition into adulthood matter more (or less) in mediating the association between breastfeeding duration and inflammation? This timing approach seeks to highlight particular windows of vulnerability during which being overweight is particularly consequential for inflammation in early adulthood. Because we are able to assess how overweight status in early adolescence may launch a “chain of risk” of overweight status that persists into later parts of the life course, our study speaks to the long-term development of biological processes and highlights how the mediatory role of overweight status on the association between breastfeeding and inflammation develops across the early life course. In exploring this issue, therefore, we conceptually capture alternative pathways between breastfeeding duration and inflammation through timing of overweight status and cumulative path of overweight status. In doing so, we are better equipped to understand breastfeeding duration, overweight status, and inflammation as dynamic processes that are active across the life course. Our hypothesis is that overweight status matters for the link between breastfeeding and inflammation not only for a given point in time, but also as a cumulative process that unfolds across the transition from adolescence to young adulthood.

Methods

Data and Sample

Add Health is a nationally representative survey that launched in 1994 with an in-school survey and followed adolescents into young adulthood through a series of four waves from 1995 to 2008 (Harris et al. 2009). The schools included in the study were selected by region, urbanicity, school size, school type, and racial composition based on a stratified sampling design. In-school data collection was done in 1994 when respondents were in grades 7–12 and was used to generate a nationally representative subsample of 20,745 students selected for Wave I in-home interviews in 1995. During Wave I in-home interviews, respondents' parents also reported on a series of demographic and background characteristics. Additional in-home interviews of respondents were conducted in 1996 (Wave II; $n = 14,738$, with Wave I high school seniors excluded), 2001–2002 (Wave III; $n = 15,197$, with Wave I high school seniors brought back in), and 2007–2008 (Wave IV; $n = 15,701$). The age ranges across waves were: 11 to 18 (Wave I), 12 to 18 (Wave II), 18 to 26 (Wave III), and 24 to 32 (Wave IV). During Wave IV, biological specimens were collected including whole blood, saliva, and cardiovascular and anthropometric measures (Whitsel et al. 2012).

The study sample is limited to respondents who were observed in Waves I, III and IV of interviews, provided biological specimens for analyses (including CRP measurements), and had a valid longitudinal sampling weight. Data from Wave II was not included given its close proximity to the Wave I interview. Among the 15,701 respondents that were observed through Wave IV, 9,421 had valid longitudinal sampling weights. To ensure measurement of CRP as a biomarker of chronic inflammation rather than acute inflammation in response to infection, our sample was further restricted to individuals who report no symptoms of infection, including cold or flu-like symptoms, fever, night sweats, nausea/vomiting/diarrhea, and/or frequent urination, in the two weeks prior to biomarker specimen collection (McDade et al. 2014). Among the 9,421 respondents with valid sampling weights, 2,993 were excluded for reporting potential acute inflammation. We further excluded women who were pregnant at Wave IV interview, or who had given birth in the 6 months prior to that interview given the correlation of pregnancy with both weight status and inflammation ($n = 153$) (e.g., Warrs et al 1991). A robustness check was performed on the subset of women who were not pregnant at each wave of data and results were consistent with those presented. Our final analytical sample size was therefore 6,275 individuals. Sampling weights were used in all analyses to account for study design effects and to correct for differential attrition across waves. All item-level missingness was estimated through full information maximum likelihood (FIML) estimation techniques, as described below.

Measures

Inflammation—The dependent variable in all analyses was inflammation, as measured by a marker of inflammation, C-reactive protein (CRP). Respondents in Wave IV were asked to provide a biological specimen sample that was analyzed for a host of biomarker levels, including CRP (Whitsel et al. 2012). Respondents were not included in the sample if they reported recent symptoms of infections, in order that CRP level reflect chronic (rather than acute) inflammation. The American Heart Association and Centers for Disease Control and Prevention (CDC) classify levels of CRP greater than 3 mg/L as high, and approximately 37% of the study sample had CRP levels that classified as such. Although sensitivity analyses were performed with the sub-sample of respondents in the 3 mg/L to 10 mg/L range, the primary analyses utilize the full range. Further, CRP values were log transformed given the distribution's positive skew. The natural log of CRP was standardized in all analyses for interpretation purposes (Goosby et al 2016).

Breastfeeding duration—During the Wave I in-home parent interviews, parents reported the duration of time that the respondent was breastfed as an infant. Although these reports rely on retrospective report, maternal recall of the initiation and duration of breastfeeding is considered valid and reliable (Li, Scanlon, and Serdula 2005). A categorical variable was created to identify whether the respondent was never breastfed (reference group), breastfed for less than 3 months, breastfed for 3-6 months, breastfed for 6-12 months, and breastfed for greater than 12 months.

Overweight status—Overweight status was captured at Wave I (adolescence), Wave III (transition to adulthood), and Wave IV (early adulthood). Self-reported height and weight at Waves I, III, and IV were used to calculate body mass index (BMI) for each time point using

the formula: $[\text{weight (kg)}]/[\text{height (m)}]^2$. The CDC sets thresholds for overweight and obesity based on BMI. For adolescents, overweight individuals are defined as having a BMI at or above the 85th percentile for age and gender. For adults, overweight individuals are defined as having a BMI of 25.0 or higher. Using BMI, therefore, binary variables (1 = overweight) were created to capture overweight status at Waves I, III, and IV. For Wave I, the CDC's adolescent standards were used, and for Waves III and IV, the CDC's adult standards were used.

Analyses consider overweight status in two ways. First, the timing of being overweight is considered by testing point-in-time indicators of being overweight as potential mediators of the association between breastfeeding and inflammation. Wave I captures overweight status in adolescence, Wave III considers overweight status during the transition into adulthood, and Wave IV represents overweight status in early adulthood. Figure 1 illustrates this conceptualization of overweight status. Pathway 1, pathway 2, and/or pathway 3 could mediate the association between breastfeeding and inflammation. By testing each pathway, we are therefore better understanding which specific timepoint(s) of overweight status mediates the association between breastfeeding and inflammation.

Second, the cumulative path of overweight status is examined via the pathway linking overweight status at Wave I to overweight status at Wave III to overweight status in Wave VI. This pathway, illustrated in Figure 2, thus speaks to a cascading process of overweight status across adolescence into young adulthood. Overweight status at Wave I may be associated with overweight status at Wave III, which is in turn associated with overweight status at Wave VI. This cumulative pathway across time is therefore also considered as a mediator of the association between breastfeeding in infancy and inflammation in young adulthood.

Covariates—Several controls were measured to account for sociodemographic position and possible spuriousness: gender (1 = female), age, race/ethnicity (non-Hispanic white, non-Hispanic black, non-Hispanic Asian, Hispanic, other/multi-racial), family structure (1 = lived with both biological parents at Wave I, 0 = other family form), family income at adolescence (measured in thousands), and parent education (a categorical variable with dummy indicators for less than high school, high school graduate, some college/ Associate's degree, Bachelor's degree, and post-baccalaureate degree; high school graduate was the reference in all analyses). Breastfeeding is not exogenous to parent's education, however, and we therefore accounted for the association between parents' education and breastfeeding in all analyses. Respondents' birth weight was a covariate in all analyses (deRosset and Strutz 2015), as was the square term of the respondents' birth weight in order to account for the non-linear association between birth weight and inflammation in early adulthood. We also performed a robustness check controlling for the number of live births each female respondent had before Wave IV interview; the results were consistent with those presented.

Descriptive statistics for C-reactive protein, weight status, and sociodemographic covariates are presented for the full sample and by breastfeeding duration in Table 1. Our descriptive results revealed lower levels of CRP and lower frequencies of being overweight at each life course stage among individuals who were breastfed for longer durations as infants.

Analytical Strategy

The primary goal of this study was to assess the mediation of the association between breastfeeding in infancy and inflammation in early adulthood by overweight status. To address this goal, analyses were performed in three steps. The first step was to test the association between breastfeeding and inflammation (Model 1), confirming previous research showing that the longer an infant is breastfed, the lower their CRP levels are expected to be (e.g., McDade et al. 2014). The second step was to introduce overweight status in a regression framework to evaluate the attenuation of the association between breastfeeding and inflammation by overweight status. The third and focal step was to test both direct and indirect pathways between breastfeeding and inflammation in a structural equation framework. The mediation analyses highlight the significant pathways between breastfeeding and inflammation through overweight status at Waves I, III, and IV, testing direct and indirect effects in a single model using path analysis. This method is preferred to Baron and Kenny's (1986) causal steps approach because a single model allows for a non-significant correlation between the predictor and the outcome when testing indirect effects. Indirect effects were tested using the Delta method and confirmed with Sobel tests.

Regression and mediation models were estimated using path analysis in a structural equation framework in the statistical software program Mplus (Muthén and Muthén 2006). FIML estimated exogenous variance for missingness, so that all cases in the sample were retained even if they had missing data on individual variables. We also employed the cluster feature in Mplus to account for students being nested within schools in the sampling frame, as well as the longitudinal sampling weight to address differential probability of being included in the frame and differential cross-wave attrition from the sample.

Results

Breastfeeding, Weight Status, and Inflammation

To test the general hypothesis of the mediation of the association between breastfeeding and inflammation by weight status, a necessary first step was to examine the direct pathway between breastfeeding and inflammation. Table 2 presents the direct pathway (Model 1), and confirms the findings of previous researchers (i.e., McDade et al. 2014) that individuals who are breastfed for 3 to 6 months ($\beta = -.156, p < .10$), 6 to 12 months ($\beta = -.182, p < .01$), or greater than 12 months ($\beta = -.154, p < .05$) have significantly lower levels of CRP than individuals who are not breastfed. CRP levels of respondents who were breastfed for less than 3 months were not significantly different than respondents who were never breastfed.

The next step of our analyses was to test whether overweight status acts as a mechanism linking breastfeeding in infancy to inflammation in early adulthood. Indeed, Model 2 of Table 2 shows that, when overweight status across adolescence into young adulthood is accounted for, the association between breastfeeding and inflammation is slightly attenuated, although still significant for respondents who were breastfed for 3-6 months ($\beta = -.105, p < .05$) and respondents who were breastfed for 6-12 months ($\beta = -.127, p < .05$) as compared to respondents who were not breastfed as infants.

To further elucidate the indirect pathways through which breastfeeding acts on inflammation through overweight status and thereby address the primary question of this study, we proceeded to test the mediation of the relationship between breastfeeding and inflammation by overweight status in a single model, evaluating direct and indirect effects. To do so, we moved to a structural equation framework. Our first step, then, was to replicate our direct pathway (i.e., Model 1) in a structural equation model; these results are depicted graphically in Figure 3. This model accounts for the impact of parents' education on breastfeeding (with high school graduates as the reference group), and finds that higher educational attainment of parents is associated with longer duration of breastfeeding. For example, college educated parents, as compared to high school graduate parents, are more likely to report breastfeeding their infant for any duration of time. Further, this model confirms our regression results that being breastfed for 3-6 months, 6-12 months, or for more than 12 months as an infant was associated with significantly lower levels of CRP in young adulthood. Approximately 6% of the variance in CRP levels was explained in Model 1.

Next, we simultaneously estimated direct and indirect pathways in Model 2 (Figure 4). As shown in Figure 4, we confirmed that the direct pathway between breastfeeding and inflammation remained significant for respondents who were breastfed for 3-6 months ($\beta = -.103, p < .05$) and for 6-12 months ($\beta = -.124, p < .05$) as compared to respondents who were never breastfed. Consistent with our regression results, the direct association between being breastfed for more than 12 months and inflammation was no longer statistically significant when overweight status was included in our model.

Indirect pathways, however, also emerged. Table 3 documents the significant indirect pathways, including the percent of the total effect that is accounted for by each. Results are not shown for respondents who were breastfed less than 3 months, given that these respondents were not significantly different than respondents who were not breastfed as infants. We confirmed significance of indirect effects with Sobel tests.

First, for respondents who had been breastfed for 3-6 months, indirect pathways accounted for approximately 41% of the effect of breastfeeding duration in infancy on inflammation in early adulthood, and the total indirect effect was significant at $p < .001$. The total indirect effects, however, worked primarily through three specific pathways: 1) individuals who were breastfed for 3-6 months had lower likelihood of being overweight at Wave I, which protected them against higher levels of CRP in early adulthood ($p < .05$; 7% of the total effect); 2) individuals who were breastfed for 3-6 months had lower likelihood of being overweight at Wave I, which was associated with being overweight at Wave III, which protected them against higher levels of CRP in early adulthood ($p < .05$; 4% of the total effect); and, 3) individuals who were breastfed for 3-6 months had lower likelihood of being overweight at Wave I, which was associated with being overweight at Wave III, which was associated with being overweight at Wave IV, which ultimately protected them against higher levels of CRP in early adulthood ($p < .05$; 6% of the total effect). The first pathway indicates that timing plays a role, while the second and third pathways support the idea of cumulative, chain-of-risk process. The remaining direct effect between being breastfed for 3-6 months in infancy and inflammation in early adulthood was significant at $p < .05$ and represented 59% of the total effect.

Second, approximately 40% of the effect between breastfeeding for 6-12 months in infancy and lower inflammation in early adulthood as compared to never breastfed individuals was indirect through weight status. Again, several pathways composed this indirect effect. Nearly 7% of the total effect was through Wave I overweight status ($p < .05$) and approximately 8% of the effect was through Wave III overweight status ($p < .01$). Each of these pathways point to the importance of timing. At the same time, two indirect pathways emerged which are indicative of a cumulative process. Nearly 4% of the total effect was through breastfeeding duration's association with Wave I weight status, which in turn is associated with Wave III weight status, which is associated with inflammation in early adulthood ($p < .01$); 11% of the total effect operated through the indirect link between weight status in Waves III and IV; and, 6% of the total effect was through the complete cumulative pathway of Wave I to Wave III to Wave IV. The remaining direct effect between being breastfed for 6-12 months in infancy and inflammation in early adulthood was significant at $p < .05$ and represented 59% of the total effect.

Third, the direct effect between breastfeeding for more than 12 months and inflammation in early adulthood was explained by the inclusion of weight status, suggesting that indirect effects were present. Indeed, 42% of the association was due to indirect pathways ($p < .01$). Weight status in Wave III accounted for 9% of the total effect ($p < .05$) and the pathway from Wave III to Wave IV accounted for 14% of the total effect ($p < .01$). The remaining direct effect represented 58% of the total effect and was not statistically significant.

Taken together, pathways of overweight status across a significant part of the life course (i.e., adolescence and into young adulthood) stood out as important mediators of the association between breastfeeding and inflammation. Breastfeeding duration, particularly for individuals breastfed between 3 and 12 months, is linked to overweight status in adolescence, which predicts overweight status across the transition to adulthood and into early adulthood, thereby impacting inflammation levels in early adulthood. The protective nature of breastfeeding against CRP, therefore, partially acts through the protective nature of breastfeeding against overweight status across the life course. No evidence of full mediation emerged for the indirect paths, however, given that the various indirect pathways accounted for only 41% of the total effect of breastfeeding duration on inflammation. Overall, approximately 22% of the variance in CRP levels in early adulthood was explained in Model 2. As in all models, moreover, Model 2 accounts for the impact of parents' education on breastfeeding, and finds that higher educational attainment of parents is associated with longer duration of breastfeeding.

In sum, overweight status partially mediates the association between breastfeeding duration and inflammation, and several significant indirect pathways emerged. Being breastfed for 3-6 months or 6-12 months as an infant is associated with lower likelihood of being overweight during adolescence (Wave I), which protects against increased CRP levels in early adulthood. This pathway highlights the importance of early life timing of overweight status. Being breastfed for 6-12 months or greater than 12 months as an infant is associated with lower likelihood of being overweight during the transition to adulthood (Wave III), which protects against increased CRP levels in early adulthood. This pathway highlights the transition to adulthood as an important time for weight status. At the same time, longer

duration of breastfeeding (i.e., 3 months or more) is associated with lower likelihood of being overweight in early adolescence, which is associated with lower likelihood of being overweight in later adolescence, which translates to lower likelihood of being overweight during the transition to adulthood, which, in turn, protects against increased CRP levels in early adulthood. This various cascading indirect pathways evidenced in our results highlight the importance of considering the overweight status as a cumulative process across the life course.

Discussion

Inflammatory processes find their root in early life exposures, linking disadvantage across childhood into adulthood. Life course approaches emphasize the longer-term implications of early life experiences with later life health outcomes, which, in the case of inflammation, means considering how processes in infancy relate to inflammatory responses throughout different stages of the life course. Such an approach can elucidate how experiences in infancy get under the skin and promote (or hinder) healthy status (i.e., low levels of inflammatory markers) in adulthood. Breastfeeding in infancy is associated with an array of short- and long-term health benefits (e.g., Horta and Victoria 2013), including lower levels of inflammation in early adulthood (McDade et al. 2014). Working from a life course approach, therefore, we tested one potential mechanism (overweight status) relating breastfeeding in infancy and inflammation in early adulthood, ultimately informing how social and biological processes across the life course influence health disparities.

We found that overweight status partially mediated the association between breastfeeding in infancy and inflammation in early adulthood. Increased duration of breastfeeding, particularly for individuals who were breastfed between 3 months and 12 months in infancy, was associated with protection against being overweight, which in turn, protected against elevated inflammatory biomarkers in early adulthood. Furthermore, the mediation was particularly salient for individuals who were overweight during adolescence or from the transition from adolescence into adulthood and for individuals who experienced being overweight across multiple life course stages. This pattern is very consistent with the concept of the “dynamic effect of early conditions” introduced by Salsberry and Reagan (2005). They argue that although early conditions such as breastfeeding may influence weight status in a temporally proximate way, early conditions may also independently influence weight status later in childhood by changing the probability of moving between weight states in later periods, conditional on prior weight.

Extending past research on the origins of health disparities through a life course lens allows us to probe mechanisms relating breastfeeding in infancy to inflammation in early adulthood and explain when and how overweight status mediates this pathway. Ultimately, however, three themes arise from the findings of this study that raise more questions, and consequently, call for future research. One such theme that emerged from our findings was the importance of considering overweight status as a life course process. By operationalizing overweight status over the life course, we were able to capture weight as a dynamic process that unfolds throughout development. We evaluated weight in adolescence and across the transition to adulthood, and confirmed two important indirect pathways of through which

breastfeeding in infancy was related to inflammation in young adulthood. These pathways are not surprising, given that overweight status in adolescence has been significantly associated with adult overweight status in past research (Harris 2010). Our findings thus confirm the necessity of a life course approach to weight. In our conceptualizations, however, we did not consider measures of early childhood weight status given data limitations. Early childhood weight status, though, has significant implications for weight across the life course (Nader et al. 2006), and overweight children are likely on trajectories that compound and magnify their exposure to being overweight. In picking up weight status in adolescence and following it through the transition into adulthood, we could therefore be missing an important component of both the timing and cumulative pathway of being overweight--- early childhood. A similar limitation of our measurement of overweight status is that BMI is self-reported in the Add Health data. Although self-reports will be consistent over time given reporting bias, objective measures of BMI (and overweight status) would be preferred. Future research should thus extend conceptualization of weight as a mediator between breastfeeding and inflammation by examining the extent to which early childhood weight determines how this mediation pathway unfolds and by using more objective measures of weight.

Another emergent theme of this study consistent with past research is that pathway analyses supported breastfeeding as endogenous to socioeconomic status. Indeed, initiation and duration of breastfeeding are highly determined by socioeconomic status, particularly maternal education (Singh, Kogan, and Dee 2007; Scott and Binns 1999). Future research considering the relation between breastfeeding and inflammation should therefore do so in light of a more comprehensive environment that can directly and indirectly promote each of these sociobiological processes. Environmental challenges of the home, such as hygiene, presence of toxins, and cleanliness, or stressful and traumatic experiences that illicit biological responses, for example, could increase the salience of the tested pathways and are variable by socioeconomic status (Evans and Kantrowitz 2002). Similarly, challenges to mother's ability to breastfeed—such as their accommodations in the work environment or maternal health—might impact duration and initiation. In this way, individuals are selected into breastfeeding in ways that are not accounted for in our analyses. Certainly, our results are limited given the lack of contextual measures available to us. Thus, a more detailed look at family of origin and household measures during infancy, childhood, and adolescence would allow for a deeper comprehension of how environments not only impact initiation and duration of breastfeeding, but also combine with breastfeeding to protect against inflammation or, conversely, stimulate inflammation.

A final issue sparked by this research is that breastfeeding impacts inflammation in direct and indirect ways, as was hypothesized by McDade and colleagues (2014) in their analyses of how birth weight and breastfeeding duration are related to CRP. Indirect pathways, or mechanisms relating these processes, are just beginning to be understood. Certainly, as the results of this study show, overweight status across the life course is one part of the story. Other mechanisms, however, are undoubtedly working in tandem with weight status, and this study is just a first pass at production of a better understanding of these complicated processes. Immune function, for example, may be another mechanism that is promoted by breastfeeding (Hanson 1998) and shapes inflammation throughout the life course (McDade

2012). Future work, therefore, should continue to unpack how breastfeeding gets under the skin, how inflammation has origins in early life exposure, and how these processes intertwine across the life course.

In conclusion, a life course approach to health disparities stresses that social and biological exposures in childhood have implications for later-life health and well-being (Montez and Hayward 2011). Using this approach to disentangle the roots of inflammation highlight how life course experiences promote inflammatory processes. Focusing on the association between breastfeeding and inflammation specifically allows us to drill into the mechanisms linking infant experiences to adult health outcomes. Elucidating socioeconomic differences, moreover, provides deeper knowledge on vulnerable populations. From a public health perspective, the importance of this research is threefold. First, understanding the early life origins of inflammation can help advocate for early intervention. Second, increasing knowledge about the benefits of breastfeeding and the ways breastfeeding influences later-life health outcomes can further support movements to increase the prevalence of breastfeeding, especially among subgroups of the population for whom direct and indirect pathways linking breastfeeding to inflammation are most salient. Third, given the importance of overweight status at each time considered, our research suggests that interventions targeting weight at any point from adolescence across the transition to adulthood would be beneficial in suppressing the negative implications that being overweight has for inflammation. In conclusion, expanding our knowledge on the association between breastfeeding and inflammation and how overweight status is an indirect mechanism linking these experiences, we highlight how experiences and exposures across the life course compound and accumulate to impact biological processes such as inflammation.

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Figure 1.
Conceptual model to test the timing of overweight status.

Figure 2.
Conceptual model to test the cumulative pathway of overweight status.

Figure 3.

Model 1, the direct effect of breastfeeding on inflammation.

Note: $n = 6,275$. Dashed lines represent insignificant pathways; only significant pathways ($p < .05$) are shown for the association between parents' education and breastfeeding duration.

* $p < .05$, ** $p < .01$, *** $p < .001$. Coefficients shown for direct effects. Model controls for gender, age, race/ethnicity, family structure, parents' education, family income in adolescence, birth weight, and birth weight squared. Covariate effects are not depicted. R^2 for inflammation = 0.063.

Figure 4.

Model 2, mediation of the association between breastfeeding duration and inflammation by timing of overweight status.

Note: $n = 6,275$. Reference group for breastfeeding duration is never breastfed. Only significant pathways ($p < .05$) shown. Effects for breastfed less than 3 months are not shown (not significantly different than never breastfed). Model controls for gender, age, race/ethnicity, family structure, parents' education, family income in adolescence, birth weight, and birth weight squared. Covariate effects are not depicted. R^2 for inflammation = 0.222.

Table 1
Descriptive statistics for full sample and by breastfeeding duration

	Mean (SD)/ %					
	Full Sample <i>n</i> = 6,275	Never Breastfed (53.89%)	Breast less than 3 months (14.76%)	Breast 3-6 months (10.65%)	Breastfed 6-12 months (13.48%)	Breastfed greater than 12 months (7.23%)
C-reactive protein	0.00 (1.00)	0.09 (1.01)	0.01 (1.00)	-0.14 (0.96)	-0.16 (0.94)	-0.17 (1.00)
Overweight status						
Overweight (WI)	26.13%	28.26%	27.06%	21.35%	20.66%	21.13%
Overweight (WIII)	46.68%	50.05%	45.35%	42.44%	39.27%	38.23%
Overweight (WIV)	65.89%	69.05%	64.29%	60.87%	59.17%	57.58%
Covariates						
Female	50.84%	52.55%	49.57%	49.14%	49.25%	49.62%
Lives with bio parents (WI)	55.89%	50.41%	62.58%	64.78%	69.47%	73.67%
Age (WI)	15.78 (1.59)	15.86 (1.57)	15.58 (1.55)	15.51 (1.56)	15.47 (1.57)	15.43 (1.56)
Family income (WI)	47.66 (54.87)	40.97 (44.67)	51.49 (62.41)	52.73 (48.87)	57.56 (57.72)	62.63 (87.24)
Birth weight (lbs)	7.33 (1.27)	7.19 (1.30)	7.38 (1.25)	7.49 (1.17)	7.58 (1.16)	7.50 (1.24)
Birth weight squared	55.30 (18.58)	53.34 (18.80)	56.00 (18.53)	57.41 (17.25)	58.82 (17.73)	57.76 (18.76)
Parent's education						
Less than high school	11.96%	14.33%	9.64%	7.98%	4.72%	7.81%
High school	29.39%	37.13%	24.16%	20.39%	19.44%	15.36%
Some postsecondary	20.35%	20.78%	23.01%	23.05%	18.47%	12.75%
College graduate	24.95%	20.85%	27.89%	29.08%	30.69%	40.36%
Post-baccalaureate	13.35%	6.91%	15.30%	19.50%	26.67%	23.70%
Race/ethnicity						
Non-Hispanic white	53.90%	52.34%	55.76%	59.28%	67.16%	66.08%
Non-Hispanic black	21.74%	28.38%	14.75%	14.43%	10.18%	8.61%
Hispanic	15.16%	13.58%	20.82%	16.84%	11.94%	13.67%
Asian	6.58%	3.16%	6.20%	6.70%	8.01%	8.86%
Other/multi-racial	2.57%	2.55%	2.35%	2.75%	2.58%	2.53%

Table 2

Regression analysis of breastfeeding, overweight status, and inflammation on natural logarithm of C-Reactive Protein levels.

	Model 1 β (SE)	Model 2 β (SE)
Breastfeeding (ref: never breastfed)		
Breastfed less than 3 months	-0.047 (0.052)	-0.050 (0.049)
Breastfed 3 to 6 months	-0.156 (0.054) **	-0.105 (0.050) *
Breastfed 6 to 12 months	-0.182 (0.061) **	-0.127 (0.057) *
Breastfed greater than 12 months	-0.154 (0.069) *	-0.112 (0.068)
Overweight WI		0.194 (0.045) ***
Overweight WIII		0.212 (0.042) ***
Overweight WIV		0.575 (0.036) ***
Covariates		
Female	0.368 (0.032) ***	0.443 (0.030) ***
Age	0.021 (0.012)	0.012 (0.011)
Adolescent family income	-0.001 (0.000) *	-0.001 (0.000)
Birth weight	0.037 (0.133)	0.157 (0.120)
Birth weight squared	-0.004 (0.009)	-0.012 (0.008)
Two biological parent household	-0.012 (0.038)	-0.020 (0.034)
Parent's education (ref: high school graduate)		
Less than high school	-0.096 (0.062)	-0.134 (0.060) *
Some college/ Associate's degree	-0.053 (0.050)	-0.055 (0.048)
Bachelor's degree	-0.104 (0.046) *	-0.050 (0.038)
Post-baccalaureate degree	-0.106 (0.065)	-0.084 (0.061)
Race/ethnicity (ref: non-Hispanic white)		
Non-Hispanic black	0.073 (0.052)	-0.020 (0.048)
Hispanic	0.124 (0.045) **	0.059 (0.042)
Non-Hispanic Asian	-0.375 (0.073) ***	-0.345 (0.067) ***
Other/multi-racial	0.156 (0.135)	0.102 (0.110)

Note: lnCRP standardized for interpretation; $n = 6,275$;

*
p < .05,

**
p < .01,

p < .001

Table 3

Direct and Indirect Pathways

Pathway	Indirect	Direct	Total	% Of Total Effect
Breastfeeding 3-6 months → CRP	-0.072 ***	-0.103 *	-0.175 **	41.14
BF 3-6 months → Over I → CRP	-0.012 *	-0.103 *	-0.175 **	6.86
BF 3-6 months → Over I → Over III → CRP	-0.007 *	-0.103 *	-0.175 **	4.00
BF 3-6 months → Over I → Over III → Over IV → CRP	-0.010 *	-0.103 *	-0.175 **	5.71
Breastfeeding 6-12 months → CRP	-0.085 ***	-0.124 *	-0.210 **	40.48
BF 6-12 months → Over I → CRP	-0.014 *	-0.124 *	-0.210 **	6.67
BF 6-12 months → Over III → CRP	-0.016 **	-0.124 *	-0.210 **	7.62
BF 6-12 months → Over I → Over III → CRP	-0.008 **	-0.124 *	-0.210 **	3.81
BF 6-12 months → Over III → Over IV → CRP	-0.023 ***	-0.124 *	-0.210 **	10.95
BF 6-12 months → Over I → Over III → Over IV → CRP	-0.012 **	-0.124 *	-0.210 **	5.71
Breastfeeding greater than 12 months → CRP	-0.077 **	-0.108	-0.185 **	41.62
BF > 12 months → Over III → CRP	-0.017 *	-0.108	-0.185 **	9.19
BF > 12 months → Over III → Over IV → CRP	-0.025 ***	-0.108	-0.185 **	13.51

Note: only significant indirect pathways shown; abbreviations: BF = breastfeeding, Over = overweight status, CRP = C-reactive protein;

* $p < .05$,

** $p < .01$,

*** $p < .001$