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# Duration of Breastfeeding in Infancy and Levels of Central Adiposity and Systemic Inflammation in Early Middle Adulthood

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## Abstract

**Introduction:** Overweight, obesity, and systemic inflammation contribute to chronic degenerative diseases that are major public health burdens associated with aging. This study investigates whether the duration of breastfeeding in infancy predicts waist circumference and chronic systemic inflammation in early middle adulthood.

**Methods:** Regression models were implemented with data from the National Longitudinal Study of Adolescent to Adult Health, a nationally representative sample of adults (33-44 years old) with information on breastfeeding history as well as measures of waist circumference, C-reactive protein (CRP), and interleukin-6 (IL-6). Fixed-effects regression models were used to analyze between-sibling differences in breastfeeding duration, waist circumference, and CRP/IL6.

**Results:** Longer duration of breastfeeding was associated with significantly lower waist circumference and lower CRP. For individuals who were breastfed for 6-12 months versus not at all, marginal mean waist circumference was 94.8 cm (95% CI: 92.5, 97.1) and 101.7 cm (95% CI: 100.2, 103.2), respectively. Marginal mean CRP was 1.59 mg/L (95% CI: 1.38, 1.84) versus 2.10 mg/L (95% CI: 1.97, 2.24). Waist circumference mediated 57.3-93.8% of the associations between breastfeeding duration and CRP, depending on duration category. Breastfeeding duration was negatively associated with waist circumference and inflammation in sibling comparisons, but estimates were imprecise and not statistically significant.

**Conclusion:** The convergence of obesogenic environments and low uptake of breastfeeding for cohorts born following the historical nadir of breastfeeding in the US may contribute to epidemics of overweight/obesity and chronic inflammation that presage risk for chronic degenerative diseases of aging.

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**Introduction**

Chronic inflammation is a well-established risk factor for all-cause mortality, as well as cardiometabolic diseases that are major public health burdens globally [1,2]. C-reactive protein (CRP) is a widely used measure of systemic inflammation in clinical and epidemiological contexts, and meta-analysis of 54 prospective studies involving 160,309 participants documents strong positive associations between baseline CRP and subsequent incidence of coronary heart disease, ischemic stroke, and vascular mortality [3].

Overweight and obesity are important determinants of chronic inflammation, with visceral adipose tissue producing interleukin 6 (IL-6) and other pro-inflammatory cytokines that promote CRP production and increase the level of systemic inflammation [4]. Most research on chronic inflammation has focused on older adults at increased risk for degenerative diseases of aging. Younger adults in the US, born in the late 1970s and 1980s, came of age in obesogenic environments that have driven secular increases in body mass index (BMI) and other adiposity measures (e.g., waist circumference) to historically high levels[5,6]. The implications for chronic inflammation are concerning: In a large, nationally representative sample of 33 to 44 year-olds, we previously documented a strong dose-response relationship between BMI and CRP, with no evidence of ceiling effects at the highest levels of obesity [7]. Of participants with BMI<25, only 11% had "high risk" levels of CRP (>3 mg/L), in comparison with 88 percent of females and 74 percent of males with BMI of 40 or higher.

It is important to understand the origins of current epidemics of obesity and chronic inflammation, and emerging evidence points to breastfeeding duration as a potentially important

factor. Human breastmilk provides nutritional and immunological support to infants, and American Academy of Pediatrics guidelines recommend exclusive breastfeeding to six months, and continued breastfeeding with complementary feeding for up to two years [8]. Breastfeeding can have direct, lasting effects on inflammation by shaping the development of immunoregulatory pathways in infancy [9,10], and indirect effects through programming of metabolic systems that control the accumulation of body fat [11]. Many studies have documented negative associations between breastfeeding duration and the emergence of overweight/obesity, however relatively few have examined outcomes beyond late childhood and adolescence, and the vast majority apply observational study designs that may be confounded by socioeconomic status or other factors that independently influence breastfeeding duration and obesity risk [12].

In this study, we use data from a large, nationally representative cohort study to test the hypothesis that longer duration of breastfeeding in infancy is associated with lower CRP and IL-6 concentrations in early mid-adulthood. We also test whether breastfeeding duration predicts waist circumference in adulthood and investigate the extent to which waist circumference mediates the association between breastfeeding and inflammation. In addition to analyses with the full cohort, we implement sibling comparison models—a form of fixed-effects modeling—to control for many household- and community-level factors that may bias estimates of the effects of breastfeeding duration on adiposity and chronic inflammation in adulthood [13].

## Methods

### *Study sample*

The National Longitudinal Study of Adolescent to Adult Health (Add Health) is an ongoing, nationally representative cohort that was initiated in 1994-95 when participants were 12–19 years old. The study enrolled a core sample of 20,745 adolescents at Wave 1, which also included a parent interview. Subsequent surveys have followed participants into adulthood across multiple waves of data collection [14]. Participants were 33-44 years old for the Wave 5 survey (2016-18), which is the focus of this analysis. A nationally representative subsample of 4,940 participants provided antecubital venous blood samples, collected in the home. Samples were stored at 4C for up to 2 hours, centrifuged to produce aliquots of serum, and overnight shipped to the laboratory for assays. CRP was quantified with a high sensitivity particle-enhanced immunonephelometric assay (Siemens BN II; n=4,603 valid results), and IL-6 was quantified with a highly sensitive electrochemiluminescent immunoassay (MesoScale Diagnostics V-plex; n=4,809 valid results) [15]. Only samples from non-pregnant participants with survey weights were eligible for inclusion in study analyses. Of the 4,268 eligible CRP samples, 3,417 complete cases (80.1%) were analyzed; and of the 4,460 eligible IL-6 analyses, 3,570 complete cases (80.0%) were analyzed. The variable-specific distributions for all non-missing values and within the complete case analytical samples are similar, with differences of less than one unit in percentage point or continuous measure unit (Supplementary Table S1).

***Measures***

Wave 5 CRP (mg/L) and IL-6 (pg/ml) values were log-transformed (base 10) to normalize the distributions. Information on participant breastfeeding duration was obtained from the Wave 1 parent interview and constructed as a categorical variable based on response options: not breastfed, less than 6 months, 6-12 months, and more than 12 months [16]. The survey asked only

about initiation and duration of any breastfeeding and did not collect information on exclusive breastfeeding. Parents also reported participant birth weight in pounds and ounces, which was converted to grams and mean-centered for analysis.

Waist circumference was measured to the nearest 0.5 cm over light clothing at the superior border of the iliac crest [17], and mean-centered. Other covariate measures included reported infectious disease symptoms (e.g., cold or flu-like symptoms; fever; night sweats; nausea, vomiting, or diarrhea) in the two weeks preceding blood collection[15], pregnancy status at Wave 5, anti-inflammatory medication use and any prescription contraceptive use in the prior four weeks, any cigarette use in the prior 30 days, age in years at Wave 5, self-reported sex at Wave 5, and parent self-reported college completion at Wave 1. All data were collected under conditions of informed consent, with protocols approved by the Institutional Review Board at the University of North Carolina, Chapel Hill. Participants with item nonresponse were excluded from the final analytical sample, resulting in a final sample size of 3,015 observations (Table 1), with a similar variable distribution in the full sample that includes item non-response (Supplement Table S1).

***Statistical analysis***

A series of ordinary least squares regression models were implemented to test whether longer breastfeeding duration and lower birth weight were associated with lower concentrations of CRP and IL-6 in early mid-adulthood. To assess overall and independent associations, model stages included breastfeeding and birth weight separately and jointly. All models adjusted for potentially confounding variables described above. Parent college completion was also

considered as an indicator of socioeconomic status that may influence both breastfeeding duration and adult health. All ordinary least squares regressions were survey-weighted to account for the survey design—including the biomarker subsample selection—and generate representative estimates for the full nationally representative cohort [18]. These analyses were also implemented using sibling fixed effects models on the subset of siblings in the study. This regression-based approach analyzed between-sibling differences to strengthen causal inference by controlling for additional shared household- and community-level factors that may confound the association between breastfeeding duration and chronic inflammation. Because there was less variation in breastfeeding duration between siblings, categories were collapsed into three groups for these models: no breastfeeding, <6 months, and ≥6 months.

Second, mediation analyses were conducted to assess the role of waist circumference, using the econometrics approach of seemingly unrelated regression models[19]. From these models, the total associations between breastfeeding and inflammation outcomes were decomposed into direct and indirect effects, and percents of the total associations mediated through waist circumference were estimated. Analyses were rerun using sibling fixed effects to further assess robustness to omitted variable bias. For fixed effects modeling, postestimation mediation parameters were calculated based on waist circumference models and CRP and IL-6 models with and without adjustments for waist circumference [20,21]. All analyses used Stata 18 (StataCorp, College Station, TX).

**Results**

Table 1 presents analytic sample variable distributions. Geometric mean CRP was 1.88 mg/L, with 35.9% of individuals above the "high risk" level of 3 mg/L (Table 1). The IL-6 geometric

mean was 0.68 pg/ml. Nearly half of participants were never breastfed. Individuals with a parent that completed college and individuals with birth weights above 2.5 kg were significantly more likely to be in one of the higher breastfeeding duration categories (Pearson F-test p values <0.001; Supplement Tables S2 and S3).

Weighted least squares regression models indicate significant negative associations between duration of breastfeeding in infancy and inflammation in early mid-adulthood (Table 2). These associations are independent of birth weight, which is weakly negatively associated with CRP. The magnitude of CRP reduction associated with breastfeeding duration is substantial, and IL-6 results were consistent but statistically weaker. For instance, individuals who were breastfed for 6-12 months were estimated to have a marginal mean CRP of 1.59 mg/L (95% CI: 1.38, 1.84) and mean IL-6 of 0.65 pg/ml (95% CI: 0.58, 0.72), in comparison with 2.10 mg/L (95% CI: 1.97, 2.24) and 0.73 pg/ml (95% CI: 0.70, 0.76) for those not breastfed (Figure 1; Supplement Table S4). A separate logistic regression model of high-risk CRP (> 3 mg/L) rendered consistent results (Online Supplement Table S5), with marginal predicted probabilities of high CRP for individuals breastfed for 12 months or longer of 0.30 (95% CI: 0.24, 0.37), compared to 0.38 (95% CI: 0.35, 0.41) for those not breastfed.

Fixed effects models suggest siblings breastfed for six months or more have a 15% lower CRP concentration than siblings not breastfed (Online Table S6, Figure S1, and Table S7). However, individual and joint tests of breastfeeding duration coefficients were not statistically significant (p>0.1). In IL-6 models, breastfeeding duration coefficients were smaller and statistically weak.

The greatest difference was between siblings with any versus no breastfeeding, after adjusting for birth weight.

Individuals who were not breastfed had waist circumferences that were 4.1 to 6.9 cm larger than those breastfed in infancy (Table 2; Figure 1). Among siblings, being breastfed six or more months was associated with 7.2-cm smaller waist circumference in adulthood (Table S6), but this association was not statistically significant. Overall, fixed effects coefficients were less precise than in the ordinary least squares models, given the smaller sample size, and were also not significant when tested jointly (Wald F tests: $p>0.1$).

The association between breastfeeding duration and CRP concentration was mediated largely by waist circumference (Table 3). In comparison with no breastfeeding, waist circumference in adulthood accounted for 57.3%, 93.8%, and 60.7% of the total associations between adult CRP and breastfeeding durations of <6 months, 6-12 months, and >12 months, respectively (all p-values<0.05). Results were similar for IL-6, with waist circumference accounting for 75.8%, 72.6%, and 54.8% of total associations between breastfeeding duration and CRP. While IL-6 results were less precise overall, mediated associations are statistically significant across duration category comparisons (all p-values<0.05), meaning confidence intervals narrowed when WC was accounted for as a mediator.

Sibling fixed-effect mediation analysis results are less precise due to the smaller sample size and narrower comparisons between siblings (Table S8). Waist circumference significantly predicted higher CRP and IL-6 concentration and partially mediated the total associations between

breastfeeding duration and each inflammatory outcome, but only in sibling comparisons of ≥6 months to no breastfeeding. Waist circumference accounted for 70.6% of the total association between breastfeeding ≥6 months and CRP, and 52.2% of the total association with IL-6, in comparison with no breastfeeding.

**Discussion**

Using data from a large, nationally representative cohort study, we document significant associations between breastfeeding in infancy and chronic inflammation in early mid-adulthood: Breastfed individuals had lower concentrations of CRP and IL6, as well as lower levels of central adiposity that accounted for much of the association between breastfeeding duration and chronic inflammation. This pattern of results may contribute to our understanding of how nutritional environments in infancy may contribute to current epidemics of overweight/obesity and chronic inflammation.

Our findings are consistent with prior studies in New Zealand, Scotland, and the US reporting negative associations between the duration of breastfeeding in infancy and CRP concentration in adulthood [16,22-24]. Similarly, meta-analysis of 159 studies indicates that breastfeeding reduces long term risks of overweight and obesity [12]. Concordantly, mechanistic studies with humans and animal models have identified immunoregulatory, metabolic, and microbiota processes through which breastmilk can have lasting effects on the accumulation of body fat and the regulation of inflammation [9,11,25]. Sibling comparisons and other strategies for addressing potential bias due to residual confounding indicate that the long-term effects of breastfeeding on adiposity and systemic inflammation are likely causal [12,16,26].

Rates of breastfeeding in the US were at their historical nadir around 1970, with less than one in three babies ever breastfed and only one in twenty breastfed to 6 months [27]. In the late 1970s, shifts in diet and growing consumption of calorie dense foods initiated increases in the prevalence of overweight and obesity [28]. Birth cohorts around 1970 therefore grew up in the context of low breastfeeding in infancy and obesogenic environments in childhood and adolescence, which may position them to be particularly vulnerable to obesity and chronic inflammation as they enter middle age. The Add Health cohort was born 1975-1985 when breastfeeding rates began trending upward, but as was the case nationally [29], only half of the participants were ever breastfed. If breastfeeding affords a degree of protection against the development of obesity and chronic inflammation, then it will be important to consider whether low rates of breastfeeding approximately 50 years ago set the stage for an epidemic of chronic inflammation in middle adulthood. Further, it is possible that waves of cardiovascular disease will follow these cohorts through older adulthood, resulting from degenerative processes of inflammaging set in motion by the historical convergence of low breastfeeding and obesogenic environments early in the life course.

Lactation support services and paid family leave policies are effective ways to increase the initiation and duration of breastfeeding [30-33] While breastfeeding is currently initiated for approximately 85% of infants in the US, only one in four are exclusively breastfed to 6 months with stark inequalities associated with socioeconomic status: Babies born to college graduates and into higher income households are significantly more likely to meet AAP recommendations for breastfeeding duration [34]. These patterns attest to the challenges faced by many mothers in

the absence of social policies and norms that support extended breastfeeding in the US [35,36]. To the extent that breastfeeding reduces obesity and chronic inflammation in adulthood, policies that promote breastfeeding in infancy may contribute to healthy aging and reduce social inequalities in cardiometabolic diseases later in life [37].

**Limitations**

Reliance on maternal recall is a limitation of our study, although previous analyses have shown that mothers are accurate reporters of breastfeeding initiation and duration [38,39]. We also use single time-point measures of CRP and IL6 to assess chronic, low-grade levels of systemic inflammation, which can be obscured by episodes of acute inflammation. This approach is commonly applied in epidemiological studies of inflammation [40-42], and we use infectious symptoms to control for a major source of acute activation, and our results are robust to alternative control strategies. Sibling comparisons generally produced negative associations between breastfeeding duration and inflammation and adiposity in adulthood, but the limited number of siblings in the subsample resulted in imprecise estimates and low statistical power.

**Conclusions**

Longer duration of breastfeeding in infancy predicts lower levels of adiposity and systemic chronic inflammation in early middle adulthood. Low uptake of breastfeeding in the US approximately 50 years ago may contribute to current epidemics of overweight/obesity and chronic inflammation that portends higher risk for chronic degenerative diseases as these cohorts age.

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***Figure 1.*** *CRP, IL-6, and Waist Circumference Predictive Marginal Means*. Predictive marginal means from fully adjusted and survey-weighted ordinary least square regression models for CRP, IL-6, probability of high-risk CRP (>3 mg/L), and waist circumference, with 95% confidence intervals. Point estimates are provided in Supplementary Table S4.

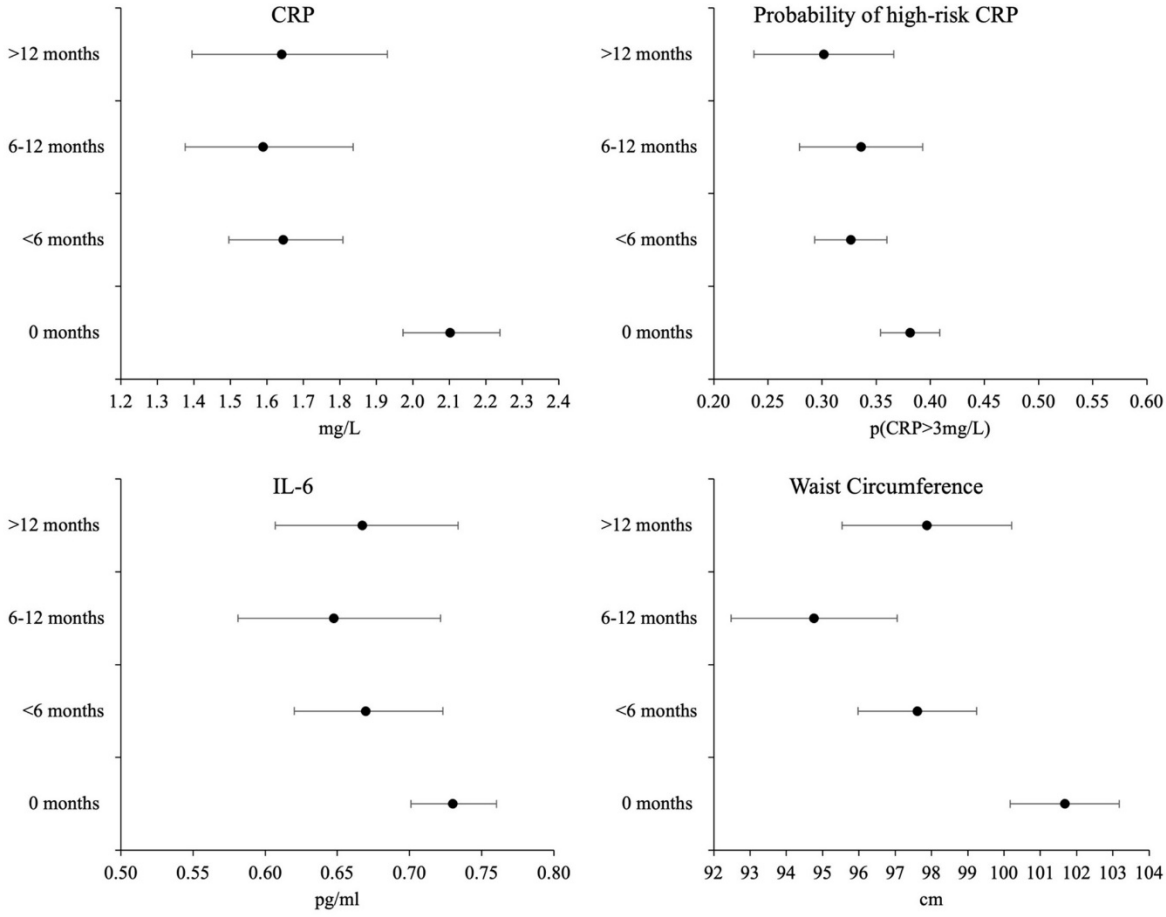

***Table 1: Sample Characteristics***. Descriptive statistics for analytical variables in complete case sample used in final analyses (n=3,417).

| | **Mean** | **SD** |
|---|---|---|
| $log_{10}$(hsCRP) W5 | 0.275 | 0.539 |
| High-risk CRP (>3 mg/L) | 0.359 | 0.480 |
| $log_{10}$(IL-6) W5 | -0.166 | 0.328 |
| Any infectious symptoms in last 2 weeks (y/n) | 0.281 | 0.450 |
| Any anti-inflammatory medication (y/n) | 0.324 | 0.468 |
| Any prescription contraceptives (y/n) | 0.069 | 0.254 |
| Any cigarettes in last 30 days (y/n) | 0.232 | 0.422 |
| Age (W5) | 37.844 | 1.908 |
| Self-reported female sex W5 | 0.591 | 0.492 |
| Parent college completion | 0.286 | 0.452 |
| Breastfeeding: 0 months | 0.491 | 0.500 |
| Breastfeeding: <6 months | 0.271 | 0.445 |
| Breastfeeding: 6-12 months | 0.151 | 0.358 |
| Breastfeeding: >12 months | 0.086 | 0.281 |
| Birth weight (kg) | 3.296 | 0.627 |
| Measured waist circumference (cm) W5 | 98.749 | 18.663 |

*Source: The National Longitudinal Study of Adolescent to Adult Health (Add Health)*

*SD=standard deviation*

***Table 2: Weighted Least Squares Regression Model Results***. Coefficients for staged CRP and IL-6 models with survey weights. Standard errors are listed below coefficients in parentheses and coefficient Wald test results are indicated as follows: *p<0.05, **p<0.01, ***p<0.001.

| | $\log_{10}$(hsCRP) | | | $\log_{10}$(IL-6) | | | WC | | |
|---|---|---|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) | | | |
| Breastfeeding duration | | | | | | | | | |
| None | (REF) | | (REF) | (REF) | | (REF) | (REF) | | (REF) |
| <6 mo | -0.109*** | | -0.106*** | -0.039* | | -0.037* | -3.816*** | | -4.064*** |
| | (0.026) | | (0.026) | (0.019) | | (0.019) | (1.079) | | (1.080) |
| 6-12 mo | -0.125*** | | -0.121*** | -0.054* | | -0.052* | -6.531*** | | -6.912*** |
| | (0.035) | | (0.035) | (0.026) | | (0.026) | (1.410) | | (1.422) |
| >12 mo | -0.109** | | -0.107** | -0.040 | | -0.039 | -3.598** | | -3.801** |
| | (0.039) | | (0.039) | (0.024) | | (0.024) | (1.375) | | (1.359) |
| Birth weight (kg) | | -0.027 | -0.016 | | -0.014 | -0.010 | | 1.419* | 1.921** |
| | | (0.021) | (0.020) | | (0.012) | (0.012) | | (0.710) | (0.694) |
| Any infectious symptoms in last 2 weeks (y/n) | 0.156*** | 0.151*** | 0.156*** | 0.067*** | 0.065*** | 0.067*** | | | |
| | (0.027) | (0.028) | (0.028) | (0.017) | (0.017) | (0.017) | | | |
| Any anti-inflammatory medication (y/n) | 0.027 | 0.030 | 0.027 | 0.004 | 0.005 | 0.004 | | | |
| | (0.027) | (0.027) | (0.027) | (0.018) | (0.018) | (0.018) | | | |
| Any prescription contraceptives (y/n) | 0.344*** | 0.347*** | 0.344*** | -0.029 | -0.028 | -0.028 | 0.060 | 0.052 | 0.004 |
| | (0.047) | (0.048) | (0.047) | (0.029) | (0.029) | (0.029) | (1.788) | (1.848) | (1.776) |
| Any cigarettes in last 30 days (y/n) | 0.073* | 0.078** | 0.072* | 0.089*** | 0.092*** | 0.089*** | -1.649 | -1.214 | -1.567 |
| | (0.029) | (0.029) | (0.029) | (0.016) | (0.016) | (0.016) | (1.147) | (1.113) | (1.136) |
| Age (W5) | 0.000 | 0.003 | 0.000 | 0.004 | 0.005 | 0.004 | -0.200 | -0.066 | -0.204 |

| | $log_{10}$(hsCRP) | | | $log_{10}$(IL-6) | | | WC | | |
|---|---|---|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) | | | |
| | (0.006) | (0.006) | (0.006) | (0.004) | (0.004) | (0.004) | (0.267) | (0.275) | (0.264) |
| Self-reported female sex W5 | 0.142*** | 0.137*** | 0.139*** | 0.056*** | 0.054*** | 0.054*** | -5.614*** | -5.335*** | -5.270*** |
| | (0.026) | (0.027) | (0.026) | (0.015) | (0.015) | (0.015) | (1.149) | (1.219) | (1.173) |
| Parent completed college | -0.111*** | -0.139*** | -0.111*** | -0.067*** | -0.078*** | -0.067*** | -4.514*** | -5.832*** | -4.575*** |
| | (0.026) | (0.027) | (0.026) | (0.014) | (0.015) | (0.015) | (0.905) | (0.973) | (0.890) |

*Source: The National Longitudinal Study of Adolescent to Adult Health (Add Health)*

***Table 3: Mediation Analysis Results***. Coefficients for CRP and IL-6 mediation models, adjusted for covariates not shown, from full sample. Separate columns include 95% confidence intervals.

| | | *95% Confidence Interval* | | | *95% Confidence Interval* | |
|---|---|---|---|---|---|---|
| | *Coefficient* | *Upper bound* | *Lower bound* | *Coefficient* | *Upper bound* | *Lower bound* |
| | **Waist circumference ($WC_5$; cm)** | | | **$WC_5$** | | |
| Breastfeeding duration (BF) | | | | | | |
| None | (REF) | | | (REF) | | |
| <6 mo | -3.039 | -4.518 | -1.560 | -3.178 | -4.630 | -1.726 |
| 6-12 mo | -5.831 | -7.681 | -3.980 | -5.796 | -7.611 | -3.982 |
| >12 mo | -4.591 | -6.899 | -2.282 | -5.087 | -7.325 | -2.849 |
| Birth weight (kg) | 2.270 | 1.285 | 3.256 | 2.218 | 1.250 | 3.187 |
| ***Direct associations*** | **$\log_{10}(CRP_5)$** | | | **$\log_{10}(IL\text{-}6_5)$** | | |
| BF | | | | | | |
| None | (REF) | | | (REF) | | |
| <6 mo | -0.035 | -0.071 | 0.000 | -0.008 | -0.031 | 0.015 |
| 6-12 mo | 0.006 | -0.039 | 0.051 | -0.017 | -0.046 | 0.011 |
| >12 mo | -0.046 | -0.101 | 0.010 | -0.033 | -0.070 | 0.002 |
| Birth weight (kg) | -0.068 | -0.092 | -0.044 | -0.025 | -0.040 | -0.010 |
| $WC_5$ | 0.015 | 0.015 | 0.016 | 0.008 | 0.007 | 0.008 |
| ***Indirect association through WC*** *(BF → $WC_5$)* | | | | | | |
| None | (REF) | | | (REF) | | |
| <6 mo | -0.047 | -0.070 | -0.024 | -0.025 | -0.036 | -0.013 |
| 6-12 mo | -0.090 | -0.119 | -0.061 | -0.045 | -0.060 | -0.031 |
| >12 mo | -0.071 | -0.107 | -0.035 | -0.040 | -0.057 | -0.022 |
| n | 3,417 | | | 3,570 | | |

*Source: The National Longitudinal Study of Adolescent to Adult Health (Add Health)*

## Supplementary material

***Table S1: Full and Complete Case Sample Comparison***. Descriptive statistics for analytical variables in full CRP sample and complete case sample used in final analyses.

| | Full CRP assay sample | | | Complete case sample | | |
|---|---|---|---|---|---|---|
| | Mean | sd | Count | Mean | sd | Count |
| log10(hsCRP) W5 | 0.278 | 0.539 | 4268 | 0.275 | 0.539 | 3417 |
| Any infectious symptoms in last 2 weeks (y/n) | 0.276 | 0.447 | 4268 | 0.281 | 0.450 | 3417 |
| Any anti-inflammatory medication (y/n) | 0.321 | 0.467 | 4212 | 0.324 | 0.468 | 3417 |
| Any prescription contraceptives (y/n) | 0.065 | 0.246 | 4268 | 0.069 | 0.254 | 3417 |
| Any cigarettes in last 30 days (y/n) | 0.236 | 0.425 | 4248 | 0.232 | 0.422 | 3417 |
| Age (W5) | 37.964 | 1.926 | 4268 | 37.844 | 1.908 | 3417 |
| Self-reported female sex W5 | 0.595 | 0.491 | 4268 | 0.591 | 0.492 | 3417 |
| Parent college completion | 0.285 | 0.451 | 3735 | 0.286 | 0.452 | 3417 |
| Breastfeeding: 0 months | 0.498 | 0.500 | 3653 | 0.491 | 0.500 | 3417 |
| Breastfeeding: <6 months | 0.267 | 0.442 | 3653 | 0.271 | 0.445 | 3417 |
| Breastfeeding: 6-12 months | 0.151 | 0.358 | 3653 | 0.151 | 0.358 | 3417 |
| Breastfeeding: >12 months | 0.085 | 0.279 | 3653 | 0.086 | 0.281 | 3417 |
| Birth weight (kg) | 3.292 | 0.631 | 3594 | 3.296 | 0.627 | 3417 |
| Measured waist circumference (cm) W5 | 98.923 | 18.990 | 4251 | 98.749 | 18.663 | 3417 |

Source: The National Longitudinal Study of Adolescent to Adult Health (Add Health)

***Table S2: Breastfeeding by parental education***. Two-way table of breastfeeding duration category frequencies by parent college completion, tested for independence using Pearson's survey-weighted and complex-design-adjusted F statistic.

| | **Parent college completion** | |
|---|---|---|
| **Breastfeeding duration** | No | Yes |
| **0 months** | 0.570 | 0.305 |
| **< 6 months** | 0.254 | 0.302 |
| **6-12 months** | 0.116 | 0.225 |
| **> 12 months** | 0.061 | 0.168 |

*Pearson design-based F(2.85, 364.57) = 38.27 (p<0.0001)*

***Table S3: Breastfeeding by low birth weight***. Two-way table of breastfeeding duration category frequencies by low birth weight (<2,500 g), tested for independence using Pearson's survey-weighted and complex-design-adjusted F statistic.

| | **Low birth weight** | |
|---|---|---|
| **Breastfeeding duration** | No | Yes |
| **0 months** | 0.484 | 0.703 |
| **< 6 months** | 0.272 | 0.197 |
| **6-12 months** | 0.153 | 0.048 |
| **> 12 months** | 0.091 | 0.053 |

*Pearson design-based F(2.97, 379.95) = 11.10 (p<0.0001)*

***Table S4: CRP and IL-6 Predictive Marginal Means***. Predictive marginal means from fully adjusted and survey-weighted ordinary least square regression models for CRP, IL-6, probability of high-risk CRP (>3 mg/L), and waist circumference, with 95% confidence intervals.

| | **CRP** (mg/L) | | | **IL-6** (pg/ml) | | |
|---|---|---|---|---|---|---|
| **Breastfeeding duration** | *Marginal mean* | *95% CI* | | *Marginal mean* | *95% CI* | |
| 0 months | 2.102 | 1.973 | 2.239 | 0.730 | 0.701 | 0.760 |
| <6 months | 1.645 | 1.496 | 1.808 | 0.670 | 0.620 | 0.723 |
| 6-12 months | 1.589 | 1.376 | 1.836 | 0.648 | 0.581 | 0.722 |
| >12 months | 1.641 | 1.395 | 1.931 | 0.667 | 0.607 | 0.734 |

| | **p('high-risk CRP')** | | | **Waist circumference** (cm) | | |
|---|---|---|---|---|---|---|
| **Breastfeeding duration** | *Marginal mean* | *95% CI* | | *Marginal mean* | *95% CI* | |
| 0 months | 0.381 | 0.354 | 0.409 | 101.674 | 100.171 | 103.177 |
| <6 months | 0.326 | 0.293 | 0.360 | 97.610 | 95.976 | 99.245 |
| 6-12 months | 0.336 | 0.279 | 0.393 | 94.762 | 92.474 | 97.049 |
| >12 months | 0.302 | 0.237 | 0.366 | 97.873 | 95.535 | 100.211 |

***Table S5: Logit Regression Model Results***. Coefficients for staged CRP logit models with survey weights. Standard errors are listed below coefficients in parentheses and coefficient Wald test results are indicated as follows: *p<0.05, **p<0.01, ***p<0.001.

| | Logit($CRP_5$>3) | | |
|---|---|---|---|
| | (1) | (2) | (3) |
| Breastfeeding duration | | | |
| None | (REF) | | (REF) |
| <6 mo | -0.262* | | -0.257* |
| | (0.100) | | (0.102) |
| 6-12 mo | -0.217 | | -0.211 |
| | (0.159) | | (0.160) |
| >12 mo | -0.385* | | -0.381* |
| | (0.188) | | (0.187) |
| Birth weight (kg) | | -0.055 | -0.032 |
| | | (0.086) | (0.086) |
| Any infectious symptoms in last 2 weeks (y/n) | 0.462*** | 0.447*** | 0.461*** |
| | (0.126) | (0.126) | (0.126) |
| Any anti-inflammatory medication (y/n) | -0.065 | -0.056 | -0.065 |
| | (0.115) | (0.114) | (0.115) |
| Any prescription contraceptives (y/n) | 1.133*** | 1.140*** | 1.134*** |
| | (0.172) | (0.172) | (0.172) |
| Any cigarettes in last 30 days (y/n) | 0.121 | 0.131 | 0.120 |
| | (0.123) | (0.122) | (0.122) |
| Age (W5) | 0.025 | 0.032 | 0.026 |
| | (0.026) | (0.026) | (0.026) |
| Self-reported female sex W5 | 0.643*** | 0.629*** | 0.638*** |
| | (0.115) | (0.118) | (0.116) |
| Parent completed college | -0.393*** | -0.463*** | -0.392*** |
| | (0.110) | (0.107) | (0.110) |

*Source: The National Longitudinal Study of Adolescent to Adult Health (Add Health)*

***Table S6: Sibling Fixed Effects Regression Model Results***. Coefficients for sibling fixed effects models. Standard errors are listed below coefficients in parentheses and coefficient Wald test results are indicated as follows: *p<0.05, **p<0.01, ***p<0.001.

| | $\log_{10}(hsCRP_5)$ | | | $\log_{10}(IL\text{-}6_5)$ | | | $WC_5$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (1) | (2) | (3) | (1) | (2) | (3) |
| Breastfeeding duration | | | | | | | | | |
| None | (REF) | | (REF) | (REF) | | (REF) | (REF) | | (REF) |
| <6 mo | -0.006 | | -0.004 | -0.021 | | -0.035 | 0.572 | | 0.356 |
| | (0.140) | | (0.143) | (0.105) | | (0.107) | (4.276) | | (4.323) |
| 6+ mo | -0.069 | | -0.068 | 0.040 | | -0.000 | -5.434 | | -7.201 |
| | (0.179) | | (0.188) | (0.135) | | (0.140) | (5.490) | | (5.682) |
| Birth weight (kg) | | 0.036 | 0.039 | | 0.036 | 0.034 | | 5.184* | 5.518* |
| | | (0.080) | (0.080) | | (0.059) | (0.060) | | (2.416) | (2.417) |
| Any infectious symptoms in last 2 weeks (y/n) | 0.105 | 0.104 | 0.102 | -0.014 | -0.012 | -0.011 | | | |
| | (0.073) | (0.075) | (0.076) | (0.055) | (0.056) | (0.057) | | | |
| Any anti-inflammatory medication (y/n) | 0.108 | 0.106 | 0.104 | 0.064 | 0.061 | 0.064 | | | |
| | (0.070) | (0.070) | (0.071) | (0.052) | (0.052) | (0.053) | | | |
| Any prescription contraceptives (y/n) | 0.189 | 0.183 | 0.184 | -0.052 | -0.048 | -0.044 | -3.824 | -3.880 | -3.892 |
| | (0.152) | (0.153) | (0.154) | (0.115) | (0.114) | (0.115) | (4.657) | (4.638) | (4.653) |
| Any cigarettes in last 30 days (y/n) | -0.119 | -0.123 | -0.126 | -0.040 | -0.038 | -0.039 | -0.338 | -0.435 | -0.855 |
| | (0.098) | (0.099) | (0.100) | (0.074) | (0.074) | (0.075) | (2.935) | (2.946) | (2.963) |
| Age (W5) | -0.005 | -0.007 | -0.007 | 0.006 | 0.005 | 0.004 | 0.310 | 0.421 | 0.354 |
| | (0.018) | (0.018) | (0.019) | (0.014) | (0.014) | (0.014) | (0.549) | (0.556) | (0.562) |
| Self-reported female sex W5 | 0.059 | 0.091 | 0.093 | 0.122 | 0.102 | 0.105 | -3.796 | -3.287 | -3.195 |
| | (0.093) | (0.101) | (0.102) | (0.070) | (0.075) | (0.076) | (2.820) | (3.024) | (3.037) |

*Source: The National Longitudinal Study of Adolescent to Adult Health (Add Health)*

***Figure S1: CRP and IL-6 Predictive Marginal Means from Sibling Fixed Effects Models***. Predictive marginal means from adjusted sibling fixed effects models for CRP, IL-6, and waist circumference, with 95% confidence intervals.

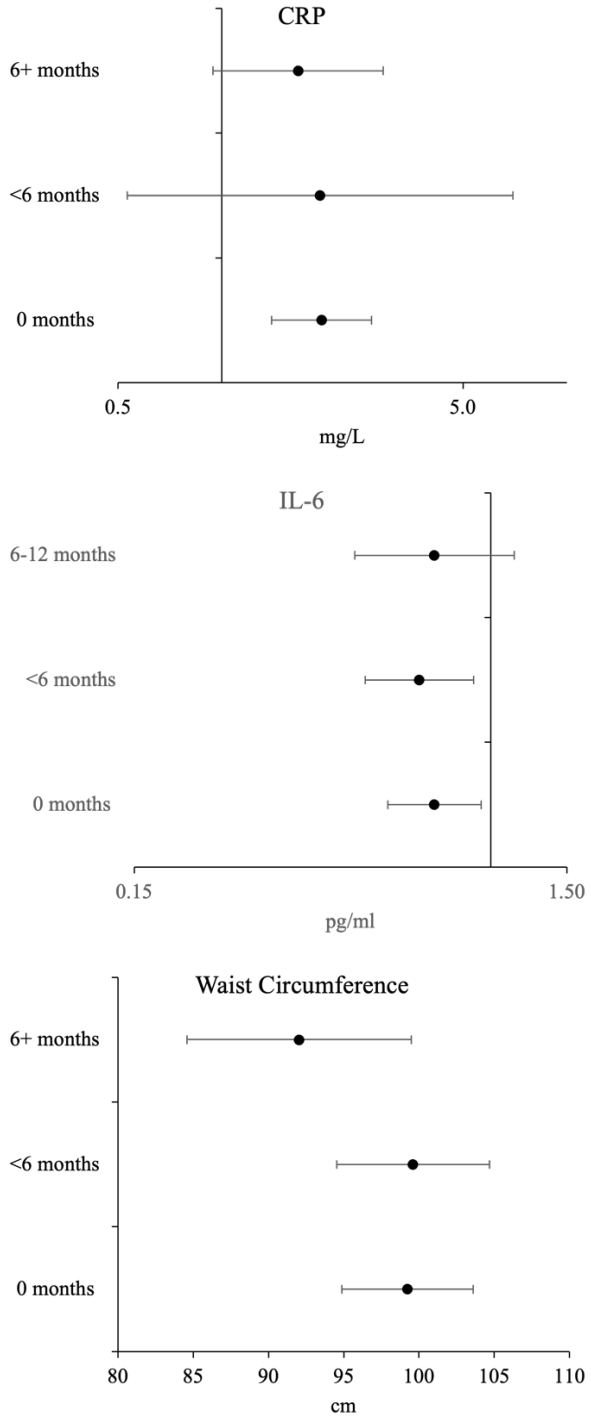

***Table S7: CRP and IL-6 Predictive Marginal Means from Sibling Fixed Effects Models***.
Predictive marginal means from adjusted sibling fixed effects models for CRP, IL-6, and waist circumference, with 95% confidence intervals.

| | **CRP** (mg/L) | | | **IL-6** (pg/ml) | | |
|---|---|---|---|---|---|---|
| **Breastfeeding duration** | *Marginal mean* | *95% CI* | | *Marginal mean* | *95% CI* | |
| 0 months | 1.945 | 1.393 | 2.717 | 0.741 | 0.578 | 0.950 |
| <6 months | 1.926 | 0.532 | 6.972 | 0.684 | 0.512 | 0.913 |
| 6+ months | 1.664 | 0.942 | 2.938 | 0.741 | 0.485 | 1.132 |

| | **Waist circumference** (cm) | | |
|---|---|---|---|
| **Breastfeeding duration** | *Marginal mean* | *95% CI* | |
| 0 months | 99.243 | 94.880 | 103.605 |
| <6 months | 99.598 | 94.526 | 104.671 |
| 6+ months | 92.041 | 84.593 | 99.489 |

***Table S8: Sibling Fixed Effects Mediation Results***. Coefficients for sibling fixed effects mediation analyses. Standard errors (SE) are listed in parentheses beside coefficients and coefficient Wald test results are indicated as follows: *p<0.05, **p<0.01, ***p<0.001.

| | *Coefficient* | *SE* | *Coefficient* | *SE* |
|---|---|---|---|---|
| **Outcome:** | **Waist circumference ($WC_5$; cm)** | | **$WC_5$** | |
| Breastfeeding duration (BF) | | | | |
| None | (REF) | | (REF) | |
| <6 mo | 0.356 | (4.323) | 0.356 | (4.323) |
| 6+ mo | -7.201 | (5.682) | -7.201 | (5.682) |
| Birth weight (kg) | 5.518* | (2.417) | 5.518* | (2.417) |
| **Outcome:** | **$\log_{10}(CRP_5)$** | | **$\log_{10}$(IL-$6_5$)** | |
| BF | | | | |
| None | (REF) | | (REF) | |
| <6 mo | -0.012 | (0.120) | -0.040 | (0.094) |
| 6+ mo | 0.054 | (0.158) | 0.079 | (0.123) |
| Birth weight (kg) | -0.053 | (0.068) | -0.026 | (0.053) |
| WC5 | 0.018*** | (0.002) | 0.012*** | (0.002) |
| ***Indirect association through WC*** *(BF → $WC_5$)* | | *% Total association* | | *% Total association* |
| None | (REF) | | (REF) | |
| <6 mo | 0.006 | 34.8% | 0.004 | 9.7% |
| 6+ mo | -0.130 | 70.6% | -0.086 | 52.2% |
| n | 935 | | 934 | |