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Title: The Quality of Early Infant-Caregiver Relational Attachment and Longitudinal Changes in Infant Inflammation Across 6 Months

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Abstract

The quality of early caregiver-infant relationships has powerful implications for health trajectories across the lifespan, including associations with adult inflammation. However, because relatively few studies have examined this association during infancy, it remains unclear when this impact occurs and whether it is associated with longitudinal changes in salivary concentrations of inflammation across infancy. In 45 infants, we investigated whether the quality of infant-caregiver attachment (secure vs. insecure) was associated not only with levels of salivary C-reactive protein (sCRP) cross-sectionally, but also with changes in sCRP across 6 months. Interestingly, while there were no cross-sectional associations between infant-caregiver attachment and inflammation at 12 months of age, infant-caregiver attachment security predicted lower levels of sCRP 6 months later. In addition, attachment security predicted decreasing levels of sCRP from 12 months to 18 months of age. Implications for understanding the influence of the quality of early relationships on biological mechanisms related to disease are discussed.

Abbreviations: sCRP- salivary C-Reactive Protein; SS- Strange Situation; T1-T4- Time 1 to Time 4

Keywords: attachment; inflammation; mother-infant relations

Introduction

The quality of attachment relationships in early life can have profound implications for health trajectories across the lifespan. Research indicates that close relationships in general wield an influence on health outcomes that is on par with those of well-known behavioral health variables, such as physical activity, smoking, alcohol consumption, and obesity (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Holt-Lunstad, Smith, & Layton, 2010). Furthermore, attachment relationships early in development are thought to be particularly influential in this process (Pietromonaco, Uchino, & Schetter, 2013). Specifically, difficulties in early infant-caregiver relationships, including insecure attachment, harsh or abusive caregiver behaviors, maltreatment, and/or exposure to parental psychopathology have been associated with alterations

of biological mechanisms associated with poorer health outcomes, such as dysregulated autonomic (Oosterman, De Schipper, Fisher, Dozier, & Schuengel, 2010) and hypothalamic-pituitary-adrenal (HPA) axis functioning (Ehrlich, Ross, Chen, & Miller, 2016), increased inflammatory processes (Ehrlich, 2019; Measelle & Ablow, 2018; Measelle, David, & Ablow, 2017; Nelson, Wright, Allen, & Laurent, 2019; Slopen et al., 2015; Taylor, Lehman, Kiefe, & Seeman, 2006), and accelerated cellular aging (Danese et al., 2008; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Nelson, Allen, & Laurent, 2018), which may ultimately lead to greater morbidity and premature mortality (Anda et al., 2009; Fagundes, Glaser, & Kiecolt-Glaser, 2013; Miller, Chen, and Parker, 2011; Puig, Englund, Simpson, & Collins, 2013). These effects may be particularly strong during the first few years of life, which is a sensitive period of cortical, motor, physical, and psychological development during which infants are dependent upon their caregiver(s) to meet all of their basic needs. Remaining questions in this area involve determining when these effects emerge, and whether they diminish, persist, or strengthen across early development.

Attachment

As noted above, one potentially important interpersonal mechanism that has been proposed to connect relationships to health is the attachment relationship an infant forms with their primary caregiver(s) (Pietromonaco & Collins, 2017)—i.e. the pattern by which the infant has learned to seek proximity to and gain comfort from their attachment figure in response to stress (Benoit, 2004; Cassidy, Jones, & Shaver, 2013; De Wolff & Van Ijzendoorn, 1997). Over time, caregivers' responses to the infant's bids are thought to consolidate as internal working models of attachment (Bowlby, 1969; i.e., internal heuristics, models, and representations about the expectations of others, self, and relationships), that, when left unmodified, go on to potentially influence relational functioning across the lifespan and across generations (Pinquart, Feubner, & Ahnert, 2013). Prior research indicates that infants tend to develop secure attachment relationship patterns with caregivers who are consistently sensitive and responsive to the child's needs, an insecure-avoidant pattern when caregivers are emotionally unavailable, an insecure-ambivalent pattern when caregivers are unreliably responsive, and a disorganized pattern when caregivers are simultaneously a source of comfort and fear for the infant, which prevents the child from relying on an organized strategy for maintaining proximity to and seeking comfort from their caregivers (Ainsworth, Blehar, Waters, & Wall, 1978; Main & Solomon, 1986).

Theoretical Model Connecting Attachment to Health

Different working models of attachment are thought to shape infants' appraisals of social threat and influence the behavioral strategies (Ein-Dor, Mikulincer, & Shaver, 2011) they utilize to elicit external (i.e. caregiver) regulation to manage negative emotions and stress, which in turn can influence physiological stress responses (Loman & Gunnar, 2010) for better or worse. In the case of securely attached infants, this manifests as infants developing, through experiences with their caregivers over time, a sense of safety and security that attachment figures can be relied upon during stressful times. This sense of security, in turn, deploys a stress-buffering effect that mitigates the impact of biological insult (Ehrlich & Cassidy, 2018).

From the evolutionary and theoretical perspective proposed by the Generalized Unsafety Theory of Stress (GUTS), physiological stress can be understood as the default response of organisms that is only inhibited from experiences of learned safety (Brosschot, Verkuil, & Thayer, 2015, 2018); therefore, the stress response is not *triggered*, but rather *disinhibited*. Examples of stress dis/inhibitory mechanisms include ventrolateral prefrontal cortex tonic inhibition of subcortical structures (Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015) and vagal regulation of heart rate via tonic inhibition of sinoatrial node activity (Thayer & Sternberg, 2006). From this evolutionary perspective, a default chronic stress response is more advantageous as it allows an organism to be prepared for threat to increase short-term survival in situations not yet shown to be safe, even if it comes at a long-term cost due to cumulative biological insult and allostatic load. From an attachment perspective, infants with secure attachment (who have had experiences of learned safety that engender a sense of confidence that caregivers can be relied upon to meet emotional and biological needs) should experience an inhibited chronic pro-inflammatory stress response via downregulated/quickly recovering sympathetic and HPA activity as the sympathetic nervous system directly innervates the inflammatory system and chronic HPA axis activity can lead to upregulated inflammation (Jänig, 2014; Morey, Boggero, Scott, & Segerstrom, 2015; Nance & Sanders, 2007). By contrast, infants with insecure and disorganized attachment (who have a generalized perception of lack of safety in their environment and uncertainty about the reliability of caregivers to meet their needs) should experience a maintained chronic inflammatory response as described in the biological embedding model of early life stress (Ehrlich et al., 2016).

Indeed, young foster children in insecure and disorganized attachment relationships have shown greater sympathetic reactivity in response to an attachment procedure (i.e., the Strange Situation) than children with secure attachment (Oosterman et al., 2010), which may in turn regulate immune cell activity by influencing cytokine and antibody gene expression through the innervation of immune organs (Nance & Sanders, 2007). In line with this reasoning, social stress in particular has been shown to influence inflammatory processes through sympathetic innervation of the immune system in both human (Kemeny & Schedlowski, 2007) and animal models (Sloan et al., 2007). Similarly, infants with secure attachment have shown less HPA activation via lower levels of cortisol during transition to child care when compared to insecure infants (Ahnert, Gunnar, Lamb, & Barthel, 2014). While short-term HPA axis activation is associated with suppressed immune response, prolonged stress and chronic HPA activation during early life has been associated with impaired glucocorticoid suppression of inflammation (Morey, Boggero, Scott, & Segerstrom, 2015).

These findings indicate that the immune system is not only activated or disinhibited in response to physical threat, such as viral and bacterial infections, but also is activated/disinhibited in response to a host of psychosocial factors including social disruption in the forms of threat, conflict, rejection, isolation, and exclusion, as well as imagined conditions of conflict (Slavich & Irwin, 2014). As such, disrupted infant-caregiver relationships in early life may prevent experiences of learned safety, allowing for unchecked autonomic and HPA activation that may translate into greater levels of inflammation across infancy. In other words, the attachment system organizes an infant's response to these types of stressors and fears—with infants in secure attachment relationships effectively using their caregiver to gain comfort when stressed and thereby regulating (i.e., maintaining inhibition of) underlying physiological stress responses. In contrast, infants in insecure and disorganized attachment relationships, tend to have more difficulty using their caregiver to co-regulate and recover from stress, so it is not surprising that infant-caregiver attachment insecurity and disorganization imparts particular risk for young children's stress physiology. Overall, this indicates that disruption of early infant-caregiver relationships may influence inflammatory functioning, which may serve as an intermediate endpoint negatively influencing health outcomes later in life (Danese & McEwen, 2012).

C-reactive protein (CRP) is an acute phase protein produced by the liver that is often measured in serum and has been widely used as an index of systemic inflammation (Karadag,

Kirdar, Karul, & Ceylan, 2008). CRP is an important marker of health risks because heightened levels are associated with morbidity (e.g., cardiovascular disease, diabetes, and cancer; Emerging Risk Factors Collaboration, 2012; Kaptoge et al., 2012; Pradhan, Manson, Rifai, Buring, & Ridker, 2001; Ridker, Stampher, & Rifai, 2001) and mortality (Emerging Risk Factors Collaboration, 2010). While CRP is often measured in blood, salivary CRP (sCRP) is painless and non-invasive and therefore has been shown to be easier to collect (Granger et al., 2007) and recommended in pediatric populations (Ouellet-Morin, Danese, Williams, & Arseneault, 2011). Currently, there are differences of opinion on the use of sCRP as a measure of local and systemic inflammation as there is mixed literature on the association between sCRP and CRP collected from blood with some studies finding no correlation (Dillon et al., 2010; Kopanczyk et al., 2010) and others finding medium to large associations between these two measures (Byrne et al., 2013; Out, Hall, Granger, Page, & Woods, 2012) even across time in a longitudinal study (Out et al., 2012) and that sCRP can be used as a valid predictor of serum CRP (Ouellet-Morin et al., 2011). One possible reason for these mixed findings is that CRP can pass from blood to saliva through gingival crevicular fluid, which indicates that sCRP can be indicative of both local and systemic inflammation (Megson, Fitzsimmons, Dharmapatni, & Mark Bartold, 2010). Regardless of the association between sCRP and CRP detected in blood, research shows that sCRP still provides health-relevant inflammation (Byrne et al., 2013; Ouellet-Morin, Danese, Williams, & Arseneault, 2011; Out, Hall, Granger, Page, & Woods, 2012). For example, researchers have found that sCRP is associated with various measures of psychological and physical health in children, adolescents, and adults (Cicchetti, Handley, & Rogosch, 2015; Goodson et al., 2014; Laurent, Lucas, Pierce, Goetz, & Granger, 2016; Naidoo, Konkol, Biccard, Dudose, & McKune, 2012; Nelson et al., 2017), while other salivary immune markers are associated with emotional processing of stress at the neural level (O'Connor, Irwin, & Wellisch, 2009).

Initial research into compromised early infant-caregiver relationships and inflammation have relied on investigating the association between adult inflammatory markers and retrospective self-reports of harsh family environments (Taylor, Lehman, Kiefe, & Seeman, 2006), childhood maltreatment (Danese, Pariante, Caspi, Taylor, & Poulton, 2007), and prenatal adversity (Slopen et al., 2015) with recent research showing a poor association between retrospective and prospective measures of childhood maltreatment (Baldwin, Reuben, Newbury, & Danese, 2019) highlighting the need for concurrent measurements of early relationships and

inflammation. Other research has identified associations between adult inflammatory markers and prospective measures of childhood victimization (Baldwin et al., 2018) or infants of mothers experiencing psychosocial stress (David, Measelle, Ostlund, & Ablow, 2017; Nelson et al., 2019). Additional research with preteen-aged children found that exposure to maltreatment earlier in life was associated with higher CRP at age 12 (Danese et al., 2011). Currently, there is a dearth of studies investigating associations between compromised early infant-caregiver relationships and inflammatory processes *during infancy*. One of the few such studies found concurrent associations between insecure-disorganized infant attachment and higher levels of sCRP at 17 months of age (Measelle, David, & Ablow, 2017). Related research in adult populations has found that individuals with an insecure-avoidant attachment pattern tend to have exaggerated inflammatory responses during conflict with their spouse (Gouin et al., 2009). These studies provide some initial evidence for associations between disruptions in the quality of attachment relationships and inflammation in cross-sectional samples of infants and adults, yet it remains to be seen whether these disruptions are associated with inflammation prior to 17 months of age and with longitudinal changes in inflammation across infancy.

In contrast to pro-inflammatory effects of compromised close relationships, positive close relationships that are supportive and warm have been shown to confer protection against negative health outcomes (Nelson et al., 2017; Repetti, Taylor, & Seeman, 2002; Sbarra & Coan, 2018; Uchino, 2006) and are associated with lower rates of morbidity and mortality (Cohen, 2004; Sbarra & Coan, 2018; Seeman, 1996). Attachment security in particular has been found to relate to childhood, adolescent, and adult health behaviors and disease (Anderson & Whitaker, 2011; Delker, Bernstein, & Laurent, 2018; McWilliams & Bailey, 2010; Puig, Englund, Simpson, & Collins, 2013; Scharfe & Eldredge, 2001) and the experience of positive and negative emotions in future adult relationships (Simpson, 1990). Therefore, it is important to understand how disruptions in the early attachment relationship between infants and their caregivers may influence underlying biological processes that increase risk for a pro-inflammatory phenotype and early onset of disease (Baldwin & Danese, 2019).

Currently, just two studies have examined this association. One study demonstrated that a secure attachment between an infant and their caregiver is associated with a lower inflammatory load score comprised of salivary interleukin 1 beta (IL-1 β), IL-6, IL-8, tumor necrosis factor alpha (TNF- α), and sCRP at 17 months (Measelle & Ablow, 2018), while another study found

that disorganized attachment was associated with higher cross-sectional levels of sCRP as compared to secure attachment at 17 months (Measelle et al., 2017). Although these studies provide a starting point for asserting attachment effects on inflammation, additional research is needed to determine when such effects emerge and whether they remain stable or are exacerbated across infant development.

Current Study

The current study extends these prior studies of attachment and sCRP in infancy by addressing sCRP at an earlier age (12 months rather than 17 months) and by using a longitudinal design to examine whether attachment predicts changes in sCRP across 6 months. We hypothesized that secure compared to insecure infant-caregiver attachment classified at 12 months of age would be associated with lower concurrent levels of sCRP and lower levels of sCRP at 18 months of age. We also hypothesized that secure attachment would predict decreasing levels of sCRP from 12 to 18 months of age.

Methods and Materials

Participants and Recruitment

Mothers were recruited from the Women Infants Children program and other community agencies serving low-income families in a mid-sized city in the Pacific Northwest region of the United States. To be eligible, mothers had to speak English, have a <12-week-old infant, and anticipate remaining in the area until this target child was 18 months old. Table 1 provides demographic information about the sample.

Of the 91 mother-infant dyads who began the study at Time 1 (T1), 45 dyads (49%) participated at all four assessment times, received an attachment classification, and provided saliva samples for sCRP assay, resulting in the final sample size. There were 27 female and 18 male infants in the final sample. Compared to non-completers, study completers tended to be older ($M = 28.18$ vs. 25.80 , $t[87.26] = -2.12$, $p = .04$), more likely to be in a long-term relationship, $\chi^2(4) = 10.26$, $p = .036$, have more biological children ($M = 1.98$, vs. 1.53 , $t[86.23] = -2.40$, $p = .019$) and report higher household income, $\chi^2(7) = 14.34$, $p = .045$. There were no overall differences in race, infant sex, likelihood of being in a relationship with the target child's biological father or degree of contact with the father, education, or employment status. In

addition, there were no differences between the groups in terms of maternal mental health (depression or anxiety symptoms).

Procedure

Prior to study participation, mothers gave written informed consent to all study procedures, which had been approved by the Institutional Review Board. Mothers completed study assessments at one home visit and three laboratory visits: at 3 months (T1), 6 months (T2), 12 months (T3), and 18 months (T4) postnatal. At T1, participants completed a home visit that involved a diagnostic interview, and at T2-T4 participants completed laboratory sessions of psychosocial stress tasks with their infant. Relevant to the current study, at T3 infants and their mother's participated in the Strange Situation (SS), a paradigm designed to elicit behavioral differences associated with infant-caregiver attachment (Ainsworth & Bell, 1970).

Measures

Salivary C-Reactive Protein (sCRP). At T3 and T4, one saliva sample (Salimetrics Infant's or Child's Swab as appropriate for age) was collected from infants at the start of the session by a trained graduate student or research assistant to capture sCRP according to Salimetrics instructions. Saliva was collected by placing the swabs in infants' mouths for two minutes in order to collect a total of 2 mL of saliva. Prior to saliva collection mothers completed a saliva collection checklist. If any of several conditions had been violated (e.g., if the infant had eaten recently or was sick with a fever), the participants were rescheduled. Samples were stored at -20° C until shipment on dry ice for assay. Infants' saliva samples were assayed in duplicate with the commercially available Salimetrics Expanded Range High Sensitivity Cortisol Enzyme Immunoassay kit by Dr. Elizabeth Shirtcliff's SPIT lab (<https://research.hs.iastate.edu/spit-lab/>). The inter-assay coefficient of variation (CV) was 2.34% and the intra-assay CV was 3.10%. sCRP levels at 12 months were significantly associated with sCRP at 18 months of age ($r = .460$, $p = .001$).

Attachment Classification. At T3, infant-mother attachment was measured using (Ainsworth & Bell, 1970), a 24-minute standardized multi-phased experimental procedure designed to observe and classify infant-caregiver attachment by assessing children's reliance on their caregivers for comfort when distressed. During the task, infant and caregiver are twice separated and reunited, and the infant's attachment behaviors during both reunion episodes are

coded for proximity-seeking, contact maintenance, resistance, and avoidance (Ainsworth & Bell, 1970; Ainsworth et al., 1978). Per Main and Solomon's (1990) later-defined description of a fourth, Disorganized attachment pattern, a single continuous disorganization score is also assigned to capture infant disorganized behaviors throughout the task. Based on these continuous codes, mother-infant dyads are assigned to one of four primary attachment classifications: secure (B), avoidant (A), resistant (C), or disorganized (D). Those not able to be classified into one of these four classifications are classified as "Cannot Classify." Strange Situation videotapes were sent for expert classification and attachment behavior coding by experienced coder and trainer Elizabeth Carlson, Ph.D. at the University of Minnesota. Because a single expert coder was utilized, no inter-rater reliability data is available for attachment scales or categorization. The sample comprised 21 Secure, 5 Resistant, 5 Avoidant, and 14 Disorganized infants. For the current study we dummy coded securely attached infants as 0 and named this "Secure," while we combined (due to power) both types of insecure-organized (anxious-resistant and avoidant) and disorganized infants into one group called "Insecure" and dummy coded these as 1. This resulted in 21 securely attached infants and 24 insecurely attached infants. Please see Supplementary Materials for Mean and SD of sCRP at T3 and T4 by each attachment group (Secure, Resistant, Avoidant, Disorganized).

Covariates. A number of variables proposed to be related to infant sCRP were examined as potential control variables. These included infant age, infant sex and race, maternal socioeconomic status (SES) markers (education, employment, and income), and maternal smoking status. In order to preserve power and avoid overfitting, only covariates significantly associated with sCRP or attachment classification were included in analyses. The only significant association found was between attachment and maternal employment, $\chi^2(6) = 15.79, p = .015$, so the employment variable was included as a covariate in model testing.

Statistical Analyses

All statistical analyses were conducted with R, version 3.3.2. Statistical significance was defined using 95% confidence intervals. Histograms as well as skew and kurtosis statistics were examined for each variable to check for normality. sCRP scores were winsorized to ± 3 SD to correct for undetectable values (this impacted 4 samples each at the 12- and 18-month assessments) and log-transformed to correct positive skew. sCRP concentrations when infants were 12 months old ranged from 3.80 to 6.86 pg/mL ($M = 4.80$ pg/mL, $SD = .96$) and from 1.61

to 7.34 pg/mL ($M = 4.24$ pg/mL, $SD = 1.39$) when they were 18 months old. Attachment classifications of Resistant, Avoidant, and Disorganized were grouped into one category to represent insecure attachment, compared to the Secure group.

T-tests were performed to assess whether there were cross-sectional attachment group differences in sCRP at T3 and T4, while a regression was used to assess whether attachment predicted sCRP at T4 after controlling for sCRP at T3.

Results

Cross-Sectional Analyses: There was not a significant difference in sCRP between Secure ($M = 4.71$, $SD = 1.02$) and Insecure ($M = 4.88$, $SD = .92$) attachment classifications at 12 months of age; $t(40.64) = -.59$, $p = .561$ (see Figure 1a). This did not change after controlling for maternal employment. In contrast, there was a significant difference in sCRP between Secure ($M = 3.56$, $SD = 1.35$) and Insecure ($M = 4.83$, $SD = 1.15$) attachment classifications at 18 months of age, $t(39.58) = -3.36$, $p = .002$, Cohen's $d = 1.008$ (see Figure 1b). This finding remained significant after controlling for maternal employment ($p = .001$), a measure of socioeconomic status¹.

Regression Analysis: Insecure attachment when infants were 12 months of age significantly predicted greater sCRP at 18 months of age after controlling for both prior sCRP levels and maternal employment, $\beta = 1.40$, $SE = .36$, $p < .001$, 95% CI [.674, 2.120], and explained 38% of the variance in sCRP change scores (see Table 2) with an effect size of 0.380 indicating more positive sCRP trajectories relative to secure infants across 12 to 18 months of age. For individual sCRP trajectories see Figure 2.

Discussion

¹ Post-hoc exploratory analyses revealed that birth weight was not associated with sCRP at 12 months of age ($r = -0.04$, $p = 0.800$) or 18 months of age ($r = -0.17$, $p = 0.270$). Similarly, post-hoc exploratory analyses using breastfeeding data when infants were 6 months of age revealed no significant difference between breastfeeding at 6 months of age with 12 month sCRP; $t(9.27) = 1.18$, $p = .269$, as well as no significant difference between breastfeeding at 6 months of age with 18 month sCRP; $t(8.36) = 0.84$, $p = .424$.

Currently, there is very little research addressing the association between stress and inflammation during infancy, specifically when it comes to disruptions to the quality of early infant-caregiver attachment relationships. The few studies that have investigated this association have only addressed cross-sectional associations between attachment insecurity and infant inflammatory processes, leaving important questions about how early such effects emerge and how they progress over time. This study was the first to investigate whether disruption in attachment security during infancy was associated with both cross-sectional differences in sCRP and longitudinal levels of sCRP across infancy.

In line with hypotheses, infants who were securely attached to their mothers at 12 months of age had significantly lower levels of sCRP at 18 months of age and decreasing levels of sCRP from 12 to 18 months of age. These findings fall in line with prior research indicating that early life adversity (Fagundes et al., 2013) in the form of harsh family environments (Taylor et al., 2006), maltreatment (Danese et al., 2008), and victimization (Baldwin et al., 2018) were associated with elevated CRP in adulthood. Our findings further indicate that this difference was not driven by insecurely attached infants increasing in sCRP, but rather by securely attached infants decreasing in sCRP from 12 to 18 months of age. This points to an anti-inflammatory association between secure attachment and sCRP, possibly via less sympathetic activation and/or better glucocorticoid-mediated inhibition of inflammation, consistent with the evolutionary and theoretical perspective of GUTS introduced earlier (Brosschot et al., 2015, 2018). That is, infants with secure attachment may have had experiences of learned safety that inhibited a chronic pro-inflammatory stress response by downregulating sympathetic activity and/or enhancing HPA axis-mediated control of inflammation. Infants with insecure attachment, on the other hand, may have learned generalized unsafety from their environment, making it more evolutionarily advantageous to maintain a chronic inflammatory response as specified by the biological embedding model of early adversity (Ehrlich et al., 2016).

However, we did not replicate the cross-sectional association between attachment insecurity and sCRP elevation that had been previously observed in a sample of 17 month old infants (Measelle & Ablow, 2018; Measelle et al., 2017) when infants in our sample were 12 months of age. One possible explanation for this is that attachment-related differences in inflammation may not consistently arise until after the first year of life. This may be due to developmental factors, such as the attachment relationship becoming more elaborated in the

second year as children's language and broader social-cognitive capacities expand, or the fact that psychosocial stress may need to accumulate over time before it influences inflammatory processes. For example, stress has been shown to have a lagged (Shonkoff, Boyce, & McEwen, 2009) or delayed (Tilders, Schmidt, Hoogedijk, & Swaab, 1999) effects on inflammatory processes such as those tapped by sCRP.

Limitations and Future Directions

While the present study makes a contribution as the first to investigate whether attachment prospectively predicts inflammation during infancy, there were a number of limitations that should be noted. First, the sample was a relatively small and demographically homogenous group, which limits the generalizability of findings. Larger and more diverse samples should be collected to replicate and extend the current results. Second, the study did not follow infants into childhood or later stages of life to determine whether heightened sCRP in those with insecure attachment went on to predict higher rates of health complaints. Future studies should employ longitudinal designs that span sensitive periods of development to elucidate how early stress translates into divergent health trajectories later on in life. Third, while our protocol made sure infants hadn't breastfed within 1 hour of the laboratory session, so as to avoid salivary contamination, we did not collect measures on whether infants were breastfed or formula fed in general and whether or not infants were teething, which have the potential to be important for inflammation levels as oral and systemic inflammatory profiles could potentially change due to receiving antibodies and bacteria from their mother. This will be important to assess in future studies as oral inflammation has been identified as a potential confound of sCRP (Pay & Shaw, 2019) and at 12 months of age a majority of infants have begun to teeth and therefore may have increased oral inflammation. This possibility may explain the lack of cross-sectional sCRP differences between secure and insecure infants at 12 months of age. While we did not collect whether or not infants were breastfeeding at 12 and 18 months of age, we did collect whether or not mothers were breastfeeding at 6 months of age, although we did not collect when mothers stopped breastfeeding, if at all during the course of the study. Post-hoc exploratory analyses using this data revealed no significant difference between breastfeeding at 6 months of age with 12 month as well as no significant difference between breastfeeding at 6 months of age with 18 month as can be seen in the footnote above. While saliva samples are preferred with infants because of the invasiveness/pain considerations noted above (Granger et

al., 2007; Ouellet-Morin, Danese, Williams, & Arseneault, 2011), future studies might consider utilizing blood spots to detect CRP in infants as a way to address concerns rising from the mixed literature on sCRP. If researchers choose to collect sCRP, they should ensure that oral inflammation is controlled for in order to provide a potentially more accurate measure of sCRP. Fourth, we did not collect a number of relevant covariates that may have been associated with levels of inflammation including body mass index at birth, current body mass index, and growth rate. While we did not collect growth rate or body mass index at the time of saliva sampling, we did collect birth weight. Post-hoc exploratory analyses revealed that birth weight was not associated with sCRP at 12 months of age or 18 months of age as can be found in the footnote above. These post-hoc exploratory findings indicate that birthweight and breastfeeding status at 6 months of age had no significant effect on inflammation at 12 and 18 months of age, although this does not preclude the ability for later body mass index or breastfeeding status to have a potential impact on inflammation. Similarly, we did not collect information on length since infant vaccination, which could likely also influence levels of inflammation. Future studies should make sure to collect for these additional variables that may influence inflammation. Fifth, while the study did use an expert coder for classification of attachment behaviors, it did not utilize a second coder, which precludes a measure of inter-rater reliability. Future studies should ensure that attachment behavior is rated by more than one coder. Finally, the current study did not collect measures of other infant stress-responsive physiological systems to probe mechanisms that may connect compromised attachment with underlying inflammatory processes. Future research should incorporate indices of sympathetic and parasympathetic activity, as well as glucocorticoid control of inflammation, in order to determine whether compromised quality of early infant-caregiver attachment contributes to pro-inflammatory phenotypes via autonomic or other neurophysiological mechanisms.

Conclusion

This study was the first to investigate whether disruption in infant-caregiver attachment during infancy relates to sCRP not just concurrently, but also prospectively. Findings revealed that infants in a secure attachment relationship had lower levels of sCRP 6 months later as compared to infants in an insecure attachment relationship. We did not detect any cross-sectional relationship between attachment and sCRP at 12 months. These findings indicate that the quality

of early relationships between infants and their caregivers may influence underlying biological mechanisms related to the early onset of disease.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Table 1

Sample Descriptives

Variable	Number	Percent of Sample
Race/Ethnic Identification		
Caucasian	36	80%
Latina	5	11.11%
Asian American	2	4.44%
Native American	2	4.44%
Infant Gender		
Female	27	60%
Male	18	40%
Relationship Status		
Single	2	4.44%
Dating	2	4.44%
Living with Someone (not a legal domestic partnership)	15	33.33%
Married	22	48.89%
Legal/Registered Domestic Partnership	4	8.89%
Relationship Length		
< 1 year	1	2.22%
1-2 years	2	4.44%
2-5 years	10	22.22%
5-10 years	3	6.67%
> 10 years	1	2.22%
Missing	28	62.22%
Education		
High school	10	22.22%
Vocational/technical school (2-year)	6	13.33%
Some college	19	42.22%
College graduate (4-year)	5	11.11%
Master's degree	4	8.89%
Other	1	2.22%

Employment		
Self-employed	4	8.89%
Part-time paid work	6	13.33%
Full-time paid work	6	13.33%
On leave	4	8.89%
Unemployed	6	13.33%
Full-time homemaker	16	35.56%
Student	3	6.67%
Household Income		
< \$4,999	11	24.44%
\$5,000-\$9,999	3	6.67%
\$10,000-\$19,999	3	6.67%
\$20,000-\$29,999	8	17.78%
\$30,000-\$39,999	6	13.33%
\$40,000-\$49,999	5	11.11%
\$50,000-\$74,999	7	15.56%
\$75,000-\$99,999	2	4.44%

Table 2. Attachment at 12 Months Predicting sCRP at 18 Months of Age

Variable	Estimate	SE	p	95% CI (LL, UL)
Constant	1.265	.922	.178	-.597, 3.128
Attachment Classification	1.397	.358	< .001***	.674, 2.120
sCRP at 12 months	.605	.173	.001***	.256, .954
Maternal Employment	-.155	.095	.111	-.348, .037

Note. sCRP = salivary C-reactive protein. * < .05, ** < .01, *** < .001.

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