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**Special Issue Article**

# Early life adversity, inflammation, and immune function: An initial test of adaptive response models of immunological programming

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**Abstract**

Much research indicates that exposure to early life adversity (ELA) predicts chronic inflammatory activity, increasing one's risk of developing diseases of aging later in life. Despite its costs, researchers have proposed that chronic inflammation may be favored in this context because it would help promote immunological vigilance in environments with an elevated risk of infection and injury. Although intuitively appealing, the assumption that exaggerated inflammatory activity predicts favorable immunological outcomes among those exposed to ELA has not been tested. Here, we seek to address this gap, examining the links between exposure to ELA, inflammation, and immune function. Consistent with others' work, results revealed that those from low socioeconomic status (SES) childhood environments exhibited exaggerated unstimulated inflammatory activity relative to what was observed among those from higher SES childhood environments. Further, results revealed that – although levels of inflammation predicted the magnitude of immunological responses in those from higher SES backgrounds – for those who grew up in low SES environments, higher levels of inflammation were unrelated to the magnitude of immunological responses. Results suggest that exaggerated inflammatory activity in the context of ELA may not predict improved ability to manage acute immunological threats.

**Keywords:** early life adversity; immunological programming; inflammation; socioeconomic status

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Over the past several decades, researchers have accumulated a significant body of evidence demonstrating the lasting effects of early life adversity (ELA) on health (see e.g., Friedman et al., 2015; Gluckman & Hanson, 2006; Shonkoff et al., 2009). In particular, this research finds that individuals who have been exposed to environmental stressors – such as poverty, maltreatment, and unpredictability – in the first years of life carry the legacy of this exposure into adulthood in the form of heightened risk of morbidity and mortality from illness and disease (see e.g., Cuijpers et al., 2011; Kittleson et al., 2006). One potent contributor to this link is the presence of chronic inflammatory activity (Baumeister et al., 2015; Rasmussen et al., 2018). Much research demonstrates that individuals growing up in conditions of ELA exhibit an immunological profile characterized by chronic inflammation, an exaggerated response to immune challenge, and insensitivity to inflammation-mitigating signals (Ehrlich et al., 2016; Elwenspoek et al., 2017), a pattern that some researchers describe as a "proinflammatory phenotype" (see e.g., Miller & Chen, 2007).

The reliability with which researchers observe the development of a proinflammatory phenotype following conditions of ELA has led a number of evolutionary-minded researchers to propose that this phenotype serves an adaptive function in the context of ELA. Although the proposed pathway through which ELA becomes linked with inflammation differs somewhat between different explanations, each assumes that – because increased inflammation is associated with greater immunological activity (Dinarello, 2000; Kato & Kitagawa, 2006; Medzhitov, 2008) – exaggerated inflammatory activity in the context of ELA may function to promote a swift and robust immunological response to the abundant physical and microbial threats in these environments. Although theoretically and intuitively appealing, this assumption has not been tested. Such a test is necessary, however, since extant research examining the links between early life poverty and each health (Gupta et al., 2007; Spencer & Acheson, 2000) and glucocorticoid resistance (Chen et al., 2016; Miller et al., 2009) suggest that exaggerated inflammation in this context may not be functional, but instead a byproduct of other developmental modifications occurring in response to stress (Elwenspoek et al., 2017).

The current research was conducted to address this empirical gap, examining the links between multiple dimensions of ELA, inflammation, and immunological function. First, we provide an overview of the extant models that have proposed a functional role for chronic inflammation among those from adverse environments. Next, we present the results of a laboratory experiment in which we test whether elevated inflammatory activity observed in those who have experienced ELA predicts the magnitude of multiple, concurrently-occurring immunological responses. Results seek to provide a much-needed test of the assumed links between inflammatory activity and immunological responses among those exposed to ELA.

## ELA, health, and chronic inflammation

Much psychological and epidemiological research finds that childhood adversity leaves a lasting and detrimental impact on adult

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health (Friedman et al., 2015; Gilbert et al., 2015; Gluckman & Hanson, 2006; Repetti et al., 2002; Shonkoff et al., 2009). Individuals reared under conditions of recurrent psychosocial stress (e.g., trauma, neglect, abuse, poverty, violence) are more likely to develop psychopathology and have worse health outcomes in adulthood compared to those from more favorable environments (Cicchetti, 2016; Nemeroff, 2016). Others find that exposure to stressors like neglect, abuse, and household violence during childhood is associated with a nearly twofold increase in the incidence of cardiovascular disease, liver disease, lung disease, cancer, and autoimmune disorders later in life (Dong et al., 2004; Dube et al., 2009; Felitti et al., 1998; Wegman & Stetler, 2009). These effects continue to the grave, as those who experience greater exposure to early life stress and adversity are more likely to suffer premature death than those who enjoy stable and secure upbringings (Brown et al., 2009; Galobardes et al., 2008; Kelly-Irving et al., 2013).

There are several factors that likely mediate relationships between ELA and poor adult health. For example, when compared to children from middle- and upper-class homes, research finds that children growing up in conditions of low socioeconomic status (SES) are exposed to more psychosocial stress (Reiss et al., 2019) and harmful chemicals (Tyrrell et al., 2013), while also having reduced access to healthcare (Fiscella et al., 2000), healthy food options (Larson et al., 2009), and safe places to play and exercise (Pinter-Wollman et al., 2018; Suecoff et al., 1999). These factors – particularly when experienced together – contribute to the health disparities observed between those from resource scarce compared to resource abundant childhood environments.

One particularly potent factor contributing to the links between adverse childhood experiences and poor adult health outcomes is exposure to chronic inflammation (Fagundes & Way, 2014; Taylor, 2010). Although inflammation is critical for survival, excessive or prolonged inflammation is known to promote or exacerbate multiple disease states (Chung et al., 2009) and contributes to accelerated aging (Conner & Grisham, 1996; Khansari et al., 2009). Several studies have now found that exposure to ELA predicts chronic inflammation (for recent meta-analyses, see Liu et al., 2017; Milaniak & Jaffee, 2019). This relationship is found to emerge as early as childhood (Schmeer & Yoon, 2016) and continues to persist into adulthood, even after statistically controlling for numerous potential confounding factors (e.g., smoking, body weight, and adult SES; Milaniak & Jaffee, 2019).

In addition to exhibiting chronic basal inflammatory activity, those who have been exposed to ELA have also been found to exhibit an especially aggressive inflammatory response to acute immunological and psychosocial stressors. For example, research finds that those who experienced low childhood SES (Azad et al., 2012) or grew up in chaotic or harsh family environments (Miller & Chen, 2010; Schreier et al., 2014) exhibit a more pronounced inflammatory response when their white blood cells are exposed to an immunological challenge *in vitro,* compared to those from more stable, resource secure environments. Several other studies have found that adults who experienced ELA – including childhood trauma, neighborhood violence, and low SES – exhibit higher *in vivo* inflammation in response to a stressful public speaking task compared to adults not exposed to ELA (Carpenter et al., 2010; Janusek et al., 2017; Lockwood et al., 2018; Shalev et al., 2020).

Why does exposure to ELA predict chronic inflammation and exaggerated inflammatory responses to immunological stimulation? Inflammation is produced by the cells of the immune system, which is the body's primary source of protection and defense from injury and infection. When the cells of the immune system detect infection or damage, they release signaling proteins, including proinflammatory cytokines such as interleukin-1 beta (IL-1β), IL-6,[1] and tumor necrosis factor alpha (TNF-α), that promote inflammatory activity, prevent and clear infections, and repair damage. Given the greater risk of harm and exposure to contaminants that exist in adverse environments, researchers have proposed that growing up in the context of ELA may influence immunological development in ways that promote immunological vigilance in stressful ecologies, but come at the expense of chronic inflammation.

The hypothesis that chronic inflammation may serve an adaptive function in adverse environments is one that is predicted by multiple lines of inquiry in the evolutionary sciences. Each of these models proposes a somewhat different pathway from adversity to inflammation; however, in each case, this activity is reasoned to promote short-term health and recovery in the context of environmental stress and pathogen exposure. These are reviewed below.

### *Biological embedding model*

The biological embedding model (Miller et al., 2011) proposes that exposure to ELA should favor monocytes' (cells of the innate immune system) developing response tendencies that would help promote healing and recovery in relatively perilous ecologies – a "proinflammatory phenotype" (Miller et al., 2009; Zhang et al., 2006). Such a phenotype is hypothesized to be characterized by a prioritization of current health (and reproduction), even if it comes at the expense of future health and longevity. According to this model, developmental modifications to the hypothalamic-pituitary-adrenal (HPA) axis (Lê-Scherban et al., 2018; Roubinov et al., 2018; Zhu et al., 2019) and the immune system (McDade et al., 2016; Miller & Chen, 2010; Miller et al., 2011) typically observed among those from conditions of ELA that promote chronic inflammation would have promoted survival in harsh and adverse early life environments (McEwen, 2012; Miller & Chen, 2013) by allowing children to deal with the immediate immunological and safety challenges of their harsh environment (Miller et al., 2011).

### *Internal predictive adaptive response (iPAR) model*

Similar to the biological embedding model (Miller et al., 2011), the iPAR model posits that chronic inflammation in the context of ELA results from developmental fine-tuning in response to stressful early life environments. However, rather than proposing that individuals exhibit developmental changes in response to cues from their external environment, the iPAR model hypothesizes that these differences emerge in response to cues present *inside* the physical body, which develops hastily and can experience substantial cellular and structural damage in response to stress (Nettle et al., 2013; Rickard et al., 2014).

According to the iPAR model, because the conditions characterized by ELA cause lasting physical damage to the body, individuals growing up in these conditions should exhibit developmental adjustments to promote fitness in the context of reduced longevity. According to this perspective, developmental adjustments that are often observed in the context of ELA – such as accelerated pubertal timing and earlier reproduction – are reasoned to occur because they promote reproductive success in the context of physically

[1]Although IL-6 can also be anti-inflammatory

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damaged body rather than in response to a harsh external environment, *per se*.

### Innate-acquired immune tradeoff model

A third theoretical model that predicts a function for the exaggerated inflammatory activity observed among those who have experienced ELA is the innate-acquired immune tradeoff model (McDade et al., 2016). According to this perspective, environmental cues of severe resource constraint, energetic demand, and mortality risk – cues associated with ELA – promote a developmental tradeoff that favors investment in innate versus acquired immunity (McDade et al., 2016). The innate immune response involves widespread, non-targeted inflammation, provides a rapid response to novel pathogens, and comes at a relatively low developmental cost since it does not require a large energetic investment early in life. Because it relies upon common pathogen-associated molecular patterns, the innate immune response also provides immediate protection from pathogens that have never-before been encountered. In contrast, acquired immunity responds less well to novel infection, but is extremely effective against previously encountered pathogens. However, due to its specificity, the development of acquired immunity is expensive and inefficient when compared to the development of the innate immune system.

Given that the costs of developing acquired immunity are highest early in life, resource constraint and mortality risk during this sensitive period are predicted to promote greater investment in the development of innate immunity, which has relatively few up-front costs, over acquired immunity, which is costlier (McDade et al., 2016). Moreover, because the benefits of investing in acquired immunity are often not realized until later in life (one of the primary benefits of acquired immunity is the longevity-promoting benefits available from lower exposure to inflammatory activity), investment in acquired immunity is less pragmatic for those from ELA environments, because their greater risk of premature death makes it less likely that this costly investment will pay off. According to this perspective, elevated inflammatory activity occurring in the context of ELA reflects increased investment in innate immunity, which is characterized, in part, by elevated inflammatory activity.

### Is chronic inflammation a byproduct of developmental responses to stress?

According to the three models reviewed above, exaggerated inflammatory activity observed in the context of ELA serves an adaptive function. Whether increasing an individual's ability to mount a rapid immune response to challenge (biological embedding model) or being part of an immunological compensatory measure in response to somatic impairment (iPAR model) or a functional immunological tradeoff (innate-adaptive tradeoff model), each of the models reviewed thus far conceptualizes the inflammatory responses of those from adverse early life environments as being purposive and functional.[2]

Although logically sound and intuitively appealing, the extant literature finds little evidence supporting the hypothesized link between ELA, inflammation, and functional immune responses. Instead, children and adolescents with early life experiences of stress, maltreatment, and other adversities tend to have poorer physical health than those without ELA (Flaherty et al., 2006, 2009; Mechanic & Hansell, 1989; Poulton et al., 2002; Wickrama et al., 1997).

For example, research finds that stressful events occurring early in life are associated with greater incidence of eye infection, ear infection, bronchitis, laryngitis, and strep throat (Stepanikova et al., 2018), even after controlling for maternal health and lifestyle factors. Similar results have been found for susceptibility to community acquired pneumonia (Azab et al., 2014), influenza (Yousey-Hindes, & Hadler, 2011), and gastrointestinal tract infections (Adams et al., 2018). Additionally, children exposed to harsh early life conditions have higher rates of illness (Gottman & Katz, 1989) and are more likely to be hospitalized due to serious illness than children who experience fewer stressors (Cutuli et al., 2016). These results demonstrate that despite exhibiting an aggressive inflammatory response, children exposed to ELA are actually *more* – not *less* – susceptible to infection and severe illness than those without such exposures.

In addition to being less resilient to acute illness, children living in adverse environments are also at an increased risk of developing chronic and autoimmune disorders than children living in more benign environments (Carlsson et al., 2014), suggesting immunological dysregulation in these populations. For example, research finds that each additional adverse childhood experience is associated with a 21% increased risk of having a chronic medical condition by age 5 (Kerker et al., 2015) as well as an elevated risk of developing autoimmune diseases such as diabetes (Faresjo, 2015).

Together, results such as these indicate that those who have experienced ELA – in addition to being at a heightened risk for developing chronic disease later in life – are also more likely to become acutely and chronically ill during childhood, adolescence, and throughout their lifetimes. This suggests that the differences in the magnitude of the inflammatory response exhibited by those who have experienced ELA – in addition to being detrimental to their long-term health – may not be associated with any benefits in the ability to manage acute health threats in the short-term. Instead, exaggerated inflammatory activity observed among those from ELA environments may emerge as an incidental, but longevity-harming byproduct of other developmental modifications that occur in the context of environmental adversity.

One possibility is that exaggerated inflammatory activity may emerge as a byproduct of hyperactivation of the HPA axis in response to chronic stress (Elwenspoek et al., 2017). The HPA axis is key pathway by which the body responds to stress, initiating release of the stress hormone cortisol. Cortisol, in addition to modulating bodily resource use in response to stress, also plays an important role in regulating inflammatory activity (Yeager et al., 2010). A large and growing body of research finds links between exposure to ELA and modifications to the activities of the HPA axis, including cellular insensitivity to the anti-inflammatory effects of cortisol (Kircanski et al., 2019; Janusek et al., 2017; Shakiba et al., 2019; Timothy et al., 2019; Trickett et al., 2010). In one study, for example, researchers collected blood samples and measures of psychological stress from adolescent girls four times over the course of 18 months (Miller & Chen, 2010). At each timepoint, the researchers measured basal inflammatory activity and stimulated participants' leukocytes with an inflammation-inducing immunostimulant, lipopolysaccharide (LPS), to assess inflammation following stimulation. Next, they introduced inflammation-inhibiting hydrocortisone to measure participants' sensitivity to anti-inflammatory signals. Results

[2]Note that, at first blush, it may appear that exaggerated inflammatory activity is incidental to nonspecific immunity and therefore does not serve a function, *per se*. However, because inflammatory activity is an inseparable feature of the nonspecific immune response, it is a functional feature of a bias toward nonspecific immune responses, making it an integral part of the adaptation.

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revealed that those who had experienced ELA exhibited an exaggerated inflammatory response to LPS compared to what was observed among those from more benign family environments. Moreover, they found that these effects were driven by cellular insensitivity to the anti-inflammatory effects of hydrocortisone, an effect which became more pronounced over time.

## The current research

In the current research, we sought to examine the links between exposure to ELA, inflammation, and immune function. If – as hypothesized by function-based models – chronic inflammation is favored among those who have experienced ELA because it promotes immunological vigilance, we should expect to find (a) elevated inflammatory activity among those who have experienced ELA and that (b) levels of inflammatory activity predict the magnitude of co-occurring immunological responses in all people, regardless of stress exposures. This expectation is grounded in much work indicating a positive relationship between levels of inflammation and immune function (Dinarello, 2000; Kato & Kitagawa, 2006; Medzhitov, 2008). However, if exaggerated inflammatory activity observed in the context of ELA is a symptom of immunological dysregulation occurring as a byproduct of other stress-based developmental changes, we should expect to find (a) elevated inflammatory activity among those who have experienced ELA, but that (b) the association between inflammatory activity and the magnitude of the immune response is moderated by exposure to ELA, such that greater inflammatory activity predicts the magnitude of the immunological responses of those with low- but not high- exposure to ELA.

We measured ELA by examining exposure to two conceptually distinct components of ELA: childhood harshness and childhood unpredictability. These two dimensions were chosen because research indicates that early life exposure to each of these environmental factors uniquely and additively contribute to variation in developmental outcomes (Belsky et al., 2012; Ellis et al., 2009). Harshness refers to the rates at which extrinsic factors cause disability and death at each age in a population, which – in Western societies – is strongly linked to SES (e.g., Adler et al., 1994; Chen et al., 2002). Exposure to harshness in childhood was therefore measured using participants' reported childhood SES (Griskevicius et al., 2011). Unpredictability refers to stochastic changes in ecological context, geography, economic conditions, family composition, or parental behavior, which make it difficult to forecast future environments based on past environments and experiences. Participants' reported exposure to unpredictability was measured using a well-validated scale to assess this dimension (Mittal et al., 2015). Although we did not have an *a priori* prediction about the relative contributions of each harshness and unpredictability to measured inflammatory activity and immune function, the links between childhood SES, inflammation, and immune function have been relatively well-established (Azad et al., 2012; Cohen et al., 2004; Dowd & Aiello, 2009; Gassen et al., 2021; John-Henderson et al., 2016; Liu et al., 2017; Lockwood et al., 2018; Milaniak & Jaffee, 2019; Miller & Chen, 2007), whereas the links with unpredictability have not been as well-tested. Including both measures will allow us to assess the unique contributions of each to the associations between inflammation and immune function.

We conducted two types of immunological assays to assess participants' immune function. Importantly, we chose assays that are specifically designed to assess facets of innate immune function, as this is the arm of the immune system that is most intimately tied to inflammation and is hypothesized to be functionally modified in each of the three function-based hypotheses.

Our first assay was a peripheral blood mononuclear cell (PBMC) proliferation assay in which we tested PBMC (the fraction of leukocytes that contain infection fighting lymphocytes and monocytes) proliferation in response to the immunological stimulant LPS. LPS is a pathogen-associated molecular pattern (PAMP) found in the cell wall of gram-negative bacteria, such as *E. coli* (Fenton & Golenbock, 1998; Guha & Mackman, 2001; Lu et al., 2019; Wright et al., 1990). LPS and other PAMPs are detected by innate immune cells that express pattern recognition receptors, including monocytes, macrophages, and dendritic cells (Kawai & Akira, 2010; Takeuchi & Akira, 2010). LPS is recognized via toll-like receptor 4 (Chow et al., 1999), inducing the release of proinflammatory cytokines that, in turn, coordinate a number of key cellular processes that function to fight infection and clear damaged cells (Lu et al., 2019; Pålsson-McDermott & O'Neill, 2004; Takeuchi & Akira, 2010). Among the most critical immune processes initiated by LPS-induced inflammation is leukocyte proliferation (Langstein et al., 2000; Sweet & Hume, 1996; Tough et al., 1997; Ulmer et al., 2000), or an increase in the rate of leukocyte growth and division which yields greater numbers of circulating immune cells. Proliferation represents a critical aspect of the early innate cellular immune response to pathogens (Iwasaki & Medzhitov, 2010; Kumar et al., 2011).

The second measure of innate immune function used in the current research is a phagocytosis assay, which measures phagocytosis of *E. coli* bioparticles. In addition to enhancing immune cell proliferation, LPS-induced inflammation also leads to the activation of innate immune phagocytes, like macrophages and neutrophils, that engulf and destroy microbes, as well as infected and damaged host cells (Dale et al., 2008; Kantari et al., 2008). This process, referred to as phagocytosis, is a core component of the innate immune response to infection (Flannagan et al., 2012). Phagocytosis of pathogens is guided by the process of opsonization whereby foreign or damaged particles are tagged by antibodies and complement proteins to trigger ingestion by phagocytes (Chan et al., 2001; Dale et al., 2008; Flannagan et al., 2012; Kantari et al., 2008; Krishnamurthy et al., 2006). The assay used in the current research involved incubating *E. coli* bioparticles with an opsonization buffer. Opsonizing these particles allows for a direct test of the innate immune process of phagocytosis in isolation of the other innate (i.e., complement system) and adaptive (i.e., antibodies) immune mechanisms typically involved in opsonization during natural infection (Chan et al., 2001; Krishnamurthy et al., 2006).

We predicted that, as is expected for healthy adults, inflammation would be positively related to PBMC proliferation and phagocytic capabilities for those reporting lower exposure to ELA. In contrast, we predicted that for those reporting higher exposure to ELA, elevated inflammation would not be associated with greater PBMC proliferation and phagocytic capabilities. If supported, these predictions would challenge the notion that excess inflammation in the context of ELA functions to promote a swift and robust immunological response to the types of elevated illness and infection threats present in adverse environments. Instead, it suggests that the elevated inflammatory activity often observed in those exposed to ELA may serve an alternative, heretofore unidentified function or occur as a non-functional byproduct of growing up under the developmental constraints and physiological modifications imposed by harsh and unpredictable environments. Additionally, we explored how different facets of ELA predict

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**Table 1.** Descriptive statistics for participant demographics and immunological measures ($N = 159$)

| Variable | *M* (*SD*) |
|---|---|
| Sex: men = 80; women = 79 | |
| Race | |
| White: 66.67% ($n = 106$) | |
| Black: 4.40% ($n = 7$) | |
| Hispanic: 15.09% ($n = 24$) | |
| Asian: 6.29% ($n = 10$) | |
| Multiracial/other: 7.55% ($n = 12$) | |
| Age (17–30) | 20.17 (2.74) |
| Childhood SES | 4.55 (1.48) |
| Childhood unpredictability | 2.37 (1.23) |
| BMI (17.8–29.8) | 23.40 (2.97) |
| Hours of weekly exercise | 4.69 (2.89) |
| Hours of nightly sleep | 6.84 (1.31) |
| Day length | .48 (.04) |
| Recent illness | 2.68 (1.46) |
| Phagocytosis of *E. coli* bioparticles (%) | 12.59 (5.89) |
| Unstimulated proliferation | .67 (.17) |
| Proliferation in response to LPS | 1.01 (.22) |
| Unstimulated release of IL-1β | 52.62 (207.37) |
| Unstimulated release of IL-6 | 307.01 (1031.63) |
| Unstimulated release of TNF-α | 135.15 (200.14) |
| LPS-stimulated release of IL-1β | 1417.09 (1288.25) |
| LPS-stimulated release of IL-6 | 4972.26 (2283.22) |
| LPS-stimulated release of TNF-α | 1931.45 (1136.58) |

relationships between inflammation and the magnitude of immunological responses to challenge to better understand the unique contributions of each childhood harshness and unpredictability on functioning of the innate immune system in adulthood.

## Methods

### Participants

Participants were recruited from the undergraduate participant pool of a university in the southern United States and from the surrounding community (see Table 1 for sample demographics). Participants completed a prescreen questionnaire to ensure they were: (1) free from chronic medical problems or mental illness, (2) of healthy weight (i.e., BMI < 30), (3) free from acute illness for at least two weeks prior to participation, (4) willing to abstain from steroidal and non-steroidal anti-inflammatory medications, exercise, and alcohol use for at least two days before participating, and (5) willing fast the morning of the session. Women were required to not be using hormonal contraceptives and participated 4–7 days after the start of their most recent menstrual cycle (i.e., early follicular phase). The final data analytic sample consisted of 159 participants (women = 79; $M_{age} = 20.17$, $SD = 2.75$). Participants from the undergraduate participant pool were compensated with nominal course credit, and community participants were compensated with $50 for their participation. All participants provided informed consent prior to participation, and the study was approved as compliant with ethical standards by the university Institutional Review Board (Approval #: 1411-117-1606).

### Procedure

After completing a demographic survey to determine study eligibility, participants came into the lab at 7:30 AM in small groups of 2–6. Upon arrival, participants were screened for adherence to study preparation requirements (e.g., fasting, anti-inflammatory medication use), then completed consent documents. Following this, participants completed a variety of behavioral tasks and questionnaires as part of a larger study (see Gassen et al., 2019). Participants then provided a 30 mL saliva sample and an 85 mL blood sample before being debriefed and dismissed. Blood was collected by venipuncture into heparinized (or EDTA-containing) Vacutainer® tubes (Becton-Dickinson, Franklin Lakes, NJ).

PBMCs were immediately isolated from whole blood using density gradient centrifugation in Ficoll® Paque Plus (Sigma-Aldrich, St. Louis, MO [GE Healthcare Life Sciences]) and then were used for various immunological assays, including those used to test the current hypothesis. The assays conducted for the current investigation included: proliferation of PBMCs in response to, and in the absence of, stimulation by LPS, measured at 24 hr post-plating; phagocytosis of opsonized *Escherichia coli* (*E. coli*) bioparticles measured at 2 hr post-plating; and PBMC release of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in response to, and in the absence of, LPS at 2 and 24 hr post-plating. For each assay, PBMCs were brought to the plating density appropriate for the respective assay in RPMI-1640 supplemented with 10% heat-inactivated fetal bovine serum (FBS), 2 mm L-glutamine, 1 mm sodium pyruvate, 100 U of penicillin/mL, 100 μg of streptomycin/mL, and 0.25 μg of amphotericin B/mL (Caisson Labs, Logan, UT). Additional information about each assay follows below.

### Materials

**Exposure to Harshness.** Participants' exposure to early-life environmental harshness was assessed using a previously validated three-item measure of childhood SES (reported in Griskevicius et al., 2011; see also Hill et al., 2016). This scale was chosen to capture the extent to which participants experienced subjective resource constraint during their childhood before age 12 (e.g., "My family usually had enough money for things when I was growing up."). All questions were measured on 7-point Likert scales (1: *Strongly disagree*, 7: *Strongly agree*). Items yielded acceptable reliability ($\alpha = .81$) and were used to create a mean composite. Higher scores indicate higher SES during childhood ($M = 4.55$, $SD = 1.48$).

**Exposure to Unpredictability.** Participants' childhood unpredictability was assessed using a previously validated three-item scale (Mittal et al., 2015). This scale was chosen to capture the extent to which participants experienced subjective chaos and uncertainty in their childhood environment before age 12 (e.g., "I had a hard time knowing what my parent(s) or other people in my house were going to say or do from day-to-day."). All questions were measured on 7-point Likert scales (1: *Strongly disagree*, 7: *Strongly agree*). Items yielded acceptable reliability ($\alpha = .81$) and were used to create a mean composite. Higher scores indicate greater unpredictability during childhood ($M = 2.37$, $SD = 1.23$).

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**Proinflammatory cytokine release assay.** PBMC release of proinflammatory cytokines was measured *in vitro* both in response to LPS stimulation, as well as in the absence of stimulation. After isolation, PBMCs were plated in triplicate at a density of $2.5 \times 10^5$ cells/well, in a 200 µL final volume. PBMCs were plated both in media only (unstimulated condition), as well as with 1µg/mL of LPS, obtained from *E. coli* (serotype 026:B6, Sigma-Aldrich, St. Louis, MO) and 50µg/mL of poly I:C (high molecular weight; InvivoGen, San Diego, CA), and were incubated at 37°C, 5% $CO_2$, and 100% humidity. Cell culture supernatants were collected at 2 and 24 hr post-plating and then stored at −80°C until assays were conducted. The 24 h measures were taken to examine cytokine release in response to LPS at the same time as PBMC proliferation (also examined at 24 h post-plating). The 2 h measures were taken to examine cytokine release to LPS (which is derived from the cell wall of *E. coli*) at the same time as the phagocytosis assay (also examined at 2 h post-plating).

Cell culture supernatants were later thawed and assayed in duplicate for levels of a trio of proinflammatory cytokines: IL-1β, IL-6, and TNF-α. Cytokines were assayed using a MILLIPLEX® MAP Human Cytokine Panel magnetic bead kit (EMD Millipore Corporation, Billerica, MA), and read using a Luminex MAGPIX® fluorescent detection system (Luminex, Austin, TX) and xPONENT® software (Version 4.2; build: 1324; Luminex, Austin, TX). Intra-assay coefficients of variation (CVs) were 8.20% (IL-6), 6.97% (IL-1β), and 5.98% (TNF-α). Inter-assay CVs were 17.27% (IL-6), 10.53% (IL-1β), and 11.62% (TNF-α). Due to a freezer failure, cell culture supernatant samples were compromised for 32 participants (see Gassen et al., 2019 for additional information). No compromised samples were assayed, and data from these samples were not included in any analysis.

**PBMC proliferation assay.** PBMCs were isolated as described above, and plated into Falcon® 96-well tissue culture plates (Corning, Corning, NY). PBMCs were plated in triplicate at a final density of $2.5 \times 10^5$ cells/well in a 200 µL final volume for two conditions: (1) with media only (i.e., unstimulated proliferation) and (2) with 1 µg/mL of LPS obtained from *E. coli* (serotype 026:B6, Sigma-Aldrich, St. Louis, MO). Plates were incubated at 37°C, 5% $CO_2$, and 100% humidity. Approximate cell density was measured at 24 hr post-plating using the CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay (Promega, Madison, WI). Each plate was read on a plate reader (BMG LabTech FLUOstar™ Omega, Cary, NC) at 490 nm.

**Phagocytosis assay.** Phagocytosis was measured using fluorescent pHrodo™ labeled Green *E. coli* BioParticles™ (ThermoFisher Scientific, Waltham, MA) opsonized using 1 mg/mL of manufacturer-provided opsonization buffer. PBMCs were plated in triplicate into BrandTech® black, flat-bottom microplates (BrandTech Scientific, Essex, CT) at a density of $5 \times 10^5$ cells/well in a 200 µL final volume. Negative controls (bioparticles plated with media only in 200 µL volume) and positive controls (bioparticles plated with pH 4.5 Intracellular Calibration Buffer [ThermoFisher Scientific, Waltham, MA]) were also plated in triplicate. Plates were incubated for 2 hr at 37°C, 5% $CO_2$, and 100% humidity before being read on a fluorescence plate reader (BMG LabTech FLUOstar™ Omega, Cary, NC) at FITC dye settings of 490 nm excitation/520 nm emission. Percent maximal fluorescence was computed by dividing experimental fluorescence by maximal fluorescence (i.e., positive control), after subtracting fluorescence in the negative controls from both, and multiplying by 100.

**Covariates.** Several variables that may influence relationships between early life conditions and immune function were measured. These variables included race, age, sex, exercise, BMI, day length, sleep, and recent illness. After specifying the hypothesized statistical models, all covariates were included in each target statistical model. Significant covariates were retained and their effects reported.

**Self-Reported Health Measures.** To better understand relationships between ELA and participants' current health beyond what could be assessed from our immunological measures, we also investigated correlational relationships between childhood SES, childhood unpredictability, and self-reported health measures collected as part of a larger study. First, participants responded to a single-item measure of general health, "In general, my health is _____.", using a 7-point Likert-type scale (endpoints: 1 = *Very Poor*, 7 = *Very Good*). Next, participants completed a nine-item scale measuring their health over the last year. Participants were asked to indicate how often they had experienced outcomes associated with being in poor health using a 7-point Likert-type scale (endpoints: 1 = *Never*, 7 = *Very Frequently*). Example items include, "Over the last year, how frequently have you experienced recurrent health problems" and "Over the last year, how frequently have you missed class/work because you weren't feeling well". A mean composite was formed from these nine items to assess participants' health this year ($\alpha = .90$). Additionally, participants responded to the question, "When was the last time you had a cold, flu, or other illness?", on a 7-point Likert-type scale (endpoints: 1 = Today, 4 = A couple of weeks ago, 7 = A year or more) to indicate how long it had been since the last time they experienced any type of illness (When Last Sick). Finally, participants also completed a five-item measure of their family health. Items from this scale included, "Most people in my family live long and healthy lives" and "People in my family are generally healthy". Questions were answered using 7-point Likert-type scales (endpoints: 1 = *Strongly Disagree*, 7 = *Strongly Agree*) and they were used to form a mean composite of participants' family health ($\alpha = .88$).

### *Data analytic strategy*

First, because all cytokine levels were positively skewed, these values were log transformed, per convention (Genser et al., 2007; Kline, 2016), which corrected the distribution to approximate normality. Prior to log-transformation, there were 24 cytokine values greater than 3 SDs above the mean of a given cytokine at a given time point. Of these outliers, five were greater than 5 SDs above the mean. However, these outliers were nearly all eliminated after log transformation; only one unstimulated IL-1β value at 3.04 SDs, one stimulated IL-1β value at 3.56 SDs, and one stimulated IL-6 value at 3.43 SDs above the mean remained. Once cytokine levels were made into latent factors of inflammation, there were no outliers on any of the latent inflammation variables. See Table 1 for raw cytokine values averaged across 2 and 24 h post-plating.

All models were estimated using MPlus statistical software (MPlus Version 7.4; Muthén & Muthén, 2012) and our data analytic plan was as follows. We first conducted confirmatory factor analyses (CFA) to verify the use of a latent factor of inflammation, comprised of IL-1β, IL-6, and TNF-α levels, both in the presence- and absence- of stimulation with LPS (at 2 and 24 hr post-plating). Next, we utilized linear regression models to examine the links between each childhood SES and childhood unpredictability on inflammation measured each in the presence and absence of

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immunological stimulation. This allowed us to examine whether these dimensions of ELA are related to elevated inflammatory activity.

After these initial models, we used a series of statistical models to test our target research hypotheses. All significance tests were two-tailed and models were tested iteratively. First, we planned to examine the interaction between unstimulated inflammation and each (a) childhood SES and (b) childhood unpredictability on unstimulated PBMC proliferation. Second, we examined the interaction between LPS-stimulated inflammation and each (a) childhood SES and (b) childhood unpredictability on LPS-stimulated proliferation. Lastly, we examined the interaction between LPS-stimulated inflammation and each (a) childhood SES and (b) childhood unpredictability on phagocytosis. For each model, the outcome variable (proliferation or phagocytosis) was regressed on the inflammation latent factor, childhood SES, childhood unpredictability, the interaction between inflammation and childhood SES, and the interaction between inflammation and childhood unpredictability.

Any significant interactions were probed by examining the relationship between inflammation and the relevant outcome variable at low (1 *SD* below the mean) and high (1 *SD* above the mean) levels of ELA (i.e., SES or unpredictability), as well as examining the relationship between ELA and the relevant outcome variable at low (1 *SD* below the mean) and high (1 *SD* above the mean) levels of inflammation. To improve model fit and preserve power, all non-significant paths (i.e., $p > .05$) were dropped before testing each model for significant effects of covariates. Additionally, we conducted a *post hoc* power simulation using the Shiny app pwrSEM (Wang & Rhemtulla, 2021). Setting the alpha level at 0.05 and the sample size at 120 (to account for missing data), results of 1000 simulations revealed an estimated power of 0.73 to detect the smallest significant interaction effect found in the current study (phagocytosis). Other interaction effects all surpassed 0.85 power in the analysis.

Complex multilevel modeling (see Muthén & Muthén, 1998–2012 for technical description) was used to analyze the cytokine release and proliferation data. The effects of unstimulated and LPS-stimulated inflammation on unstimulated and stimulated proliferation, respectively, were tested simultaneously in a multivariate model. In this model, the covariance structure of the latent inflammation variables were estimated to account for the fact that these two conditions were nested within participants. The phagocytosis scores did not contain nested structures and therefore were analyzed in a single-level regression model. Finally, we also investigated correlational relationships between childhood SES, childhood unpredictability, and self-reported health as a means of providing additional context to our analysis of the links between exaggerated inflammatory activity and health outcomes.

## Results

### CFA: latent variables of inflammation

Latent variables of inflammation (unstimulated and LPS-stimulated) were estimated using CFA. All unstimulated and LPS-stimulated inflammatory factors loaded well onto the latent variables of unstimulated inflammation and LPS inflammation, respectively (see Table 2 for final statistics). Thus, all subsequent analyses utilized the latent variables of inflammation composed of levels of each IL-6, IL-1β, and TNF-α.

**Table 2.** Summary of inflammation CFA factor loadings

| Factor | | B | β | SE | t |
|---|---|---|---|---|---|
| 24 h unstimulated inflammation | IL-6 | 1.15 | .98*** | .01 | 93.24 |
| | IL-1β | 1.00 | .93*** | .02 | 53.09 |
| | TNF-α | .71 | .93*** | .02 | 59.58 |
| 24 h LPS-stimulated inflammation | IL-6 | 1.79 | .77*** | .04 | 18.90 |
| | IL-1β | 1.00 | .72*** | .05 | 15.97 |
| | TNF-α | 1.35 | 1.00 | .00 | 999.00 |
| 2 h unstimulated inflammation | IL-6 | 1.73 | 1.01*** | .10 | 9.79 |
| | IL-1β | 1.00 | .61*** | .17 | 3.65 |
| | TNF-α | 1.47 | .84*** | .10 | 8.83 |
| 2 h LPS-stimulated inflammation | IL-6 | 1.82 | .91*** | .10 | 8.93 |
| | IL-1β | 1.00 | .40*** | .09 | 4.33 |
| | TNF-α | 1.35 | .70*** | .10 | 7.41 |

*Note.* ***$p \leq .001$.

### Linear regressions: does ELA predict inflammation?

The results of the linear regressions revealed that childhood SES was negatively related to unstimulated inflammation 2 h post-plating, $b = -.21$ ($SE = .10$), $t = 2.09$, $p = .036$, such that lower childhood SES predicted higher unstimulated inflammation after 2 h. There was a marginally significant relationship between childhood SES and unstimulated inflammation at 24 h post-plating, $b = -.17$ ($SE = .10$), $t = 1.79$, $p = .074$, with lower childhood SES predicting higher unstimulated inflammation after 24 h. The relationship between childhood SES and LPS-stimulated inflammation was not significant at 2 ($p = .384$), or 24 h post-plating ($p = .989$).

Childhood unpredictability was negatively related to unstimulated inflammation 2 h post-plating, $b = -.22$ ($SE = .10$), $t = 2.22$, $p = .026$, such that greater childhood unpredictability was associated with lower unstimulated inflammation after 2 h. The relationship between childhood unpredictability and unstimulated inflammation at 24 h post-plating was not significant ($p = .109$). The relationship between childhood unpredictability and LPS-stimulated inflammation was also not significant at 2 ($p = .965$), or 24 h post-plating ($p = .680$).

### Structural equation models: does ELA predict the relationships between inflammation and the magnitude of immunological responses to challenge?

Results of the main statistical model revealed that higher childhood SES was associated with greater spontaneous proliferation; however, this result was marginally significant, $b = .03$ ($SE = .01$), $t = 1.76$, $p = .078$. The interaction between childhood SES and unstimulated inflammation on unstimulated proliferation was significant (unpacked below), $b = .05$ ($SE = .02$), $t = 2.41$, $p = .016$, however. There was also a significant main effect of childhood SES on LPS-stimulated leukocyte proliferation, $b = .03$ ($SE = .01$), $t = 2.45$, $p = .014$, such that higher childhood SES was associated with greater proliferation in response to LPS stimulation. Additionally, there was a significant interaction between childhood SES and LPS-stimulated inflammation on LPS-stimulated proliferation, $b = .16$ ($SE = .07$), $t = 2.22$, $p = .027$. There was not a significant main effect of childhood SES on phagocytosis ($p = .241$), however, the interaction between childhood SES and LPS-stimulated inflammation was significant, $b = 10.01$ ($SE = 4.30$), $t = 2.33$, $p = .020$.

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**Table 3.** Summary of main effects and interaction effects of childhood socioeconomic status and inflammation on immune responses

| | Primary model | | Covariates model | |
|---|---|---|---|---|
| | Estimate (SE) | t | Estimate (SE) | t |
| *24 hr unstimulated proliferation* | | | | |
| Childhood SES | .02 (.01) | 1.36 | .01 (.01) | .58 |
| Unstimulated inflammation | .08 (.02)*** | 3.74 | .06 (.02)*** | 3.24 |
| Childhood SES × inflammation | .05 (.02)* | 2.20 | .03 (.02) | 1.73 |
| *24 hr LPS-stimulated proliferation* | | | | |
| Childhood SES | .03 (.01)* | 2.31 | .03 (.01)* | 2.36 |
| LPS-stimulated inflammation | .00 (.08) | .04 | .06 (.08) | .74 |
| Childhood SES × inflammation | .15 (.07)* | 2.16 | .14 (.06)* | 2.19 |
| *2 hr LPS-stimulated phagocytosis* | | | | |
| Childhood SES | .71 (.57) | 1.24 | – | |
| LPS-stimulated inflammation | 11.94 (5.67)* | 2.11 | – | |
| Childhood SES × inflammation | 8.38 (3.51)* | 2.39 | – | |

*Note.* $^{*}p < .05$. $^{***}p \leq .001$.

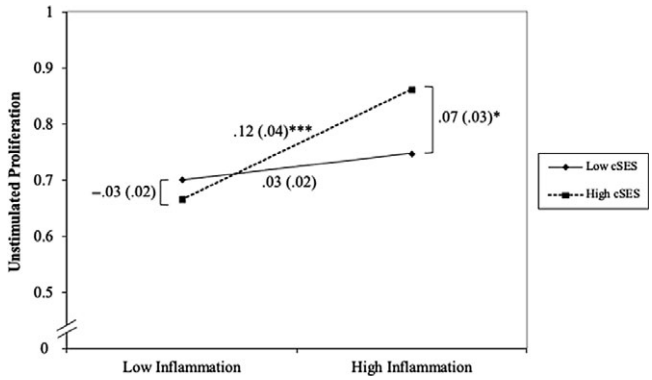


**Figure 1.** Interaction between unstimulated inflammation and childhood socioeconomic status (SES) on unstimulated PBMC proliferation. High and low inflammation and SES refer to one standard deviation above and below the mean of these variables, respectively. *Note*. $^{*}p < .05$. $^{***}p \leq .001$.

Conversely, results revealed that there were no significant main effects of childhood unpredictability on either measure of leukocyte proliferation or the phagocytosis measure ($ps \geq .214$), nor were there any significant interactions between inflammation and childhood unpredictability on either measure of leukocyte proliferation or the phagocytosis measure ($ps \geq .124$).

The results of our initial model demonstrate that childhood SES, but not childhood unpredictability, has an impact on the relationship between inflammatory activity and the magnitude of the immunological response on each of our three measures. To probe more deeply into these relationships, we dropped childhood unpredictability from the model and conducted a series of follow-up models to examine the links between childhood SES, inflammation, and immunological response on each of our three functional immunological assays.

***Unstimulated PBMC Proliferation.*** To examine relationships between childhood SES, unstimulated inflammation, and spontaneous (i.e., unstimulated) proliferation, we again tested for an interaction between childhood SES and unstimulated inflammation on unstimulated PBMC proliferation (Figure 1, Table 3). Consistent with inflammation's instrumental role in PBMC proliferation, results revealed that unstimulated inflammation was a significant positive predictor of proliferation, such that those with higher levels of unstimulated inflammation had higher levels of unstimulated proliferation. Childhood SES did not predict unstimulated proliferation, however, these effects were qualified by a significant interaction between unstimulated inflammation and childhood SES on unstimulated proliferation (see Table 3 for statistics, Figure 1 for interaction effect).

Probing the interaction (Figure 1) between childhood SES and unstimulated inflammation on proliferation revealed that, for those with high childhood SES, higher levels of unstimulated inflammation predicted higher levels of proliferation, $b = .12$ ($SE = .04$), $t = 3.50$, $p \leq .001$, while there was no relationship between levels of unstimulated inflammation and unstimulated proliferation for those with low childhood SES, $b = .03$ ($SE = .02$) $t = 1.39$, $p = .164$. Probing the interaction the other way revealed that, for those with high levels of inflammation, higher childhood SES predicted greater unstimulated PBMC proliferation, $b = .07$ ($SE = .03$), $t = 2.19$, $p = .028$, while there was no relationship between childhood SES and unstimulated proliferation for those with low levels of inflammation, $b = -.03$ ($SE = .02$), $t = 1.31$, $p = .190$. Next, we investigated the impact of potential covariates on these relationships. Although the pattern of results remained the same, controlling for significant covariates of unstimulated proliferation (i.e., day length, exercise), lead to an only marginally significant interaction between childhood SES and unstimulated inflammation on unstimulated proliferation, (see Table 3).

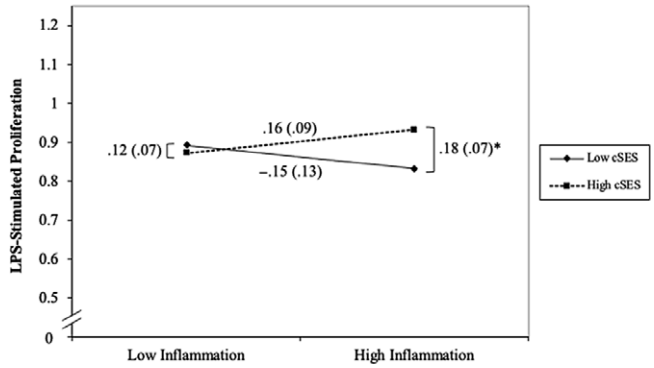


**Figure 2.** Interaction between LPS-stimulated inflammation and childhood socioeconomic status (SES) on LPS-stimulated PBMC proliferation. High and low inflammation and SES refer to one standard deviation above and below the mean of these variables, respectively. *Note*. $^{*}p < .05$.

***LPS-Stimulated PBMC Proliferation.*** Next, we examined the relationship between LPS-stimulated inflammation and childhood SES on LPS-stimulated proliferation (Figure 2, Table 3). Unstimulated inflammation (24 h) was also included in the model to control for non-LPS-specific related inflammatory activity. Results revealed a significant relationship between childhood SES and LPS-stimulated proliferation, such that higher childhood SES predicted increased proliferation. There was no main effect of LPS-stimulated inflammation on proliferation, however, these effects were qualified by a significant interaction between LPS-stimulated inflammation and childhood SES on proliferation, (see Table 3 for statistics, Figure 2 for interaction effect).

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Unpacking the interaction (Figure 2) between childhood SES and LPS-stimulated inflammation on proliferation revealed a marginally significant, positive relationship between LPS-stimulated inflammation and proliferation for those with high childhood SES, $b = .16$ ($SE = .09$), $t = 1.80$, $p = .073$, while there was no relationship between LPS-stimulated inflammation and proliferation for those with low childhood SES, $b = -.15$ ($SE = .13$), $t = 1.19$, $p = .235$. Additionally, at high levels of inflammation, higher childhood SES predicted greater unstimulated PBMC proliferation, $b = .18$ ($SE = .07$), $t = 2.49$, $p = .013$, while the relationship between childhood SES predicted and proliferation was marginally significant at low levels of inflammation, $b = -.12$ ($SE = .07$), $t = 1.75$, $p = .081$.

The pattern and significance of these results remained largely unchanged when controlling for significant covariates (i.e., day length, exercise; see Table 3). The relationship between LPS-stimulated inflammation and proliferation remained marginally significant for those with high childhood SES, when controlling for day length and exercise, $b = .15$ ($SE = .09$), $t = 1.79$, $p = .073$, and was not significant at low childhood SES, $b = -.15$ ($SE = .13$), $t = 1.19$, $p = .235$. Additionally, when including these covariates, the relationship between childhood SES and proliferation remained significant for those with high levels of inflammation, $b = .19$ ($SE = .08$), $t = 2.33$, $p = .020$, while there remained no relationship between childhood SES and proliferation for low with low levels of LPS-stimulated inflammation, $b = -.08$ ($SE = .11$), $t = .73$, $p = .466$.

***Phagocytosis.*** Next, we examined relationships between childhood SES and LPS-stimulated inflammation (measured 2 hr post-plating) on percent of phagocytosis of *E. coli* bioparticles. Unstimulated inflammation (2 h) was also included in the model to control for non-LPS-specific related inflammatory activity. Results revealed a significant main effect of latent LPS-stimulated inflammation on phagocytosis, such that greater LPS-stimulated inflammation predicted a higher percentage of phagocytosis of *E. coli* bioparticles. There was no main effect of unstimulated inflammation or childhood SES on phagocytosis. These effects were qualified by a significant two-way interaction between childhood SES and LPS-stimulated inflammation, while controlling for unstimulated inflammation, on phagocytosis, $b = 8.38$ (see Table 3 for statistics, Figure 3 for interaction effect).

Probing the interaction (Figure 3) between childhood SES and LPS-stimulated inflammation on phagocytosis revealed a significant, positive relationship between LPS-stimulated inflammation and phagocytosis for those with high childhood SES, $b = 20.32$ ($SE = 8.21$), $t = 2.48$, $p = .013$, and no relationship between LPS-stimulated inflammation and phagocytosis for those with low childhood SES, $b = 3.56$ ($SE = 4.65$), $t = .77$, $p = .443$. For those with high levels of inflammation, higher childhood SES predicted greater phagocytosis, $b = 9.05$ ($SE = 3.61$), $t = 2.51$, $p = .012$, while there were no differences between those with high and low levels of childhood SES for those with low levels of inflammation, $b = -7.65$ ($SE = .57$), $t = 1.24$, $p = .172$. There were no significant covariates predicting phagocytosis, thus no further models were tested.

### *Exploratory correlational results: does ELA relate to self-reported health?*

Finally, we investigated the relationship between ELA and participants' self-reports of health (see Table 4 for statistics). Results revealed that childhood SES was positively related to self-reports of general health and family health, and negatively related to the length of time that had passed since they were last sick. Childhood SES was not related to health this year. Childhood unpredictability was negatively related to childhood SES and general health. Childhood unpredictability was not related to health this year, the length of time that had passed since they were last sick, or family health. Results are consistent with past research (e.g., Gottman & Katz, 1989; Poulton et al., 2002) demonstrating that ELA is associated with worse, not better, acute health outcomes.

**Table 4.** Correlations between early life adversity and self-reported health measures

| | Childhood unpredictability | General health | Health this year | When last sick | Family health |
|---|---|---|---|---|---|
| Childhood SES | −.309** | .209** | .074 | −.198* | .338** |
| Childhood unpredictability | | −.293** | .085 | .034 | .125 |
| General health | | | −.430* | .069 | .403** |
| Health this year | | | | −.207** | −.164* |
| When last sick | | | | | −.107 |

*Note.* *$p < .05$. **$p < .01$.

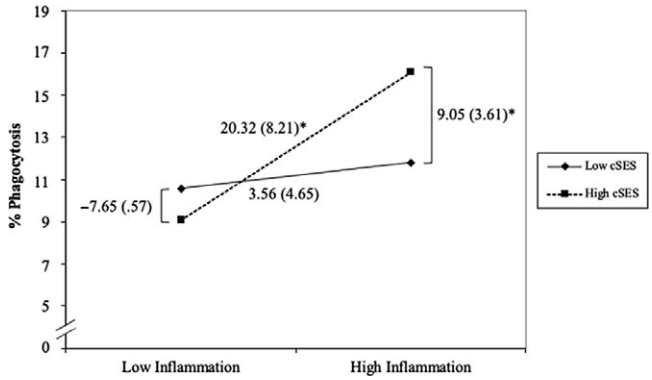


**Figure 3.** Interaction between LPS-stimulated inflammation and childhood socioeconomic status (SES) on % phagocytosis of *E. coli* bioparticles. High and low inflammation and SES refer to one standard deviation above and below the mean of these variables, respectively. *Note*. *$p < .05$.

## Summary of results

Consistent with past research, we found evidence that low childhood SES was linked to higher levels of basal inflammatory activity. Specifically, we found that low childhood SES was associated with higher levels of unstimulated inflammation at both 2- and 24-h post-plating (although the 24 h measure was only marginally significant). This result is consistent with previous research which finds that adults exposed to ELA exhibit higher levels of basal inflammation than people with fewer adverse experiences in childhood (Baumeister et al., 2015; Coelho et al., 2013). Although previous research finds that ELA exposure is associated with exaggerated inflammatory responses to immunological stimulants like LPS (Azad et al., 2012; Schreier et al., 2014), we did not find this relationship in our sample. We speculate that this is likely a result

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of the already-exaggerated levels of inflammatory activity occurring in these participants' PBMCs prior to plating with LPS.

Additionally, we found that high childhood unpredictability – rather than being linked with elevated inflammatory activity – was associated with lower levels of unstimulated inflammation at 2 h post-plating and was unrelated to inflammatory measures taken at any other timepoint. Although this result is inconsistent with previous research finding that greater exposure to chaotic childhood environments is associated with elevated basal inflammation (Crosswell et al., 2014), extant research on the relationship between childhood unpredictability and inflammation is mixed (see e.g., Robles, 2020; Schreier et al., 2014). Together, these results suggest that exposure to childhood harshness (i.e., low childhood SES) may promote the development of exaggerated inflammatory activity, but that exposure to childhood unpredictability may not.

Next, we examined the links between inflammatory activity and immunological responses. Specifically, we assessed the relationship between levels of inflammation and each PBMC proliferation in the presence and absence of immunological stimulation from LPS, as well as phagocytosis of *E. coli* bioparticles. Across measures, we found a positive relationship between levels of inflammation and the magnitude of immunological responses. This was the expected pattern, as one of the primary functions of inflammation is to recruit immune cells to action to combat potential threats (Medzhitov, 2010). However, we also found a consistent pattern wherein childhood SES moderated the links between inflammatory activity and the magnitude of the inflammatory response. Probing these interactions consistently revealed that the positive relationship between inflammatory activity and the magnitude of immunological responses was limited to those from higher SES childhood environments. For those from low SES environments, there were no significant links between the magnitude of their inflammatory activity and the magnitude of their immunological responses. These results suggest that the exaggerated inflammatory activity that is often observed among those who have experienced ELA may not be associated with a heightened ability to manage immunological threats.

A third pattern that emerged from our results is the finding that those who reported higher childhood SES exhibited a more robust immunological response to LPS stimulation than those who reported lower childhood SES. This pattern is also consistent with past research, which finds that those from higher SES childhood environments exhibit better immune function compared to what is observed in those from lower SES backgrounds (Cohen et al., 2004; Dowd & Aiello, 2009). Indeed, the current research also found that those reporting higher childhood SES reported being in better health and coming from healthier families compared to those from lower childhood SES environments.

Across measures, we found no main effects of childhood unpredictability on immunological function and no significant interactions between inflammation and childhood unpredictability on any of our immunological function measures. While those who had experienced higher unpredictability in childhood reported worse general health than those with more predictable childhoods, there were no relationships between childhood unpredictability and the other three measures of self-reported health. These results further suggest that exposure to unpredictability early in life is unlikely to, in itself, modify inflammatory processes or immune function in young adults, as those with both high and low levels of exposure to childhood unpredictability displayed similar patterns of immune responses and self-reports of health.

## General discussion

Decades of research finds that ELA places individuals at an increased risk for disease in adulthood (Felitti et al., 1998; Gilbert et al., 2015; Repetti et al., 2002). Although there are numerous factors which contribute to the association between ELA and heightened morbidity and mortality risk, one potent contributor to this link is the presence of chronic inflammatory activity, which is frequently observed among those exposed to ELA (Baumeister et al., 2015; Coelho et al., 2013; Rasmussen et al., 2018). Much research demonstrates that individuals growing up in conditions of ELA exhibit a "proinflammatory phenotype" characterized by chronic inflammation, an exaggerated response to immune challenge, and insensitivity to inflammation-mitigating signals (Ehrlich et al., 2016; Elwenspoek et al., 2017).

Given that inflammation plays a critical role in the recruitment of cells involved in the innate immune response, it makes intuitive and theoretical sense to predict that exaggerated inflammatory activity observed among those who have experienced ELA serves an adaptive function. Indeed, there are at least three distinct evolutionary developmental frameworks that predict a functional role for exaggerated inflammatory activity in the context of ELA. Existing theoretical models predict that higher inflammation in the context of ELA may function to (1) minimize the threat of illness or injury in highly hazardous environments (Miller et al., 2011), (2) compensate for decrements in immunological functioning that have occurred in response to somatic damage incurred during development (Nettle et al., 2013; Rickard et al., 2014), or (3) increase resistance to novel pathogens by biasing investment in favor of innate (relative to acquired) immune function (McDade et al., 2016). Despite the appeal of these models, research examining the links between exposure to ELA and measures of acute health in the first two-to-three decades of life are not consistent with the hypothesis that exaggerated inflammatory activity is health promoting early in life. Instead, this research finds that children exposed to ELA are more susceptible to infectious disease than children with low-risk upbringings (e.g., Nielsen et al., 2011; Stepanikova et al., 2018). Such research raises the possibility that – rather than serving an adaptive function, itself – exaggerated inflammatory activity observed in the context of ELA may be an incidental byproduct, potentially of stress-induced modifications of the HPA axis (see Del Giudice et al., 2011; Miller et al., 2014).

To examine the links between early life exposure to ELA, inflammation, and immune function, we conducted a study in which we investigated the relationship between inflammatory activity and two facets of the innate immune response: (1) PBMC proliferation in the presence and absence of LPS and (2) phagocytosis of *E. coli* bioparticles. Specifically, we tested (a) whether participants' inflammatory response to *E. coli* would predict the magnitude of their immune responses to stimulation and (b) whether this relationship would differ depending on exposure to different dimensions of ELA. We also tested these patterns in participants' unstimulated PBMCs (i.e., examining spontaneous cytokine release and proliferation). If elevated inflammatory activity occurring in the context of ELA functions to promote health (whether in response to trade-offs being made to favor improved response to illness and injury hazards in harsh environments, to compensate for some other decrement in immune function occurring in response to somatic damage, or through adaptively biased investment in innate vs acquired immune function), we would expect to find a relationship between measured inflammatory activity and our measures of immune function among those

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who experienced ELA. If inflammatory activity is an incidental byproduct of stress-induced modifications to the HPA axis, we would expect to find no relationship between inflammatory activity and these measures in those who experienced ELA. Lastly, we also evaluated whether two distinct dimensions of ELA – harshness (measured by childhood SES) and unpredictability – have differing impacts on the links between inflammation and immune function. Although environmental harshness and unpredictability frequently occur together, previous research finds each of these environmental factors have potent but often independent influences on developmental outcomes (Belsky et al., 2012).

With respect to environmental harshness, the results of our study found higher levels of inflammation predicted a more robust immune response among those who grew up in higher SES environments. For these participants, there was a positive relationship between inflammatory activity and (a) unstimulated PBMC proliferation, (b) LPS-stimulated PBMC proliferation, and (c) phagocytosis of *E. coli* bioparticles. This is the pattern one should expect to see, as one of the primary functions of inflammation is to recruit immune cells to action to combat potential threats (Medzhitov, 2010).

For participants who reported growing up in lower SES environments, however, levels of inflammation were not related to unstimulated PBMC proliferation, LPS-stimulated proliferation, or phagocytic ability. Moreover, those from low SES early life environments who exhibit exaggerated inflammatory activity performed no better on our immunological challenges than those from the same environments who display a more tempered inflammatory response. In addition to detracting from the idea that inflammatory activity in the context of harshness may reflect immunological adaptation, these results suggest that harshness may be associated with immunological dysregulation, as cytokine levels should be related to the magnitude of the immunological response (see e.g., Murphy & Weaver, 2016). Indeed, those from lower SES environments also reported being in poorer health than those without such exposures, suggesting that exposure to harshness may contribute to adverse health outcomes as a result of impaired immune function occurring across immunological modalities.

The assays chosen for the current investigation assess more than just the effect of childhood SES on proliferation at high and low inflammation. These assays examined two distinct patterns of cellular events, with PBMCs differing both in composition and states of activation in each (Chiba et al., 2017; Gessani et al., 1993; Sharif et al., 2007). That similar effects were found in each case suggests that the impact of childhood SES on the relationship between inflammation and proliferation is robust and present across different PBMC populations at different states of activation.

With respect to unpredictability, the results of our study found no indication of a relationship between childhood exposures, inflammation, and immune function. This indicates that the dysregulated immune response exhibited by those with a proinflammatory phenotype may emerge in response to developing under the stressful conditions of resource constraint and environmental harshness, rather than experiences of ELA, broadly. Although extant findings on the relationship between childhood unpredictability and inflammatory activity are mixed (see e.g., Crosswell et al., 2014; Schreier et al. 2014), these results are in line with a recent review which found no consistent relationship between childhood unpredictability and inflammation (Robles, 2020). Indeed, ELA covers a broad range of environmental conditions and childhood experiences, and different kinds of adversities may have differing effects on immune function (e.g., Colich et al., 2020). The current results underscore the importance of examining distinct dimensions of ELA in future research.

Together, the results from the current study do not provide support for the hypothesis that exaggerated inflammatory activity occurring in those who experienced harsh childhood environments functions to promote acute health or healing among those from harsh environments. Instead, they are more consistent with the possibility that exaggerated inflammatory activity occurring in those who experienced harsh childhood environments may be an incidental byproduct of other developmental modifications or perturbations occurring in response to chronic childhood stress exposure. For example, much research finds links between exposure to recurrent psychological stress due to ELA and modifications to the activities of the HPA axis (Kircanski et al., 2019; Janusek et al., 2017; Shakiba et al., 2019; Timothy et al., 2019; Trickett et al., 2010) such as those resulting in an attenuated cortisol response to stress (Bunea et al., 2017). Although these modifications may themselves guide psychological and behavioral tradeoffs that promote survival and reproductive success in adverse environments (Del Giudice et al., 2011; Gatzke-Kopp, 2011; Hostinar et al., 2017), recurrent and intense HPA activation has been found to inhibit the anti-inflammatory properties of GCs (Cohen et al., 2012; Miller et al., 2014).

Because of the regulatory role that GCs such as cortisol play in the inflammatory process and associated immune response, it is possible that GC insensitivity may cause leukocytes to become insensitive to signaling by cytokines. Typically, elevated inflammation is associated with a more robust immune response (Kato & Kitagawa, 2006; Medzhitov, 2008), however, the current results demonstrate a decoupling of this relationship in those from harsh early life environments. This is in line with previous research finding dysregulated immune function in chronically stressed, low income individuals exhibiting GC insensitivity (Cohen et al., 2012; Corwin et al., 2013; Pace et al., 2007). In the context of chronically elevated inflammation, it is likely that inflammation responses would serve as a less effective signal to immune cells than they would outside the context of chronically elevated inflammation. While this is one promising mechanism for the patterns of results observed here, it should be noted that GC insensitivity is one of a number of possible mechanisms that may guide the development of a proinflammatory phenotype in response to ELA. As the current study was designed to investigate if elevated inflammation in those who experienced ELA was functional, further research will be needed to understand the mechanisms driving the (lack of) relationships observed between inflammation and immune function in those from low childhood SES environments in the current study.

### *Limitations and future directions*

While the results of the current research do not provide support for the hypothesis that exaggerated inflammatory activity occurring among those who have experienced harsh childhood environments serves an adaptive immunological function, these results should not be interpreted as evidence of the absence of *any* adaptive function for elevated inflammation in the context of exposure to early life harshness. For example, developing a proinflammatory phenotype in response to harsh childhood environments could serve some alternative, untested function unrelated to health or immune function, such as in the domains of learning and social behavior, both of which are known to be influenced by inflammatory activity

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(Gangestad & Grebe, 2014; Segerstrom, 2000; Ziv et al., 2006). Additionally, the absence of a relationship found between childhood unpredictability and immune function in the current study does not necessarily mean that this link does not exist in all populations, or under all conditions of unpredictability. Future research would benefit from developing and testing alternative hypotheses about the function served by chronic inflammation in the context of ELA, and how these functions would confer benefits under both harsh and unpredictable environmental conditions.

As the current research assessed inflammation and immune function *in vitro*, it is possible that exaggerated inflammatory activity associated with ELA could provide immunological advantages inside the bodies of those from harsh early life environments, even if the cellular response is impaired. Future research would benefit from examining immune responses of those who have experienced ELA in response to live, *in vivo* pathogenic challenges. We are also somewhat limited in our ability to draw broad conclusions about the links between harshness, unpredictability, chronic inflammation, and immune function, generally, given that we investigated two specific facets of participants' innate immune response (proliferation and phagocytosis) to one type of immunological stimulant (*E. coli*). Although the results of our immunological assays were consistent with participants' self-reported health, it is possible that those from low childhood SES backgrounds would have excelled at combating other, unassessed, immunological challenges. It is also important to note that although inflammation is generally positively associated with immune responses (a pattern which we largely replicated for those with high childhood SES), the overall associations between inflammation and proliferation were weak. As such, the results should be interpreted with caution until more is known about influential factors aside from cytokine levels which may influence these relationships.

Although the results of the current research are consistent with the hypothesis that chronic inflammation exhibited by those who experienced harsh early life environments occurs as a byproduct of stress-based modifications to the HPA axis, such as GC insensitivity, this is just one potential explanation for the observed patterns. Importantly, these links were not tested in the current research. That is, we did not test whether, for example, GC insensitivity predicted the lack of relationship observed between inflammatory activity and immune function observed among those from harsh environments. Although beyond the scope of the current investigation, future research would benefit from a more detailed analysis of the nature of the inflammatory cascade both in the presence and absence of stimulation among those from low versus high childhood SES environments. Research which examines both GC insensitivity and leukocyte insensitivity to cytokine signaling could provide valuable insights into potential mechanisms leading to the development of the proinflammatory phenotype.

Additionally, future research could benefit from examining potential differences in the composition of leukocytes between those who have experienced ELA and those who have not. As leukocytes include several different cell types, it is possible that inflammatory and immune responses are impacted by the number and variety of these cells. An immunophenotyping study (e.g., Maecker et al., 2012) on those from low and high childhood SES environments is warranted in the future.

Further, it is important to emphasize that these results should not be interpreted as bearing on causal pathways, but on the nature of the associations between immune responses and inflammation. This is especially important to consider as the relationship between inflammation and leukocyte proliferation is bidirectional in nature (that is, while the release of pro-inflammatory cytokines stimulates immunological responses like leukocyte proliferation, leukocytes themselves release cytokines; Gulati et al., 2016). In the current research, inflammation and the immune response assessed in each model were measured *in vitro*, in the same sample, at the same timepoint, in order to examine whether the associations between inflammatory activity and immune response vary as a function of exposure to ELA. As such, the current results should not be interpreted as evidence of inflammation causing leukocyte proliferation (in high, but not low childhood SES individuals), but rather should be interpreted as evidence of these processes being related (in high, but not low childhood SES individuals).

The current research has three additional limitations that should be considered when interpreting the results. First, the study utilized a college-aged sample, and although useful for examining the health implications of the proinflammatory phenotype at peak reproductive age, the immune function of young adults may be different than that of older adults. Second, the sample was not exceptionally diverse – 66.7% of participants were white, and 65.4% were of high childhood SES, and 88.7% reported predictable childhood environments. It is possible that different patterns may have emerged if the sample included a greater proportion of individuals with adverse early life experiences. Third, childhood SES and unpredictability were measured retrospectively, and longitudinal designs that track the effects of harshness and unpredictability throughout the life course may prove better suited to examine these relationships.

Lastly, future research should consider genetic effects which may contribute to the relationship between ELA and immune function. Because both ELA and immune function have heritable genetic components, isolating genetic influences from the downstream inflammatory effects of stress-modified HPA axis function will advance our understanding of the development of this proinflammatory phenotype. Additionally, there are many other less-explored factors present in early life environments which may impact the relationships between ELA and the development of a proinflammatory phenotype. Previous research has identified factors such as maternal care and social support which may buffer children from the negative health impacts of ELA (Chen et al., 2011; Lu et al., 2008, 2019; Miller et al., 2009; Thayer et al., 2020), and understanding the impact of these factors may prove particularly important for developing effective, data-driven interventions to improve the health and well-being of those who have experienced ELA. In sum, the current results are preliminary and warrant further investigation.

## Conclusions

It is often assumed that the exaggerated inflammatory activity observed among those who have faced ELA serves an adaptive function in the context of harsh or unpredictable environments. For example, existing theoretical models predict that higher inflammation in the context of ELA may function to minimize the threat of illness or injury in highly hazardous environments (Miller et al., 2011), to compensate for decrements in immunological functioning that have occurred in response to somatic damage incurred during development (Nettle et al., 2013; Rickard et al., 2014), or to increase resistance to novel pathogens by biasing investment in favor of innate (relative to acquired) immune function (McDade et al., 2016).

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Despite the intuitive and theoretical appeal of these models, the current research found no evidence linking inflammatory activity occurring in those who have experienced low childhood SES and the magnitude of their immunological responses to challenge. This raises the question of what, if any, alternative function might such chronic inflammatory activity serve? Or if, as we have proposed, these patterns are byproducts of stress-based modifications to the HPA axis, how can this insight be used to develop interventions that can mitigate the chronic inflammation and its health-harming sequalae in vulnerable populations? It is our hope that the current research will serve as a springboard for research into these important questions.

These questions are of incredible importance. Childhood adversity is alarmingly common and the long-term effects on health can be profound. Research suggests that at least 44% of children in developed countries and 59% in developing countries have been victims of physical, emotional, or sexual violence or have witnessed domestic or community violence (Hillis et al., 2016). Researchers estimate that these exposures cost individuals from adverse environments an average of $505 more per year in health expenses (Schickedanz et al., 2019) and an average of 5.8 years lost to disability (Cuijpers et al., 2011), compared to individuals who experience stable and secure childhood environments. Future research aimed at understanding the pathways by which those who have experienced harsh early life environments exhibit exaggerated inflammatory activity and dysregulated immunological responses will therefore be an important part of developing interventions to promote healthier children and adults.

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