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Psychological Stress During Childhood and Adolescence and Its Association With Inflammation Across the Lifespan: A Critical Review and Meta-Analysis

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Psychological stress during childhood and adolescence increases risk of health problems across the lifecourse, and inflammation is implicated as an underlying mechanism. To evaluate the viability of this hypothesis, we used meta-analysis to quantify the association between childhood/adolescent stress and inflammation over the lifecourse. Furthermore, we addressed three unresolved conceptual questions: (a) Does the strength of this association change over the lifecourse? (b) Are different types of childhood/adolescent stressors differentially associated with inflammation? (c) And which components of the inflammatory response are involved? A systematic search identified 187 articles reporting 922 associations. Meta-analyses were conducted using a three-level multilevel approach and controlled for study quality, conversion confidence, and whether effect sizes were unadjusted or adjusted (n = 662, 72%). Results indicated a small but reliable overall adjusted association ($\hat{r}$ = .04). The magnitude of the association strengthened across the lifecourse—effect sizes were smallest in studies that measured inflammation in childhood ($\hat{r}$ = .02) and became progressively larger in studies of adolescence ($\hat{r}$ = .04) and adulthood ($\hat{r}$= .05), suggesting the impact of early stress strengthens with time. By contrast, effect sizes did not vary by adversity type (socioeconomic disadvantage, maltreatment, other interpersonal stressors, and cumulative exposure across stressors), or component of inflammation (circulating biomarkers of low-grade inflammation vs. cytokine responses to microbial stimuli). Implications and future directions are discussed.

Public Significance Statement
Stressful experiences during the early decades of life increase susceptibility to health problems across the lifespan. Excessive inflammation is thought to be an important biological mediator of this relationship, but there has yet to be a comprehensive synthesis of the literature relevant to this hypothesis. Thus, we conducted a meta-analysis of 187 studies on the association between stress during childhood and/or adolescence and inflammation that were performed over the past 2 decades. The results indicated that inflammatory markers were higher among individuals who had experienced major psychological stress during childhood and/or adolescence. The relationship between childhood/adolescent stress and inflammatory markers increased in magnitude over the lifecourse, suggesting the influence of early adversity may compound with time. These findings refine our understanding of the role that inflammation plays in connecting early stress and lifecourse health.

Keywords: early adversity, childhood socioeconomic status, maltreatment, health, development

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Exposure to psychosocial stressors during childhood and/or adolescence—particularly stressors that are chronic or severe in nature such as maltreatment, parental mental illness, socioeconomic disadvantage, and/or violence—elevates risk for a plethora of adverse outcomes across the lifespan and across multiple domains. It has long been known that individuals who experienced psychosocial stress in their childhood and/or adolescent years tend to achieve less academically, have lower lifetime earnings, and have higher risk for developing mental health problems (Currie & Widom, 2010; Romano et al., 2015; Teicher & Samson, 2013). However, during the past 2 decades,

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new evidence has emerged indicating these risks extend to physical health, and in particular to chronic diseases associated with aging. For instance, in a study of over 17,000 adults, those who reported growing up in a household marked by stressors such as family violence and maltreatment were more likely to have cardiovascular disease (CVD), diabetes, cancer, lung problems, and autoimmune diseases (Dong et al., 2004; Dube et al., 2009; Felitti et al., 1998). Corroborating these findings, a meta-analysis linked childhood maltreatment to elevated risk for a similar set of physical health conditions (Wegman & Stetler, 2009). Prospective studies have also linked childhood socioeconomic disadvantage to elevated risk for adulthood CVD, respiratory disease, some cancers, as well as premature mortality (e.g., Galobardes et al., 2006; Kittleson et al., 2006). Although most of these findings derive from observational studies, there is mounting evidence from animal models, within-person longitudinal designs, and intervention trials to support a causal interpretation (Avitsur et al., 2006; Chiang, Park, et al., 2019; Kruschinski et al., 2008; Miller et al., 2014; Murphy et al., 2013; Roque et al., 2016; Shtoots et al., 2018; Wang et al., 2018).

These findings have captured the attention of researchers, clinicians, policy-makers, and the general public (Flaherty et al., 2010; Garner et al., 2012). For example, in 2012, the American Academy of Pediatrics encouraged pediatricians to routinely screen youth for exposure to severe, chronic stressors (Garner et al., 2012), and in 2018, the American Heart Association published a Scientific Statement summarizing this literature and recommending directions for research and treatment (Suglia et al., 2018). More recently, leading pediatricians have advocated for a transformation of their discipline that leverages discoveries about the biology of adversity to promote health and prevent illness across the lifecourse (Shonkoff et al., 2021).

Over the last 2 decades, researchers have paid special attention to underlying mechanisms that connect stress during childhood and adolescence with lifespan health and have proposed several conceptual models (Berens et al., 2017; Chiang, Taylor, & Bower, 2015; Danese & McEwen, 2012; Fagundes et al., 2013; Miller et al., 2011; Nusslock & Miller, 2016; Repetti et al., 2011). These models have highlighted inflammation as a key underlying pathway, noting that it is both sensitive to childhood/adolescent stress and is involved in a heterogenous set of health problems. Numerous studies have since been conducted to evaluate these models' basic proposition—that stress experienced during childhood or adolescence increases inflammation—and we are now well positioned to synthesize this body of evidence and determine how the general hypothesis is faring. Thus, the first goal of the current meta-analytic investigation was to comprehensively synthesize the literature on childhood/adolescent stress and inflammation. The second goal was to address three unresolved questions that are important for advancing theory in this literature, and potentially important for improving policy and practice for stress-exposed youth: (a) Does the strength of these associations change over the lifecourse? (b) Are different types of childhood and adolescent stressors differentially associated with inflammation? (c) And which components of inflammation are associated with childhood and adolescent stress?

Childhood and Adolescent Stress

Children and adolescents can experience stress in a variety of forms. However, the adversities that seem likely to contribute to serious health problems across the lifespan are probably chronic or severe in nature (Cohen et al., 1995; Evans & Kim, 2013; McLaughlin et al., 2019; Miller et al., 2011; Shonkoff et al., 2012). Stress is considered chronic when the precipitating stimulus remains present over a lengthy period of time (e.g., a child who lives with a persistently depressed parent), or when it manifests in a recurring manner (e.g., a child who lives in a neighborhood where gang violence regularly erupts). Initially acute stressors can also transition into more chronic stressors, such as when an initial event triggers a cascade of secondary stressors (e.g., the death of a parent may lead to chronic economic hardship) or elicits a threat that lingers for an extended period of time (e.g., the death of parent leads to a looming sense of danger and helplessness). The specific properties that characterize a severe stressor are challenging to define. Both theory and research have struggled to find concrete definitions of severity, and it is outside the scope of the current article to resolve this issue (Cohen et al., 1995; Epel et al., 2018). Instead, we follow precedent in the literature (Ehrlich, Miller & Chen 2016; McLaughlin et al., 2019; Shonkoff et al., 2012), and define severe childhood and adolescent stressors as threatening and often unmanageable experiences that fall outside the range of what children and adolescents typically experience in contemporary developed societies.

Research on the link between childhood and adolescent stress (hereafter, collectively referred to as "childhood stress") and inflammation has largely focused on parental maltreatment and socioeconomic disadvantage. A smaller number of studies has considered other targeted experiences of childhood stress such as bullying, community violence, loss of a parent, parent psychopathology, as well as broader forms of stress such as overall household dysfunction and cumulative indices of individual forms of adversities. Under the definition proposed above, these experiences can all be considered chronic or severe forms of childhood stress and are therefore included in the current meta-analysis. Some studies have focused on acute, mundane stressors such as daily hassles (e.g., arguing with a friend, demands at home; Fuligni, Telzer, Bower, Cole, et al., 2009); however, given that they are typically measured over a 1- or 2-week period and represent everyday occurrences, we do not consider them to be chronic or severe in nature and therefore do not include them in the present investigation. We also do not include physical stressors, such as malnutrition, infection, and pollution, because our focus is on psychosocial adversities, and the effects of these exposures on the developing immune system have been reviewed elsewhere (Bhutta et al., 2017; John et al., 2017; Jones et al., 2014; Olvera Alvarez et al., 2018).

Inflammation

Inflammation is one of the body's primary defense mechanisms against invading pathogens and tissue damage. Inflammation begins with an acute response, when circulating neutrophils, monocytes, and dendritic cells sense microbial invasion or tissue damage and release communication molecules known as inflammatory cytokines (Bartekova et al., 2018). These cytokines, including interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α, orchestrate a series of events that generally culminates in the removal of the pathogen or repair of the damaged tissue (Barton, 2008). This acute response generally succeeds in eliminating the threat or resolving the injury, and inflammation subsides (Barton, 2008; Nathan, 2002). However,

inflammation can become chronic if the precipitating stimulus remains present or if immune cells fail to receive or register inhibitory signals. Some of those inhibitory signals emanate from the immune system—for example, the anti-inflammatory cytokine IL-10 (Iyer & Cheng, 2012)—whereas others are released systemically by neuroendocrine circuits—for example, the adrenal hormone cortisol (Irwin & Cole, 2011).

When an inflammatory response becomes chronic, cells of the adaptive immune system, like T and B lymphocytes, and a wide variety of cytokines typically become involved. The exact repertoire of cytokines involved, however, depends on the target, the cells responding to it, and the body compartment (Armstrong et al., 2006). For example, an infection in the lungs will often trigger an inflammatory response involving T-helper cells, B lymphocytes, and eosinophils, coordinated by the cytokines IL-4, IL-5, and IL-13 (Halim et al., 2012; Müller et al., 2012). By contrast, the immune response to viruses that have infected the airways often involves dendritic cells, T-helper, and T-cytotoxic cells, guided by IL-12, interferon α, β, and γ (Dahl et al., 2004; Herold et al., 2015; Newton et al., 2016). In autoimmune diseases like rheumatoid arthritis, neutrophils and T-helper-17 cells attack the host's own tissue, a process orchestrated by cytokines like IL-17, IL-21, and IL-8 (Dinesh & Rasool, 2018; Hwang et al., 2004; Niu et al., 2010; Shahrara et al., 2009). In the case of atherosclerosis, monocytes enter the blood vessel wall to repair an injury, but once there, gorge themselves on cholesterol fragments (Hansson et al., 2006; Libby et al., 2002). These bloated cells recruit additional monocytes to the vessel wall via cytokines like IL-1β, TNF-α, and MCP-1, and via T-helper and smooth muscle cells, in the process transforming the inflammatory response from acute to chronic, and facilitating the growth of atherosclerotic plaque (Hansson et al., 2006; Libby et al., 2002).

In studies of humans, access to sites where inflammation is occurring, such as the arteries that supply the heart, or cells that line the airways, is generally limited for ethical reasons. Consequently, human studies often rely on indirect measurements of inflammation that quantify levels of cytokines in a standard venous blood sample (Yeh & Willerson, 2003) or from drops of blood drawn from capillaries at the tips of fingers (McDade, 2014). The inflammatory cytokines IL-6 and TNF-α are commonly assessed, as are the acute-phase proteins C-reactive protein (CRP) and fibrinogen. Although the latter proteins are not directly involved in the immune response, they are released by the liver in inflammatory conditions, making them useful proxies (Davalos & Akassoglou, 2012; Thompson et al., 1999; Yeh & Willerson, 2003). The absolute quantity of these inflammatory biomarkers in circulation is quite low, and as such, they are thought to reflect low-grade, chronic, inflammatory activity, which over multiple decades contributes to disease progression (Singh & Newman, 2011; Yeh & Willerson, 2003). Using these indirect measurements, numerous epidemiological studies have indeed found that circulating inflammatory biomarkers forecast subsequent health outcomes. Meta-analyses indicate that these outcomes include premature death (Li et al., 2017), as well as morbidity and mortality from diabetes, myocardial infarction, and stroke (Danesh et al., 2000, 2008; also see Pearson et al., 2003, for review). Meta-analyses also indicate that circulating inflammatory biomarkers longitudinally predict depressive symptoms (Valkanova et al., 2013), and the course of bipolar illness (Dargél et al., 2015) and schizophrenia (Goldsmith et al., 2016).

Despite the predictive utility of these biomarkers of low-grade inflammation, the fact remains that their tissue source cannot easily be localized. Cytokines are not only released by immune cells, but in tissues across the body, including those of the adipose (Black, 2003; Mohamed-Ali et al., 1998), skeletal (Pedersen & Febbraio, 2005), and respiratory systems (Adler et al., 1994; Iwamura & Nakayama, 2008). Thus, with circulating measures of inflammation, whether the origin is immunologic cannot be ascertained. Recognizing these interpretational challenges, some research has adopted a more direct approach that involves challenging immune system cells with stimuli in vitro and quantifying the ensuing production of cytokines. A variety of different stimuli can be used in these studies, ranging from bacterial and viral products to molecules released following cellular injury. Greater production of cytokines in these studies is interpreted as a sign of more aggressive inflammatory responding. This approach clarifies the triggering stimulus and immunologic source of inflammation and facilitates understanding of what exposures cause the immune system to become activated, and which cellular actors initiate and maintain that response. Another approach expands on this basic paradigm by including an anti-inflammatory molecule (e.g., cortisol, IL-10) to assess how sensitive immune cells are to its inhibitory signals. However, because of the technical demands, these approaches are less common in the literature.

Childhood Stress and Inflammation

Inflammation was first recognized as a plausible pathway linking childhood stress to health problems in the late 2000s when several studies demonstrated an association between childhood stress and CRP and IL-6 among adults and children (Carpenter et al., 2010; Danese et al., 2007; Howe et al., 2010; Taylor et al., 2006). Drawing on environmental programming, lifecourse, and allostatic load models, these hypotheses were formalized and elaborated on in the Biological Embedding of Childhood Stress Model, which provided a mechanistic framework for understanding how childhood stress might influence inflammatory processes across the lifespan (Miller et al., 2011). Focusing on immune cells known as monocytes, the model proposed that childhood stressors engender a pro-inflammatory phenotype via *programming* effects, where adversity gets durably embedded in cellular functions during sensitive periods of immune development, and via *accentuating* effects, whereby adversity shapes trajectories of psychosocial and behavioral development in ways that perpetuate inflammation across the lifespan. As a consequence of these effects, childhood stress is hypothesized to engender a pro-inflammatory phenotype that is manifested in (a) exaggerated inflammatory responses to microbial threats, (b) reduced sensitivity to anti-inflammatory signals, and (c) low-grade chronic inflammatory activity. Over the past 2 decades, numerous studies have tested these propositions, and the current investigation not only synthesizes the entire body of work on this topic, but importantly, also addresses three unresolved questions of theoretical and practical importance, as outlined below.

Does the Strength of the Childhood Stress–Inflammation Association Change Over the Lifecourse?

The first question is whether the adversity–inflammation relationship changes in strength across the lifecourse. Answering this

question is important for building theory because understanding the timeline of the effects of childhood stress on inflammation may provide clues about whether inflammatory effects accumulate and widen over the lifecourse, potentially spawning further investigation into underlying mechanisms. Such knowledge could help elucidate optimal times during development for intervention, making this question important for practice as well.

There are conceptual reasons to hypothesize that childhood adversity's relationship with inflammation will strengthen across the lifecourse. For example, the aforementioned Biological Embedding Model suggests that although functional properties of monocytes are "programmed" by early experiences, these effects are progressively accentuated by psychosocial, behavioral, and hormonal changes related to childhood adversity (Miller et al., 2011). Importantly, the sequelae of childhood stress involve the wearing and tearing down of systems, a process that takes time to arise, accumulate, and become established. It is unlikely that a single episode of a negative social interaction, a single cigarette, or a single surge of sympathetic hormones produces a state of low-grade chronic inflammation. More plausible is that their repeated occurrence accumulates over time to eventually foster a state of chronic inflammation (Danese & McEwen, 2012). Additionally, some of the relevant accentuators or mediators may not become operative or firmly established until later in the lifespan—for isntance, patterns of substance use and dietary intake often do not emerge and solidify until late adolescence and young adulthood (Paavola et al., 2004).

Although theoretical work suggests that the link between childhood stress and inflammation may strengthen across the lifespan, addressing this question requires decades-long studies is resource-intensive, making it very challenging to address in primary studies. Meta-analysis offers a complementary means for addressing this question, but it requires a large pool of effect sizes[1] and variability in life stage (Hedges & Pigott, 2004; Hempel et al., 2013). Therefore, to address the unresolved question of whether the childhood stress–inflammation link changes across the lifecourse, we take a comprehensive approach and include studies with samples from on different developmental stages, rather than focusing on a single developmental stage.

Are Different Types of Childhood Stressors Differentially Associated With Inflammation?

The second unresolved question centers around the specificity of exposure. A wide variety of adversities has been assessed in the literature, ranging from socioeconomic disadvantage (e.g., low family income or parental education), to maltreatment (e.g., abuse and neglect), to other interpersonal stressors (e.g., family conflicts, parental psychopathology, peer conflicts). The various types of stressors examined in the literature have raised the question of whether the magnitude of associations with inflammation differs by the kind of adversity a child or adolescent experiences. The answer to this question is conceptually important because advancing theory partly relies on whether the body's immune responses to chronic childhood stress are agnostic or sensitive to the kind of adversities experienced. The answer is also important for clinical practice, as it can elucidate whether prevention and intervention strategies should target specific types of childhood stressors.

There are reasons for hypothesizing both specificity and similarity effects on inflammation. With respect to the former, several conceptual models suggest that childhood stressors can be organized into core underlying dimensions, such as threat versus deprivation (McLaughlin et al., 2014), harshness versus unpredictability (Belsky et al., 2012), and physical trauma versus disrupted caregiving versus unpredictability (Kuhlman et al., 2017), and that these dimensions have unique influences on outcomes. For example, the dimensional model of adversity and psychopathology (DMAP; McLaughlin et al., 2014) posits that threatening experiences, like abuse and violence, alter the development of neural circuits underlying emotional learning and processing, whereas deprivation experiences, such as socioeconomic disadvantage and neglect, alter the development of neural circuits underlying cognitive and executive control (Lambert et al., 2017; Machlin et al., 2019; Sheridan et al., 2017; Sheridan & McLaughlin, 2014). Although inflammation is outside the scope of what the DMAP seeks to explain, other theoretical analyses connect the neurodevelopmental profiles it highlights to downstream inflammatory. As such, to the extent that childhood stressors can be categorized as being more characteristic of a particular dimension of stress, there may be differential associations with inflammation.

However, it may be that different stressors have similar effects on inflammation (Miller et al., 2011). The various types of childhood adversities examined in the literature tend to co-occur, with stress-exposed youth rarely experiencing only one type of stressor (Smith & Pollak, 2020). For instance, maltreatment and peer victimization are more prevalent among socioeconomically disadvantaged families (Imran et al., 2019; Kim & Drake, 2018; Tippett & Wolke, 2014). Maltreated youth are also more likely to be bullied compared to their nonmaltreated peers (Shields & Cicchetti, 2001). Furthermore, various childhood stressors tend to share common features (Miller et al., 2011; Smith & Pollak, 2020). For instance, low socioeconomic status (SES) and abuse often involve exposure to conflict and less sensitive parenting (Repetti et al., 2002). A possibility, then, is that different types of childhood stressors may actually represent the same underlying construct (Smith & Pollak, 2020). Given the co-occurrence and shared features of various stressors, one may postulate common effects of various stressor types on inflammation.

Prior work suggests competing hypotheses as to whether various types of stressors have distinct effects on inflammation. We address this question by leveraging the various operationalizations of the broad construct of childhood stress across extant research and meta-analytically examine whether the magnitude of associations with inflammation diverges by type of adversity, namely SES, maltreatment, family stress, other interpersonal stress, and cumulative or composite indices of adversity. Additionally, because SES and maltreatment, the two most commonly assessed childhood stressors, can be further differentiated into subtypes, we also explore whether the link between childhood stress and inflammation varies by subtypes of SES and maltreatment. SES was differentiated between resource-based measures (e.g., income, savings) and prestige-based measures (e.g., parental education and occupation) as has been done in prior research (Bradley & Corwyn, 2002; Braveman et al., 2005; Krieger et al., 1997). For maltreatment, we made two distinctions:

[1] Assuming 100 participants in each study and moderate-to-high heterogeneity (I^2 = 70%), 210 effect sizes are necessary to detect a significant moderation by developmental stage with 80% power (incremental increase in r of .05 from childhood to adolescence to adulthood, if r = .07 for childhood based on Kuhlman, Horn, et al., 2020).

(a) between broader dimensions of abuse and neglect collapsed across physical, emotional, and sexual subtypes (i.e., abuse: physical, emotional, or sexual; neglect: physical, emotional); (b) and between dimensions of physical, emotional, or sexual subtypes collapsed across abuse and neglect dimensions (i.e., physical: abuse or neglect; emotional: abuse or neglect; sexual: abuse).

Which Components of Inflammation Are Associated With Childhood Stress?

A third unresolved question centers around whether childhood stress has distinct patterns of associations with different components of the inflammatory process. Low-grade inflammation is the process commonly assessed in this literature and is measured by quantifying biomarkers like IL-6 and CRP in circulating blood. As mentioned above, interpretation of these biomarkers is complicated because their trigger source and stimulus are unknown, leading some researchers to measure the production of inflammatory cytokines after stimulating immune cells with microbial products in vitro. These procedures yield a different perspective, reflecting how aggressively immune cells react to inflammatory stimuli.

Examining this distinction is important beyond methodological reasons, as it has implications for theories of howand when adversity and low-grade inflammation become linked. Childhood stress is postulated to sensitize youth's monocytes to mount exaggerated cytokine responses to challenge and become insensitive to anti-inflammatory signals;these functional tendencies, in turn, are hypothesized to precipitate low-grade inflammation over time (Miller et al., 2011). Thus, the distinction between different components of the inflammatory response also specifies a temporal ordering, where adversity first influences monocytes' response to challenge, and through that process, eventually fosters low-grade inflammation. In the current meta-analysis, we examined whether childhood stress is differentially associated with these two different components of the inflammatory process by taking a broad immunologic scope and including both studies with low-grade inflammation measures and studies using microbial-stimulation paradigms.

In addressing this question, we collapse across specific cytokins and markers of inflammation. However, a wide variety of cytokines are involved in chronic inflammatory processes, as described above, and studies have increasingly examined more cytokines because of technological advances like multiplex immunoassays that allow quantifying multiple analytes simultaneously. Currently, little is known about whether childhood stress impacts various biomarkers of inflammation similarly, and addressing this question can inform methodological decisions for data reduction, such as whether biomarkers can be aggregated as a composite, which may in turn help with Type I error control by avoiding the multiple comparisons problem. Therefore, we also examined whether the link between childhood stress and CRP, the most assessed biomarker from our search, was different from the association with fibrinogen, IL-6, IL-10, and markers of the IL-1 family, TNF family, and IFN family.

Current Meta-Analysis

Four meta-analyses have recently quantified associations between childhood stress and inflammation, and all reported small but reliable associations, as shown in Table 1 (Baumeister et al., 2016; Kuhlman, Horn, et al., 2020; Liu et al., 2017; Milaniak & Jaffee, 2019). Each of these meta-analyses focused on a specific type of adversity (e.g., only SES), specific biomarkers (e.g., only circulating biomarkers like CRP, IL-6), and/or a specific developmental stage (e.g., only adulthood). This approach reduces heterogeneity in both the exposure and outcome variables, ensuring that the synthesized effect size is net of variation in the way constructs are defined or measured. In the current meta-analysis, we take a different approach, leveraging the conceptual and methodological variation in the literature to conduct a more comprehensive synthesis that covers a larger portion of the lifespan, a broad range of serious adversities that children and adolescents face, and different components of the inflammation process. Using data from 187 studies published over the past 2 decades, we estimate the overall effect size between childhood stress and inflammation, and address three specific questions with relevance for theory, research, and practice while controlling for heterogeneity from other sources via inclusion of covariates: (a) Does the strength of the childhood stress–inflammation association change over the lifecourse? (b) Are different types of childhood stressors differentially associated with inflammation? (c) And which components of inflammation are associated with childhood stress? The present meta-analysis was preregistered on Open Science Framework on 24th August 2018 (https://osf.io/vpk83/?view_only=9728f45756344cbd992a9375321139c7).

Method

Search Strategy and Study Selection

Electronic searches were performed through July 2021 in the Pubmed and APA PsycINFO databases using a combination of search terms for childhood stress and inflammation. Search terms for childhood stress included "early adversity," "early-life stress," "child maltreatment," "child abuse," "child neglect," "childhood trauma," "adolescent stress," "bullying," "family stress," "early socioeconomic status," "childhood socioeconomic status," "child poverty," "maternal education," "parental education," "economic hardship," and "victimization." Search terms for inflammation included "inflammation," "inflammatory," "cytokine," and "interleukin." Reference lists from reviews on childhood stress and health were also examined for additional studies (Baumeister et al., 2016; Coelho et al., 2014; Kuhlman, Horn, et al., 2020; Liu et al., 2017; Milaniak & Jaffee, 2019; Muscatell et al., 2018; Slopen et al., 2012). Duplicate articles were first removed, after which remaining titles were screened and irrelevant articles removed. Each abstract of remaining articles was reviewed based on the following inclusion criteria: (a) peer reviewed; (b) published in the English language; (c) empirical in nature; (d) examined human subjects; (e) included at least one measure of stress experienced during childhood and/or adolescence (through age 19; World Health Organization [WHO], 2021); and (f) included at least one marker of inflammation. Nonempirical articles (i.e., review articles) and animal studies were excluded. As noted above, studies that focused on only daily or physical stressors were also excluded. All articles whose abstracts met inclusion criteria were retrieved. Abstracts that did not provide sufficient information to determine eligibility were kept for further review (e.g., studies that included a measure of childhood stress as a covariate and not a primary predictor). Full

Table 1
Summary of Meta-Analyses on Subsets of the Literature on Childhood Stress and Inflammation

Authors, Year	Childhood stressor	Sample	CRP	IL-6	TNF-α	Fibrinogen
Baumeister et al. (2016)	Maltreatment	Adults only	$r = .10$ $k = 18$	$r = .08$ $k = 15$	$r = .23$ $k = 10$	—
Liu et al. (2017)	SES	Adults only	RC = 1.25 $k = 15$	—	—	—
Milaniak and Jaffee (2019)	SES	Any age	$r = .05$ $k = 24$	$r = .08$ (n.s.) $k = 8$	—	— $k = 3$
Kuhlman, Horn, et al. (2020)	Broadly defined	Youth only	$r = .07$ $k = 12$	$r = .17$ (n.s.) $k = 7$	—	—

Note. CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor alpha; SES = socioeconomic status (expressed in direction of disadvantage); r = correlation coefficient (transformed from reported Fisher's Z); k = number of studies included; RC = ratio change in geometric mean of CRP between low and high SES; Youth = under 18 years old. Kuhlman, Horn, et al., 2020 included maltreatment, socioeconomic status, and child adversity/trauma in general. When reported, adjusted effect sizes are presented. All effect sizes were statistically significant unless otherwise noted with n.s. En dash refers to missing either due to marker not included or statistics unreported (e.g., for Milaniak & Jaffee, 2019, SES and fibrinogen).

reports were then evaluated, and relevant data were extracted. Study search and selection were conducted by the first and second authors.

Data Extraction, Coding, and Processing

Study Characteristics

A number of sample and methodological characteristics were extracted, including measure of childhood stress, stressor reporting approach (concurrent or retrospective), component of inflammation assessed (low-grade inflammatory marker or inflammatory response to microbial challenge, marker(s) of inflammation, sample mean age, age range during which inflammation was assessed, proportion of female participants, proportion of White participants, sample mean body mass index (BMI), study design (cross-sectional, longitudinal, or other), and year of publication. The first author extracted study characteristic for all studies, and the second author independently extracted study characteristics for 94 studies (50% of included studies) to assess reliability in data extraction. Interrater reliability between the two coders was then assessed by computing intraclass correlation coefficients (ICCs) for continuous variables and Cohen's κs for categorical variables. There was strong agreement for all extracted characteristics (ICCs and κs = 1.0), except for age range during which inflammation was assessed (ICCs = .94 for min and .99 for max), study design (cross-sectional, longitudinal, or other; κ = .97), and year of publication (reliability not computed because data were imported from databases). Inconsistencies were resolved by consensus.

Several extracted variables were recoded to facilitate moderator analyses. First, sample mean age was extracted to examine moderation by developmental stage. Because sample mean age was not equally distributed across the lifespan, it was recoded into three developmental stage groups based on prior work (Repetti et al., 2011; WHO, 2021): (a) childhood, through 12 years old; (b) adolescence, 13 through 19 years old; and (c) adulthood, 20 years or older. Given that age cutoffs for defining developmental stages vary across fields and perspectives (e.g., Arnett et al., 2014; Healthy People, 2020; Repetti et al., 2011; Sawyer et al., 2018; WHO, 2021) we conducted additional analyses that redefined childhood, adolescence, and adulthood according to other common age thresholds, several of which further categorized these stages into early, middle, and late/older stages. Second, for analyses examining moderation by adversity type, childhood stress measures were classified into five types of adversity: (a) SES, including education, income, occupation, and subjective social status; (b) maltreatment, including physical, sexual, emotional abuse or neglect; (c) family stress, including nonmaltreatment harsh discipline, family conflicts, maternal stress, parent psychopathology, and household chaos; (d) other interpersonal stress, including targeted rejection, bullying, and peer conflicts; and (e) cumulative indices of childhood stress—that is, total number of exposures to different types of adversity. Lastly, for analyses examining moderation by marker of inflammation assessed, inflammatory markers were grouped into nine categories, in some cases reflecting families of molecules: (a) CRP; (b) IL-6; (c) TNF-α, soluble receptor for TNF-α Type I and II (sTNFαI and sTNFαII); (d) interferon (IFN)-α and IFN-γ; (e) IL-10; (f) IL-1α, IL-1β, and IL-1 receptor antagonist; (g) fibrinogen; (h) other inflammatory markers, such as IL-2, -4, -8 (excluded from specific marker moderator analyses because cannot be meaningfully interpreted); and (i) composites of multiple inflammatory markers (excluded from specific marker moderator analyses because there were too few studies; $k = 9$).

Study Quality Coding

To account for variation in the quality of studies, which could increase measurement error and interpretational biases, we devised an 11-item coding scheme that considered the quality of adversity measurement, inflammation measurement, and analytical approach (see Supplemental Material). Specifically, quality of adversity measures was gauged with three items considering their validity, reliability, and susceptibility to recall and self-report biases. Quality of inflammatory measures was assessed with six items considering fasting status, duplicate assaying, coefficient of variations, and appropriateness in handling nondetectable values, nonnormal distributions, and outliers. Analytical approach was assessed with two items considering whether potential confounds were accounted for and whether the statistical approach was appropriate for addressing the research questions. A weighted sum was computed to ensure that each of the three domains was weighed equally ($M = 7.03$, $SD = 1.74$, range = 1.83–10.39). The first author coded 142 studies (76% of included studies), and the second author coded the remaining 45.

Ninety-four studies (50% of included studies) were coded by both authors to determine interrater reliability, which was strong (ICC = .92).

Effect Sizes

We were primarily interested in adjusted associations because they provide information regarding whether childhood stress uniquely relates to inflammation after adjustment for several known potential confounds. This aligns with primary research in the field: potential confounds are typically accounted for either statistically or by study design, and childhood stress–inflammation links are generally considered robust only if upheld when adjustments are made. As such, the target effect size was the partial correlation coefficient. In a small number of cases where adjusted statistics were not available, we extracted unadjusted statistics to minimize missing data. In these cases, the target effect size was a bivariate correlation coefficient. Most studies had multiple effect sizes to contribute to the current meta-analysis because they contained multiple indicators of childhood stress and/or inflammation (e.g., childhood maltreatment and inflammation as well as childhood socioeconomic disadvantage and inflammation reported in a single study). We extracted statistics representing each unique childhood stress–inflammation association and handled within-study dependencies in effect size analytically (described below).

Extraction. Many studies reported multiple statistical estimates for the same association (e.g., both unstandardized regression coefficient, *b*, and percent changes in outcome derived from exponentiated logistic regression, *b*). Therefore, we a priori established guidelines for which values to extract based on our confidence in the fidelity of effect size conversions. For instance, in data from regression models, we prioritized using *b* coefficients over percent changes in outcome because converting the latter values into a partial correlation coefficient requires additional steps (i.e., natural log-transforming the change estimate and its corresponding confidence interval to estimate *b* in log of raw units and its corresponding standard error, respectively, before *t-statistics* and then the *partial correlation coefficient* can be estimated).

Statistics for the same association were reported when studies (a) examined both unadjusted and adjusted models, (b) presented a series of adjusted models with different sets of covariates, and when they (c) examined the same association at different time points. As described above, we prioritized adjusted associations over unadjusted ones. Statistics from unadjusted models were extracted only if those from adjusted models were inaccessible (either as reported in the article or via email correspondence) or when statistics from the adjusted model were inferior (e.g., if the unadjusted model provided regression coefficients and the adjusted model only provided a rough significance level, such as $p < .10$). When several adjusted associations with different sets of covariates were reported, we extracted statistics from the most stringent model—that is, the model with the most complete set of covariates. Exceptions were made when the most stringent model included a covariate that was being tested or interpreted as a mediator, or when the statistics from the most stringent model were inferior to those from a less stringent model. In cases where the same association at different time points were reported, we similarly prioritized statistics from the most stringent model—that is, the model with the longest lag time between assessment of adversity and inflammation—again, except for when statistics were inferior to a less stringent model. Statistics for quantifying effect sizes were extracted by the second author. To assess reliability, the first author independently extracted statistics for 94 studies (50% of available pool). The two coders demonstrated strong agreement, ICC = 1.0, and inconsistencies were resolved by consensus.

Conversion. Extracted statistics, which derived from several different types of study designs and analyses, were converted to partial correlation coefficients for adjusted associations or Pearson's correlation for unadjusted associations. Both partial and bivariate correlations were coded such that higher values indicated a stronger positive association between childhood stress and inflammation. Partial correlation coefficients were estimated based on study design, the statistical tests conducted, and the metrics extracted, and then converted to Fisher's *Z*, following convention (Hedges & Olkin, 1985). Below, we provide a brief overview, but specific details about the range of included statistics, study design, and type of analysis, along with the equations and series of steps used to estimate Fisher's *Z*s and their corresponding sampling variances can be found in Table S1 of Supplemental Material.

Most extracted statistics ($n = 816$, 89% of total included associations) were based on correlational designs that utilized regression techniques. The extracted regression metrics were used to compute *t*-statistics, which in turn were used to compute partial correlations (Aloe & Thompson, 2013; Gustafson, 1961). Some extracted statistics ($n = 106$, 11% of included associations) were based on group difference designs and compared inflammation between an exposed and nonexposed group. Values extracted from these studies were used to estimate *t*-statistics, and subsequently converted into partial correlations, and then into Fisher's *Z*. An exception applied to a small portion of statistics ($n = 18$, 2% of included associations) extracted from studies that utilized an extreme groups design or dichotomized measures of childhood stress to examine group differences. Some of these studies dichotomized continuous stress measures into more than two groups (e.g., low vs. moderate vs. high childhood stress by tertiles), in which case statistics only for the comparison representing the largest difference in childhood stress was selected (i.e., low vs. high adversity exposure). For both types of cases, we followed the recommendations and equations specified by Pustejovsky (2014; see Supplemental Material) to estimate Fisher's *Z* and its variance.

In cases where only exact two-tailed *p*-values were reported ($n = 62$, 7% of total included associations), partial correlations were computed using converted one-tailed *p*-values and their corresponding degrees of freedom (Rosenthal & Rubin, 2003). Some articles ($n = 40$, 4% of total included associations) only reported nonsignificant associations with inexact *p*-values—that is, $p < .10$, $p < .05$, or $p < .01$. In such cases, we followed other recent meta-analyses (Adam et al., 2017; Weisz et al., 2017) and estimated partial correlations using *p*-values of .075, .025, or .005, respectively. Finally, when insufficient information was provided for computing partial correlations, we contacted the corresponding authors of the studies to request necessary information. Associations for which there were no responses after 2-week and 4-week follow-ups were excluded from analyses ($n = 98$, 9% of possible pool of effect sizes). All transformations were computed using *R* package *michaela* (Lam & Chiang, 2020). Specific functions, and their corresponding equations, used are detailed in Table S1 of Supplemental Material.

Conversion Confidence. Given the variability in how easily statistics reported by studies could be converted into the target effect sizes, we also rated our confidence in the computed effect size estimate. This rating was generally based on the number of

conversion steps necessary to estimate partial correlations (or Pearson's correlations for unadjusted statistics). For instance, converting a regression coefficient (*b*) and its standard error (*SE*) into a partial correlation requires two steps (i.e., *b* and *SE* to *t* to *r*). By contrast, the conversion for percent change in outcome takes four steps (i.e., percent change and confidence intervals [CI] to *b* and CI in logged raw units to *b* and *SE* to *t* to *r*). Our confidence in an effect size estimate declined as the number of steps required to calculate it increased given that more calculations, rounding, and assumptions were involved with each additional step. Based on this reasoning, we made confidence ratings for each derived effect size, reflecting the number of computational steps required to estimate the target effect sizes. Ratings were then inversed, such that lower scores reflected less confidence in the resulting estimates. Exceptions to this approach are detailed in Supplemental Material. The mean confidence score was 5.63 ($SD = 2.28$, range = 1–8).

Analytical Approach

Data Preparation

Prior to conducting primary analyses, several adjustments were made to the data. Multiple studies analyzed data from the same sample of participants, potentially creating dependencies and duplicates in extracted effect sizes. Thus, we first reexamined all studies and identified potential sources of overlap. These included analyses based on the same publicly available data sets (e.g., the Midlife in the United States Study, and National Longitudinal Study of Adolescent Health) or on samples collected by the same lab group. Studies that shared the same participant pool were treated as a single sample in analyses. For duplicate effect sizes within a sample, the finding based on the larger sample size was used except when the smaller sample provided more accurate statistical estimates. Nine studies reported only duplicate effect sizes and were thus excluded from analyses. Some articles reported statistics separately for subpopulations within a study (e.g., separately for men and women). For these studies, associations were treated as coming from two separate samples, a common procedure used in other meta-analyses (Adam et al., 2017; Cooper et al., 2009). Effect sizes were then inspected for outliers, defined as greater than 3 *SD*s from the mean, which were subsequently excluded from analyses ($n = 29$, 3% of possible associations; Badr & Krebs, 2013; Lipsey & Wilson, 2001).

Preliminary Analyses

The majority ($n = 662$, 72%) of effect sizes were partial associations that had been adjusted for potential confounds (Supplemental Material Table S8 presents frequencies of common adjustments), but a sizeable minority were bivariate associations. Pooling unadjusted and adjusted effect sizes can introduce heterogeneity and complicate interpretation. Thus, we conducted prespecified sensitivity and moderator analyses to determine whether partial and bivariate effect sizes could be synthesized in a single meta-analysis (Aloe et al., 2016). Specifically, we conducted separate meta-analyses for the pools of bivariate and partial effect sizes and examined the 95% confidence intervals of the synthesized effect sizes and variance estimates (both between- and within-sample variances). Overlapping confidence intervals would suggest insufficient evidence that the two models differ from each other. We also performed combined analyses that pooled bivariate and partial effect sizes and tested two moderators: (a) an effect-coded variable reflecting partial versus bivariate effect size and (b) a count of the number of covariates the study modeled. Because the count variable was right-skewed, we ran an additional moderator analysis where number of covariates modeled in the study was recoded into one of four categories: 0 covariates, 1–5 covariates, 6–10 covariates, or more than 10 covariates. Significant moderation by any of these variables would suggest that partial and bivariate effect sizes were different from each other.

If any one of these prespecified analyses suggested that the magnitude or the variance between bivariate and partial effect sizes differed, we decided a priori that bivariate effect sizes would be excluded from analyses. Otherwise, they would be pooled in a single meta-analysis, while adjusting for whether effect sizes were partial versus bivariate in primary analyses and for the count or categorized number of covariates in sensitivity analyses. Furthermore, to ensure results were not driven by the inclusion of bivariate effect sizes, we decided a priori that additional sensitivity analyses would be done excluding bivariate effect sizes.

Primary Analyses

All analyses were conducted in R-Studio 1.2.1335 (RStudioTeam, 2018) using the packages *metafor* (Viechtbauer, 2010) and *robumeta* (Fisher & Tipton, 2015). Multiple relevant effect sizes were extracted from the majority (72%) of studies, which may create dependencies among effect sizes and violate the independence assumption of traditional meta-analysis. Previous meta-analyses in this area have either averaged effect sizes within each study or selected only one effect size to include. However, these approaches may obscure a large number of potentially informative effect sizes, increase the risk of biased standard errors of parameter estimates, and preclude modeling of within-study heterogeneity in moderation analyses, limiting the research questions that can be investigated (Cheung, 2014; Hedges, 2007; Hedges et al., 2010; Moeyaert et al., 2017; Tipton, 2015). Therefore, we included multiple effect sizes within studies and conducted three-level meta-analyses, such that individuals were nested within effect size, which was nested within samples (Supplemental Material presents the equations). Models were fit via restricted maximum-likelihood estimation and hypothesis tests were based on *t* and *F* distributions, rather than *Z*-distribution, to improve Type I error control (Knapp & Hartung, 2003).

Consistent with prior meta-analytic work (Cheung, 2014; Konstantopoulos, 2011; Van den Noortgate et al., 2013), a likelihood-ratio test (LRT) confirmed that the model fit of the three-level model (Akaike's Information Criteria [AIC] = −1972.31, Bayesian Information Criteria [BIC] = −1948.30) was significantly better compared to the more traditional two-level model (AIC = −1875.31, BIC = −1856.02 ; LRT = 99.10, $p < .001$), supporting the use of the three-level model. Although there are other approaches to account for dependencies within samples, such as robust variance estimation (Fisher & Tipton, 2015; Hedges et al., 2010), we a priori opted for a multilevel framework because this approach not only *accounts* for within-sample dependencies, but also allows for *modeling* of within-sample variances. Furthermore, a recent simulation study comparing methods for handling dependent effect sizes recommends three-level multilevel modeling over robust variance estimation if there are over 50 samples included

and if variance estimates within and between samples are of interest (Moeyaert et al., 2017).

Using the three-level multilevel approach, we conducted meta-analyses in two phases. In the first phase, we conducted mixed-effects meta-analysis for the overall association between childhood stress and inflammation and computed τ^2 statistics to examine the expected heterogeneity in effect sizes within and between samples. A series of sensitivity analyses were then conducted to test whether estimates were robust to influential outliers, meta-analytic approach, and publication bias. Influential outliers were assessed by first computing studentized deleted residuals of the overall model to detect potentially influential effect sizes (Viechtbauer & Cheung, 2010) and then recomputing the meta-analytic effect size for the overall association with these cases excluded. To examine whether estimates were robust to approach, we also conducted random-effects meta-analysis with robust variance estimation to account for dependencies (Hedges et al., 2010).

Publication bias was first examined visually by creating a funnel plot that graphs the effect sizes against the inverse of the standard errors (Egger et al., 1997; Sterne & Egger, 2001). However, to the best of our knowledge, currently no method accounts for both publication bias *and* dependencies in effect sizes. Thus, we adapted concepts from the precision-effect test (PET) and precision-effect estimate with standard error (PEESE; Stanley & Doucouliagos, 2014) for use in multilevel models by entering the standard error as a predictor. The PET models a linear relationship and the PEESE models a quadratic relationship between the standard error and effect size. In both cases, the intercept coefficient (i.e., when sampling error is zero) can be interpreted as the effect size between childhood stress and inflammation adjusting for small-study effects in a hypothetical study with infinite sample size. Following recommendations (Stanley & Doucouliagos, 2014), if the estimate from PET was statistically nonsignificant (i.e., the estimated true effect is not distinguishable from zero), then results from PET were considered final, and if the estimate from PET was statistically significant, results from PEESE were considered final.

Lastly, because childhood adversity often cascades across the lifecourse (Hostinar, Lachman, et al., 2015; Mosley-Johnson et al., 2021; Raposa et al., 2014), sensitivity analyses also examined whether the association between childhood stress and inflammation may reflect current ongoing stress, particularly in adulthood. To test this hypothesis, we examined whether controlling versus not controlling for adulthood stress emerged as a signfiicant moderator and performed a subgroup analysis that synthesized effect sizes that adjusted for stress levels in adulthood.

In the second phase, we conducted moderator analyses to test whether the developmental stage at which inflammation was assessed, the type of childhood stress, and the component and marker of inflammation assessed influenced the magnitude of the association between childhood stress and inflammation. We coded developmental stage at which inflammation was assessed linearly. We coded type of childhood stressor categorically, focusing on socioeconomic disadvantage, maltreatment, other interpersonal stress (collapsing across family and other interpersonal stressors due to smaller number of samples for each), and cumulative indices of adversity with maltreatment dummy coded as the reference group. Because socioeconomic disadvantage and maltreatment are the two most common types of adversity examined in the literature and are both multifaceted (Brown et al., 1999; Chen et al., 2016), we also explored whether effect sizes would differ by subtypes of SES (i.e., financial resources- vs. prestige-based measures) and by subtypes of maltreatment (i.e., physical, emotional, vs. sexual in one model and abuse vs. neglect in another). Lastly, component of inflammation assessed was dummy coded as low-grade inflammation versus cytokine responses to microbial challenge, and specific markers of inflammation were coded with CRP as the reference group compared against fibrinogen, IL-6, IL-10, IL-1 family, TNF family, and IFN family.

As acknowledged above, taking a broad approach in comprehensively synthesizing existing literature potentially introduced additional noise sourced from the variability in study quality and variability in effect size conversion. To account for this potential *garbage-in, garbage-out* issue common in meta-analysis (Borenstein et al., 2009; Egger et al., 2001; Ioannidis, 2016), all analyses were conducted with both rated study quality and conversion confidence held constant at the mean.[2]

Additional Moderation and Subgroup Analyses

In additional analyses, we explored whether the effect size for childhood stress and inflammation was sensitive to other sample and methodological characteristics. Specifically, we explored whether the sex (% female) or racial (% White) composition of sample, average BMI of sample, study design (cross-sectional vs. longitudinal), and publication year were significant moderators. We also examined whether moderations were independent in a model that included all sample and methodological factors, except sample mean BMI ($k = 78$, $n = 330$) and proportion of White participants ($k = 98$, $n = 560$) because the list-wise deletion N would be reduced by 54%. In addition, to retain the maximum analytical N ($k = 153$), stressor reporting approach (concurrent vs. retrospective) and study design (cross-sectional vs. longitudinal) were entered as two separate variables.

Lastly, we synthesized effect sizes of subsets of studies categorized by sample characteristics and methodological factors in additional analyses. These subgroup analyses were conducted to provide further descriptive information, and it is critical to note that inferences about differences in effect sizes should only be made based on significance tests from moderator analyses. Because some of the subgroup analyses involved fewer than 50 samples, the recommended size for multilevel modeling (Moeyaert et al., 2017), we present results from both multilevel modeling and robust variance estimation models with small sample adjustment applied (Hedges et al., 2010; Tipton, 2015). Results from robust variance estimation models were deemed unreliable and thus excluded when the Satterthwaite degrees of freedom were below 4, which can result even when sample size is large since small degrees of freedom can stem from other factors, such as high leverage and large imbalance (Tipton, 2015; Tipton & Pustejovsky, 2015). In addition, the Supplemental Material presents additional subgroup analyses (e.g., type of stressor by type of marker), subgroup and moderator analyses stratified by adjusted and unadjusted effect sizes, and subgroup and moderator analyses within only low-grade inflammation markers. Study materials, including data and code, are available at https://osf.io/j8yh4/.

[2] Exceptions apply to funnel plot and PET/PEESE models, which conventionally do not include predictors, to retain their intended interpretations.

Results

Study Characteristics

Figure 1 presents details of the systematic literature search. Searches in Pubmed and APA PsycINFO and review of reference lists yielded 13,409 records. After removing duplicates and articles without relevant data, 286 remained for full-text evaluation, of which, 90 were subsequently excluded, leaving 196 studies that met inclusion criteria. However, seven studies did not have sufficient data to quantify an effect size after contacting corresponding authors to obtain more information, and 29 effect sizes emerged as outliers (two studies excluded as a result). Thus, the final number of associations included in analyses was 922, which emanated from 187 articles reporting on 168 unique samples involving 173,089 unique participants.

Characteristics of each study are described in the Appendix, and descriptive statistics for the literature as a whole are presented in Table 2. The most common form of childhood stress assessed was low SES, and the most common aspect of inflammation assessed was low-grade inflammation, and in particular CRP. Most studies used cross-sectional designs, in which retrospective reports of childhood stressors were linked to inflammation measurements collected in adulthood.

Preliminary Analyses

We first compared the magnitudes and variances of effect sizes from models that included bivariate (sample $n = 60$, effect size $n = 260$) versus partial (sample $n = 128$, effect size $n = 662$) correlations. Results revealed overlap in the 95% confidence intervals for

Figure 1
Flow Diagram of Literature Search Based on PRISMA Guidelines

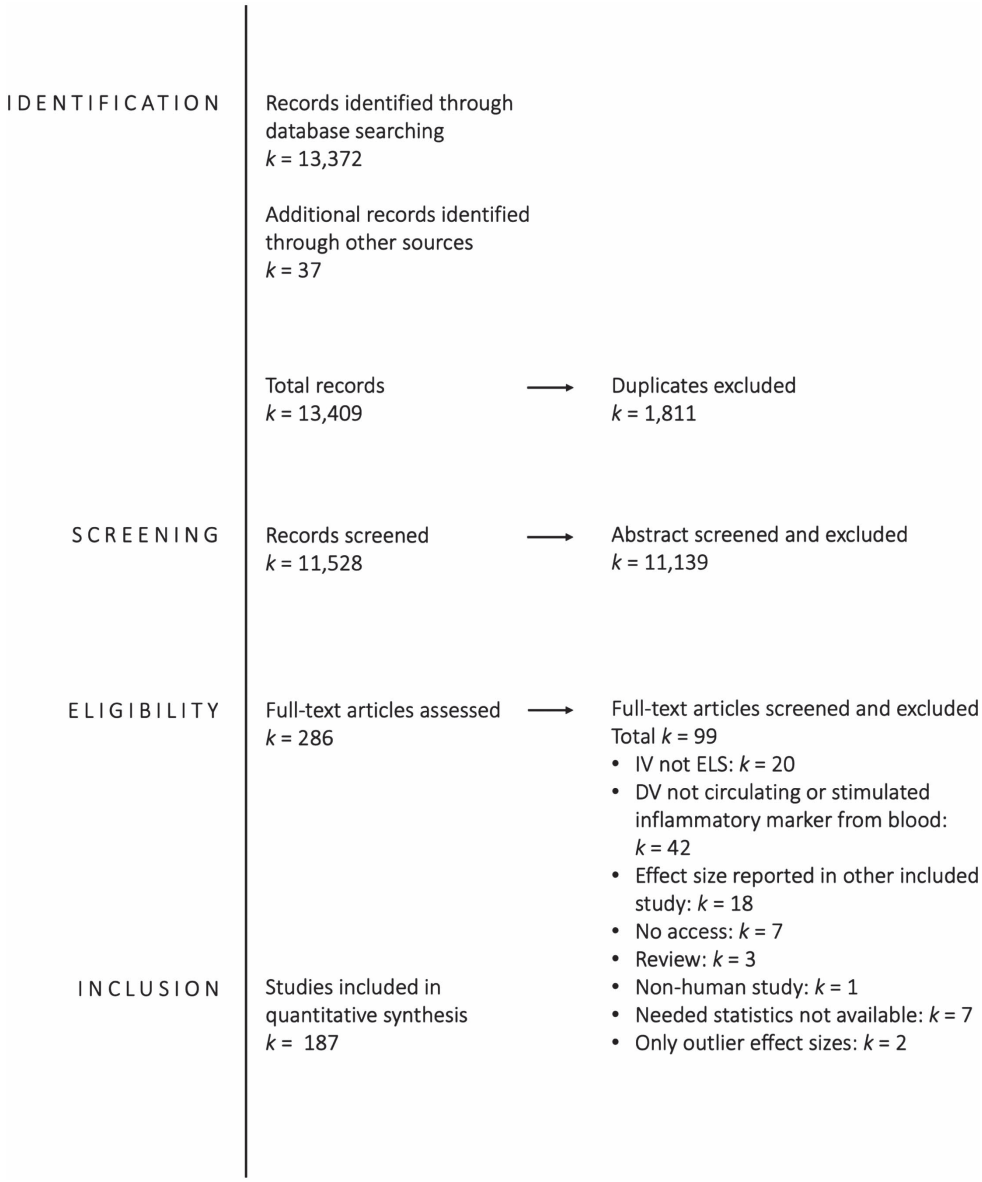


Table 2
Descriptive Statistics of Sample and Methodological Characteristics (Analytical N of Effect Sizes = 922)

Study characteristics	Frequency (%)
Type of childhood/adolescence stress	
Socioeconomic status	298 (32%)
Maltreatment	243 (26%)
Family or household stress	185 (20%)
Non-family interpersonal stress	26 (3%)
Cumulative adversity	170 (18%)
Component of inflammation measured	
Low-grade inflammation	673 (73%)
Cytokine response to microbial challenge	249 (27%)
Specific marker of inflammation measured	
CRP	273 (30%)
IL-6	208 (23%)
TNF-α, sTNFRI, sTNFαII	94 (10%)
IL-10	55 (6%)
IFN-α and IFN-γ	53 (6%)
Fibrinogen	43 (5%)
IL-1β, IL-1α, IL-1RA	32 (3%)
Other inflammatory markers	142 (15%)
Composites of multiple inflammatory markers	22 (2%)
Developmental stage at inflammation assessment	
Childhood (< 13 years old)	247 (27%)
Adolescence (13–19 years old)	266 (29%)
Adulthood (> 19 years old)	412 (45%)
Study design	
Cross-sectional	540 (58%)
Longitudinal	254 (27%)
Other	131 (14%)

Note. CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor alpha; sTNFRI = soluble receptor of tumor necrosis factor receptor Type I; sTNFαII = soluble receptor of tumor necrosis factor alpha Type II; IL-10 = interleukin-10; IFN-α = interferon alpha; IFN-γ = interferon gamma; IL-1β = interleukin-1 beta; IL-1α = interleukin-1 alpha; IL-1RA = interleukin-1 receptor antagonist. Examples of other inflammatory markers include interleukin-2 (IL-2), interleukin-8 (IL-8). Examples of other study design include inflammation assessed prior to childhood/adolescence stress assessment, and early adversity averaged across multiple time points and inflammation assessed at the last time point.

the overall effect sizes (bivariate model: $\hat{r} = .042$, $\hat{Z} = .042$, 95% CI_z [.020, .065] vs. partial model: $\hat{r} = .042$, $\hat{Z} = .042$, 95% CI_z [.032, .052]), for the within-sample variation at Level 2 (bivariate model: $\tau^2 = .000$, 95% CI [.000, .001] vs. partial model: $\tau^2 = .001$, 95% CI [.000, .001]), and for the between-sample variation at Level 3 (bivariate model: $\tau^2 = .005$, 95% CI [.003, .009] vs. partial model: $\tau^2 = .002$, 95% CI [.001, .003]). These findings are inconsistent with the hypothesis that bivariate effect sizes differed substantively from adjusted effect sizes.

We then pooled both types of effect sizes into a single model, and introduced moderator variables that reflected (a) whether each effect size was derived from a partial versus bivariate correlation and (b) the number of covariates (count or binned) included. Whether effect sizes were partial or bivariate did not moderate the overall effect size, $b = .005$, $SE = .007$, $p = .486$. Also, estimated values for bivariate $\hat{r} = .039$, $\hat{Z} = .039$, 95% CI_z [.026, .052] and partial $\hat{r} = .044$, $\hat{Z} = .044$, 95% CI_z [.034, .054] were similar. Neither the count of covariates, $b = .000$, $SE = .001$, $p = .745$, or binned count, $b = -.002$, $SE = .003$, $p = .588$, moderated the overall effect size.

Based on these patterns, our primary analyses pooled bivariate and partial effect sizes, but included a covariate reflecting this feature. We also conducted sensitivity analyses focusing exclusively on partial effect sizes and report results from additional models that adjust for the count of covariates in Supplemental Material (Table S2).

Primary Analyses

Overall Association Between Childhood Stress and Inflammation

As depicted in Figure 2 (Panels A and B for raw and predicted effect sizes), there was a small but reliable overall association between childhood stress and inflammation, $\hat{r} = .041$, $\hat{Z} = .041$, 95% CI_z [.032, .051], $p < .001$. This association accounted for study quality, $b = .000$, $SE = .002$, 95% CI [−.004, .004], $p = .954$, conversion confidence, $b = -.002$, $SE = .001$, 95% CI [−.005, .000], $p = .068$, and whether effect sizes were partial or bivariate, $b = -.005$, $SE = .007$, 95% CI [−.009, .018], $p = .486$. There was significant estimated heterogeneity in the association between childhood stress and inflammation both within samples, $\tau^2 = .0006$, 95% CI [.0004, .0009], and between samples, $\tau^2 = .002$, 95% CI [.0012, .0030]. In addition, total variance was distributed across the three levels such that 31% of total variance was attributed to sampling variances (at the individual level), 17% was attributed to within-sample variances in effect sizes (at the effect size level), and 53% was attributed to between-sample variances (at the sample level).

Sensitivity Analyses. We then tested whether the estimates were robust to influential cases, meta-analytic approach, and publication bias. Fifty-four (6% of included associations) studentized deleted residuals were identified as significantly large. However, under standard hypothesis-testing assumptions, approximately 5% of residuals would be expected to be significantly large by chance (Viechtbauer & Cheung, 2010). Nonetheless, we repeated the meta-analysis with influential cases removed, and found comparable results, $\hat{r} = .040$, $\hat{Z} = .040$, 95% CI_z [.032, .048]. The results were also similar when using robust variance estimation to account for dependencies in effect sizes within samples, $\hat{r} = .04$, $\hat{Z} = .04$, 95% CI_z [.024, .050]. For assessment of publication bias, the funnel plot is presented in Figure 2 (Panel C). Because PET indicated that sampling error was a significant predictor of effect size, $b = .44$, $SE = .11$, $p < .001$, we used PEESE to estimate overall effect size adjusting for publication bias and other small-study effects. This conservative estimate was similar in magnitude to what is reported above, $\hat{r} = .033$, $\hat{Z} = .033$, 95% CI_z [.022, .043], $p < .001$.

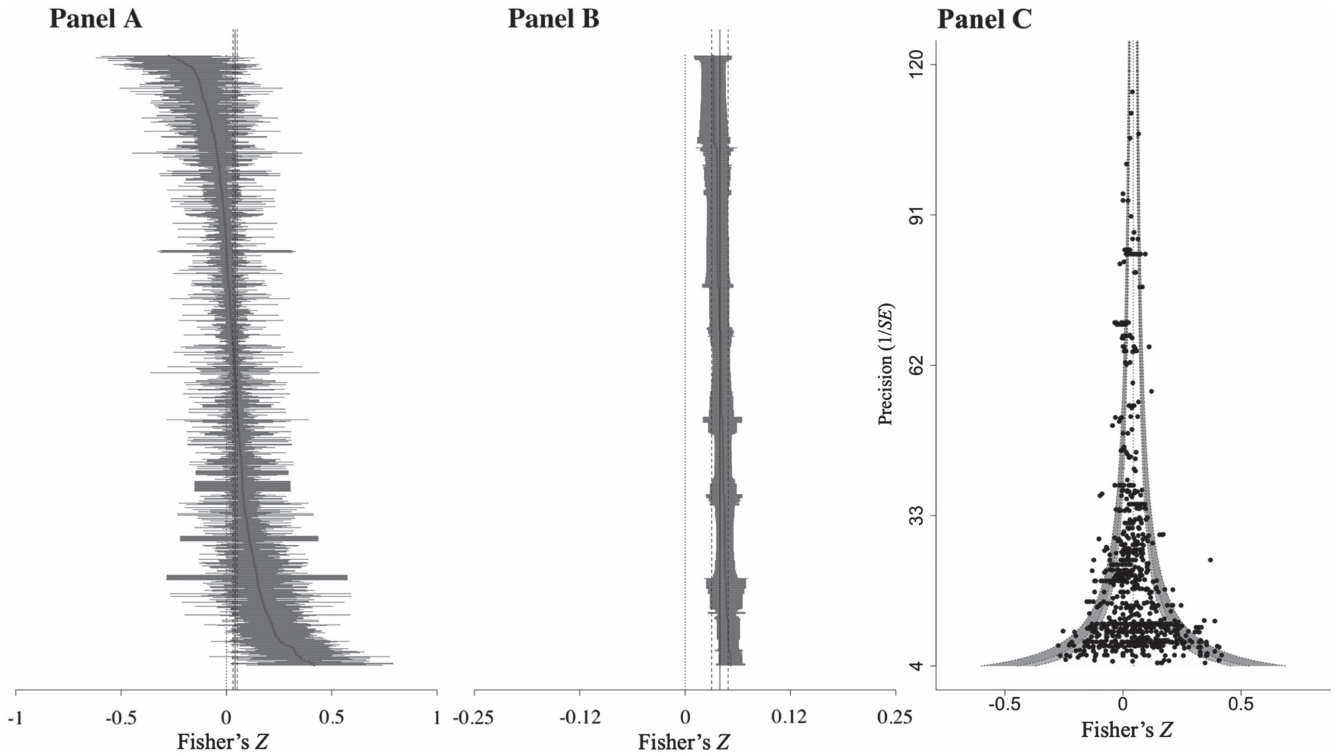
Lastly, we examined whether the observed associations actually reflected circumstances in adulthood. In moderation analyses, we found that the synthesized effect sizes of studies that did versus did not control for adulthood stress were not different, $b = -.009$, $SE = .007$, $p = .198$. In addition, subgroup analysis synthesizing effect sizes that adjusted for stress levels in adulthood revealed similar results, $\hat{r} = .042$, $\hat{Z} = .042$, 95% CI_z [.024 .060]. These results provide some support that the observed associations between childhood stress and inflammatory measures are not solely an artifact of exposure to stress later in the lifecourse.

Does the Strength of the Childhood Stress–Inflammation Association Change Over the Lifecourse?

Next, we tested whether the association between childhood stress and inflammation differed by developmental stage when

Figure 2

Caterpillar Plots of the 990 Original (Panel A) and Predicted (Panel B) Effect Sizes in Fisher's Z and Their 95% Confidence Intervals



Note. Predicted effect sizes in Panel B were adjusted for study quality, conversion confidence, and whether effect sizes were bivariate versus partial. The vertical solid lines indicate the synthesized effect size, the vertical dashed lines indicate their 95% confidence intervals, and the vertical dotted line is at 0. Panel C shows a funnel plot of effect sizes in Fisher's Z and the inverse of their corresponding standard errors.

inflammation was measured. As depicted in Figure 3, developmental stage was a significant moderator, $b = .017$, $SE = .005$, 95% CI [.007, .027], $p < .001$. Specifically, effect sizes were smallest when low-grade inflammation was assessed in childhood, $\hat{r} = .02$, $\hat{Z} = .02$, 95% CI_z [.003, .035], and progressively increased when measurements were collected in adolescence, $\hat{r} = .04$, $\hat{Z} = .04$, 95% CI_z [.026, .046], and adulthood, $\hat{r} = .05$, $\hat{Z} = .05$, 95% CI_z [.041, .066]. The pattern of moderation remained when bivariate effect sizes were excluded, $b = .013$, $SE = .006$, 95% CI [.002, .024], $p = .023$.

Sensitivity Analyses. Because 98% of the microbial challenge effect sizes (88% of microbial challenge studies) came from studies of children or adolescents, we next examined whether developmental stage remained a significant moderator among studies focusing on childhood stress and *low-grade inflammation.* Moderation patterns were also evident in this smaller pool of effect sizes, $b = .017$, $SE = .005$, 95% CI [.007, .028], $p = .002$.

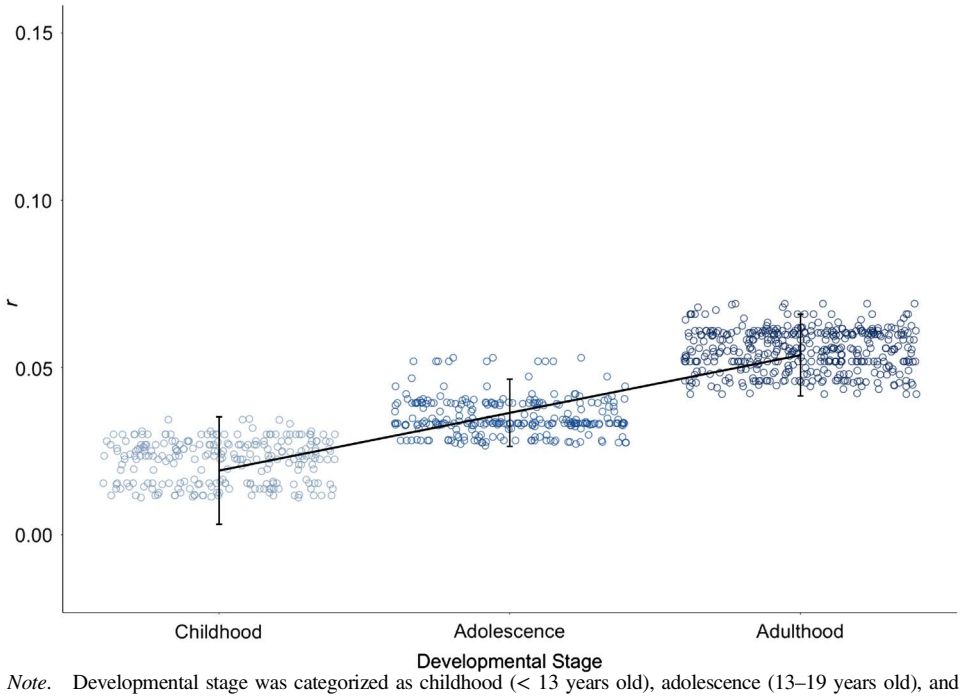
We could not perform a stand-alone moderation analysis of studies that measured *cytokine responses to microbial challenge*, as there was insufficient variability in developmental stage (i.e., the vast majority of studies were of youth, as noted above). We also could not examine whether microbial challenge effect sizes varied between children and adolescents because there were too few studies in each developmental stage ($k = 6$ and $k = 9$, respectively).

Given that studies of adults largely relied on retrospective reports of adversity (85%) whereas studies of children and adolescents generally had concurrent reports (88%), and that reporting approach may affect the magnitude of the link between childhood stress and health (Reuben et al., 2016), we considered the possibility that the moderation by developmental stage was an artifact of these study design features. Specifically, we conducted sensitivity analyses with a covariate that coded for use of concurrent reports and longitudinal designs ($k = 31$) versus use of retrospective reports and cross-sectional designs ($k = 73$). Results indicated a significant moderation, $b = .02$, $SE = .009$, $p = .048$, such that studies using concurrent reports and longitudinal designs yielded larger effect sizes ($\hat{r} = .05$, 95% CI [.03, .07]), relative to those using retrospective reports and cross-sectional designs ($\hat{r} = .03$, 95% CI [.02, .05]). However, independent of this effect, the moderation by developmental stage remained significant, $b = .03$, $SE = .009$, $p < .001$. The same pattern of developmental stage moderation was evident in a more stringent analysis that was restricted to the subgroup of studies that utilized concurrent reports and longitudinal designs, $b = .02$, $SE = .006$, $p = .011$. These findings indicate that the moderation by developmental stage was not simply a reflection of methodological differences between studies that focused on youth relative to those that focused on adults.

As developmental stage categories were based on sample *mean* age, the age ranges of samples sometimes fell outside the boundaries of the developmental category to which the study was assigned. Thus, in further sensitivity analyses, we excluded samples with

Figure 3

The Link Between Childhood/Adolescent Stress and Low-Grade Inflammation Moderated by Developmental Stage at Which Inflammation Was Assessed



Note. Developmental stage was categorized as childhood (< 13 years old), adolescence (13–19 years old), and adulthood (> 19 years old). Bars indicate 95% confidence intervals and points indicate predicted correlations (*r*), adjusted for study quality, conversion confidence, and whether effect sizes were bivariate or partial correlations. Analyses were performed in Fisher's *Z* units, but the presented effect sizes and their confidence intervals were transformed back into correlation coefficients for interpretation. See the online article for the color version of this figure.

unknown age ranges or age ranges spanning more than one developmental stage ($k = 109$). Again, the moderation effect by developmental stage remained significant, $b = .02$, $SE = .007$, $p = .013$. Finally, because age cutoffs for defining developmental stages vary across fields and perspectives, we repeated analyses using other categorization thresholds, several of which involved even more fine-grained categorizations of developmental stages. As summarized in Table 3 and S3 (in Supplemental Material), the moderation effects by developmental stage remained significant regardless of which thresholds and combinations of thresholds were applied.

Are Different Types of Childhood Stressors Differentiallyy Associated With Inflammation?

We then tested whether the association between childhood stress and inflammation differed by the type of childhood stressor, namely maltreatment, socioeconomic disadvantage, other interpersonal stress, and cumulative adversity, with maltreatment coded as the reference group. As depicted in Figure 4, all associations were significant, and the magnitude of each association did not differ when the effect size for maltreatment was used as the referent (socioeconomic disadvantage: $b = .001$, $SE = .007$, $p = .946$; other interpersonal stress: $b = -.009$, $SE = .007$, $p = .242$; cumulative adversity: $b = .004$, $SE = .008$, $p = .609$). Patterns were similar when bivariate effect sizes were excluded (socioeconomic disadvantage, $b = .005$, $SE = .007$, $p = .449$, other interpersonal stress, $b = -.004$, $SE = .007$, $p = .613$, cumulative adversity, $b = .013$, $SE = .008$, $p = .110$).

Next, we tested whether the association between socioeconomic disadvantage and maltreatment and inflammation differed according to their respective subtypes. As depicted in Figure 4, there was no moderation by dimension of socioeconomic disadvantage when comparing resources—and prestige-based measures, $b = .013$, $SE = .008$, $p = .103$. There also was no evidence of moderation by maltreatment subtype (Figure 4) when contrasting neglect (reference) versus abuse ($b = .000$, $SE = .008$, $p = .963$) or physical (reference) versus emotional ($b = .002$, $SE = .008$, $p = .824$) and sexual ($b = .010$, $SE = .008$, $p = .206$).

Which Components of Inflammation Are Associated With Childhood Stress?

We then examined whether associations varied by the aspect of inflammation assessed, namely low-grade inflammation versus cytokine response to microbial challenge. There was no evidence of significant moderation, $b = -.005$, $SE = .014$, $p = .738$, even after bivariate effect sizes were excluded, $b = .007$, $SE = .016$, $p = .658$. These patterns suggest that childhood stress has associations of similar magnitude with these two aspects of inflammation.

There was also no significant moderation by the specific low-grade inflammatory marker assessed. Using CRP as the referent, other markers of low-grade inflammation had associations with childhood stress of similar magnitude (IL-6, TNF family, IFN family, IL-1 family, IL-10, and fibrinogen; $ps > .068$). We could not conduct moderation analyses by specific cytokine in studies of

Table 3
Moderation by Recoded Developmental Stage at Inflammation Assessment

Theoretical basis	Developmental stage categorizing	Low-grade inflammation	Both components of inflammation
Recoding childhood			
Repetti et al. (2011)	Early childhood: <6 years old	$\hat{r}$ = .01 [−.01, .04]	$\hat{r}$ = .01 [−.01, .04]
	Mid and late childhood: 6–12 years old	$\hat{r}$ = .03 [.01, .04]*	$\hat{r}$ = .03 [.01, .04]*
	Adolescence: 13–19 years old	$\hat{r}$ = .04 [.03, .05]*	$\hat{r}$ = .04 [.03, .05]*
	Adulthood: >19 years old	$\hat{r}$ = .05 [.04, .06]*	$\hat{r}$ = .05 [.04, .06]*
	Linear moderation:	*b* = .013, *SE* = .004*	*b* = .013, *SE* = .004*
Healthy People (2020)	Early childhood: <9 years old	$\hat{r}$ = .02 [−.005, .04]	$\hat{r}$ = .01 [−.004, .03]
	Mid and late childhood: 9–12 years old	$\hat{r}$ = .03 [.01, .04]*	$\hat{r}$ = .03 [.01, .04]*
	Adolescence: 13–19 years old	$\hat{r}$ = .04 [.03, .05]*	$\hat{r}$ = .04 [.03, .05]*
	Adulthood: >19 years old	$\hat{r}$ = .05 [.04, .06]*	$\hat{r}$ = .05 [.04, .06]*
	Linear moderation:	*b* = .012, *SE* = .004*	*b* = .013, *SE* = .004*
Recoding adolescence			
WHO (2021)	Childhood: <10 years old	$\hat{r}$ = .01 [−.005, .03]	$\hat{r}$ = .01 [−.003, .03]
	Adolescence: 10–19 years old	$\hat{r}$ = .03 [.02, .04]*	$\hat{r}$ = .03 [.02, .04]*
	Adulthood: >19 years old	$\hat{r}$ = .05 [.04, .07]*	$\hat{r}$ = .05 [.04, .07]*
	Linear moderation:	*b* = .020, *SE* = .006*	*b* = .020, *SE* = .005*
Sawyer et al. (2018)	Childhood: <10 years old	$\hat{r}$ = .01 [−.01, .03]	$\hat{r}$ = .01 [−.004, .03]
	Adolescence: 10–24 years old	$\hat{r}$ = .03 [.02, .04]*	$\hat{r}$ = .03 [.02, .04]*
	Adulthood: ≥25 years old	$\hat{r}$ = .06 [.04, .07]*	$\hat{r}$ = .06 [.04, .07]*
	Linear moderation:	*b* = .022, *SE* = .006*	*b* = .022, *SE* = .005*
Recoding adulthood			
Arnett et al. (2014)	Childhood: <13 years old	$\hat{r}$ = .02 [.01, .04]*	$\hat{r}$ = .02 [.01, .04]*
	Adolescence: 13–19 years old	$\hat{r}$ = .03 [.02, .05]*	$\hat{r}$ = .03 [.02, .04]*
	Early adulthood: 20–29 years old	$\hat{r}$ = .04 [.03, .05]*	$\hat{r}$ = .04 [.03, .05]*
	Mid and late adulthood: ≥30 years old	$\hat{r}$ = .05 [.04, .07]*	$\hat{r}$ = .05 [.04, .07]*
	Linear moderation:	*b* = .01, *SE* = .004*	*b* = .01, *SE* = .004*

Note. WHO = World Health Organization. Estimated partial correlations ($\hat{r}$) and 95% confidence intervals in brackets at each level of recoded developmental stage. Analyses were performed in Fisher's *Z* units, but the results (predicted effect sizes and their confidence intervals) were transformed back to correlation coefficients for presentation. Additional moderation analyses using combinations of recoded developmental stages (e.g., Repetti and colleagues' definition of childhood + WHO's definition of adolescence) are presented in Supplemental Material Table S3.
* $p < .05$.

microbial stimulation because there were too few samples ($k = 16$) relative to the number of cytokines assessed ($n = 12$).

Additional Moderation and Subgroup Analyses

Moderation by Other Methodological and Sample Characteristics

Exploratory analyses tested additional moderators. There was no evidence for moderation by proportion of female, $b = .000$, $SE = .000$, $p = .052$, or non-White participants, $b = .000$, $SE = .000$, $p = .941$, or by study design (cross-sectional vs. longitudinal), $b = .001$, $SE = .007$, $p = .894$.

However, as depicted in Figure 5, there was a significant moderation by sample mean BMI, $b = .004$, $SE = .002$, 95% CI [.001, .007], $p = .024$, $k = 89$, $n = 415$. Specifically, the link between childhood stress and inflammation was stronger for samples with higher mean BMI (1 *SD* above mean), $\hat{r} = .04$, $\hat{Z} = .04$, 95% CI_z [.017, .053], relative to samples with lower mean BMI (1 *SD* below mean), $\hat{r} = .06$, $\hat{Z} = .06$, 95% CI_z [.043, .079].

As depicted in Figure 6, a significant moderation by publication year also emerged, $b = -.003$, $SE = .001$, $p < .001$, such that the strength of the link between childhood stress and inflammation decreased as publication year increased from 2011 (−1 *SD* of mean), $\hat{r} = .05$, $\hat{Z} = .05$, 95% CI_z [.042, .064], to 2019 (+1 *SD* of mean), $\hat{r} = .03$, $\hat{Z} = .03$, 95% CI_z [.018, .041].

Independent Moderations by Methodological and Sample Characteristics

Controlling for type of stress, component of inflammation, type of marker, study design, proportion of female participants, study quality, conversion confidence, and whether effect sizes were unadjusted or adjusted for confounds, developmental stage at which inflammation was assessed ($b = .03$, $SE = .008$, $p = .001$), year of publication ($b = -.003$, $SE = .001$, $p < .001$), and whether stressor was reported concurrently or retrospectively ($b = .03$, $SE = .012$, $p = .020$), remained significant independent moderators.

Subgroup Analyses

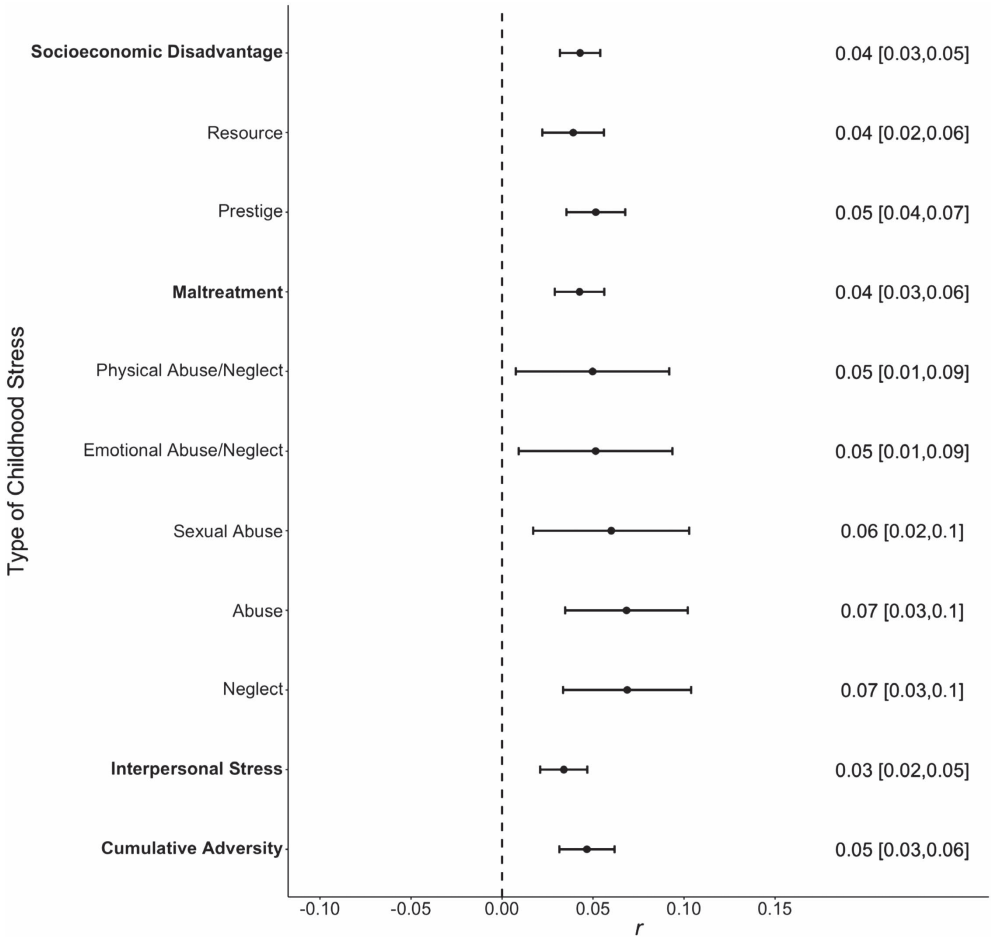
Table 4 presents synthesized effect sizes that are stratified by characteristics of conceptual interest. We emphasize that these effect sizes are presented for descriptive purposes only. The moderator analyses reported above are the appropriate tests of whether moderators played a role in strength of the association between childhood stress and inflammatory outcomes in a statistically significant manner.

Discussion

Seeking to identify the mechanisms that connect early adversity with subsequent health, hundreds of studies have examined the relationship between childhood stress and inflammatory activity

Figure 4

A Forest Plot of Predicted Correlations (r) and 95% Confidence Intervals by Each Type and Subtype of Stress

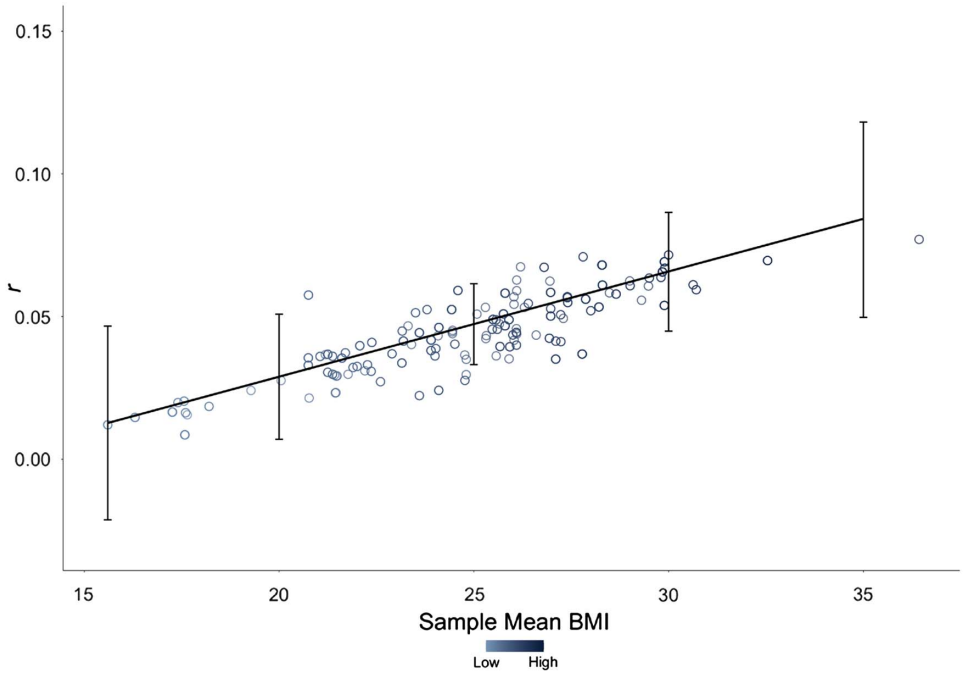


Note. Types of stressor are boldfaced. Analyses were performed in Fisher's *Z* units, but the presented effect sizes and their confidence intervals were transformed back into correlation coefficients for interpretation. Estimates are adjusted for study quality, conversion confidence, and whether effect sizes were bivariate or partial correlations.

over the last 2 decades. The current meta-analysis synthesized findings from over 170,000 individuals across 168 unique samples spanning various types of childhood stress, developmental stages across the lifespan, and components and markers of inflammation. As such, it represents the most comprehensive quantitative review to date of this literature, which not only increases generalizability of results, but also allows the opportunity to meaningfully test moderator hypotheses by leveraging variability in key sample characteristics. Across studies, the majority of which adjusted for potential confounds, we found that childhood stress was associated with higher inflammation. This pattern was observed across and within each developmental stage, but notably, the strength of the childhood stress–inflammation association increased across the lifecourse. The association was also evident across stressor types, with no evidence that the magnitude of the association differed by type of stressor. Lastly, the association was evident for both circulating biomarkers of low-grade inflammation and indicators of leukocyte cytokine production following microbial challenge, though it did not vary by these components of inflammation. Additional moderator analyses indicated that the magnitude of the stress–inflammation association was larger in samples with higher BMI and decreased with publication year. Primary findings support a central premise of multiple theories that highlight inflammation as a common mechanistic pathway through which childhood stress increases vulnerability to mental (e.g., depression, bipolar disorder, substance abuse) and physical (e.g., CVD, some cancers, autoimmune disease) health problems across the lifecourse (Danese & Baldwin, 2017; Danese & McEwen, 2012; Fagundes et al., 2013; Miller et al., 2011; Nusslock & Miller, 2016; Repetti et al., 2011; Taylor et al.,

Figure 5

The Association Between Childhood/Adolescent Stress and Inflammation Moderated by Sample Mean BMI



Note. BMI = body mass index. The solid line indicates the meta-regression slope and vertical bars indicate 95% confidence intervals. Points are predicted correlations (*r*) adjusted for study quality, conversion confidence, and whether effect sizes were bivariate or partial correlations. Analyses were performed in Fisher's *Z* units, but the presented effect sizes and their confidence intervals were transformed back into correlation coefficients for interpretation. When the highest sample mean BMI (36.4; 3.4 *SD* above the mean) was removed, the moderation effect remained significant. See the online article for the color version of this figure.

2011). The current findings build on past theories by highlighting that the association changes across the lifespan.

Effect Size

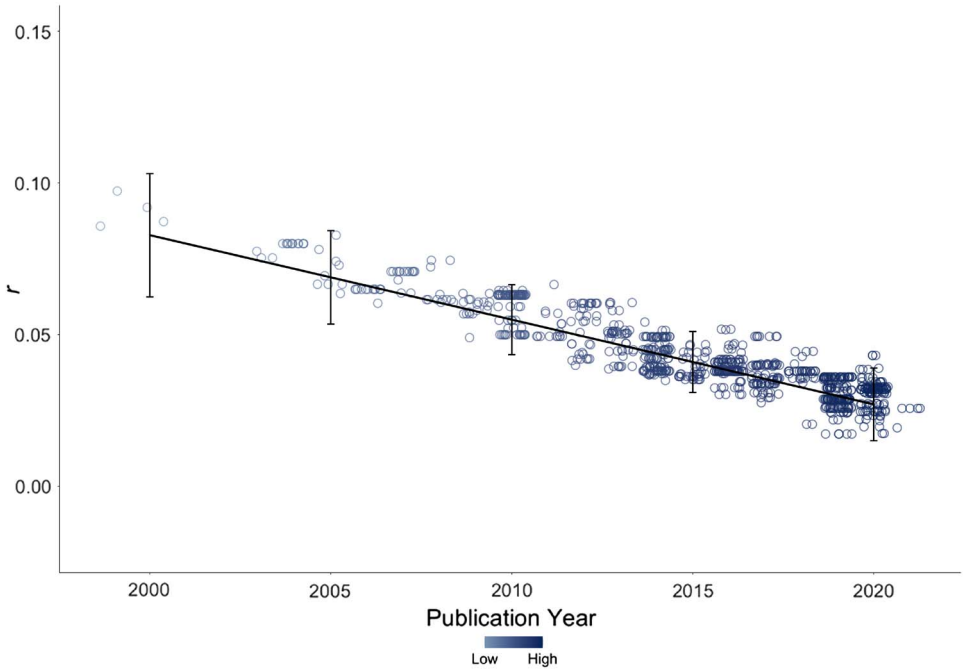
The overall effect size observed between childhood stress and inflammation was .04 and ranged from .03 to .09 in subgroup analyses. These effect sizes are considered by convention to be small (Ferguson, 2009). However, it may be more meaningful to interpret effect sizes by comparing them to other well-understood associations and by considering their practical consequences rather than by measuring them against conventional thresholds (Funder & Ozer, 2019). Indeed, in clinical medicine and public health, it is not uncommon to base treatment decisions on effect sizes that conventionally would be viewed as "small." Aspirin, for instance, is commonly used to reduce the risk for heart attacks and is based on a correlation of .034 (Steering Committee of the Physicians' Health Study Research Group, 1988). Similarly, many dietary interventions emphasize importance of increasing fruit and vegetable consumption, but the benefit for weight loss and abdominal obesity of doing so amounts to an effect size of −.05 (Schwingshackl et al., 2015).[3] The effect sizes we observed in the present meta-analysis are comparable to these benchmarks.

To understand the meaning of effect sizes, it is also useful to consider the context where the phenomenon of interest has bearing. In the U.S., a substantial proportion of youth are exposed to adversity—for instance, 14.4% youth are estimated to live in poverty (Semega et al., 2019), and nearly 26% of youth have reported maltreatment by a caregiver (Finkelhor et al., 2015). Adversities also tend to co-occur (e.g., Kim & Drake, 2018), and multiple adversities may have compounding effects. In addition to relatively high rates of exposure to adversity, people's immune systems repeatedly encounter microbial and sterile threats that elicit an inflammatory response, and each such response involves multiple different cytokines. Thus, even if childhood stress only has a small effect on inflammation, when this is aggregated across multiple stressors, microbial and sterile threats, and cytokines over a lifetime, the cumulative impact on inflammatory burden could plausibly be substantial. How to quantify the magnitude of this burden, and the extent of its clinical relevance, is a crucial topic for future research.

[3] The reported synthesized odds ratios were converted into Cohen's *d*s, which were then converted into correlation coefficients.

Figure 6

The Association Between Childhood/Adolescent Stress and Inflammation Moderated by Publication Year



Note. The solid line indicates the meta-regression slope and vertical bars indicate 95% confidence intervals. Points are predicted correlations (*r*) adjusted for study quality, conversion confidence, and whether effect sizes were bivariate or partial correlations. Analyses were performed in Fisher's *Z* units, but the presented effect sizes and their confidence intervals were transformed back into correlation coefficients for interpretation. See the online article for the color version of this figure.

Correlation or Causation?

Because of apparent ethical reasons (i.e., cannot randomly assign children to chronically stressful conditions), the studies that comprise this literature predominantly have observational designs. This raises questions about causal inference, specifically about the potential for reverse directionality, selection effects, and residual confounding. Without access to experimental methods, these alternative explanations are challenging to evaluate. However, a handful of studies have applied creative and rigorous designs in attempts to do so. For example, several groups have used discordant-twin designs to minimize heritable genetic influences. These studies have found that even among twin pairs, childhood exposure to bullying, maltreatment, and other adversities is related to higher inflammation (Baldwin et al., 2018; Rooks et al., 2012). There are also legitimate concerns about non-genetic confounds—for instance, environmental pollutants and birth complications occur at higher rates in low-SES contexts and can upregulate inflammation. To address these concerns, some teams have used within-subject designs with multiple waves of assessment, which eliminate the influence of between-person confounds. These studies have generally found that inflammatory activity is higher during certain stressful periods compared to nonstressful periods (Chiang, Park, et al., 2019; Murphy et al., 2013, 2015). Intervention studies also provide a means for getting at causality, in that they presumptively ameliorate the impact of stress. At least one past study found that low-SES youth randomly assigned to a family-oriented intervention had lower inflammation relative to controls 8 years later (Miller et al., 2014). This study had a key weakness—it was not designed to assess health outcomes, so did not have pretreatment measures of inflammation—but its results suggest the possibility of causal effects. Finally, studies in animals can experimentally manipulate early-life conditions and provide an (imperfect) analogue for human experience. These experiments consistently show that maternal separation and adolescent stress increases inflammation in the brain and lungs, and upregulates cytokine responses to challenges in adulthood (Avitsur et al., 2006; Kruschinski et al., 2008; Pyter et al., 2013; Roque et al., 2016; Shtoots et al., 2018; Wang et al., 2018). Although these studies are not proof of a causal effect in humans, they collectively provide a reasonable basis for inferring that childhood stress can, in principle, causally increase inflammatory activity.

Developmental Stage

The meta-analysis found that effect sizes varied by developmental stage at which inflammation was assessed, with the magnitude increasing linearly from childhood to adolescence to adulthood. This pattern is consistent with recent findings that socioeconomic disparities in inflammation widen across the lifespan (Lam et al.,

Table 4
Subgroup Analyses by Sample and Methodological Characteristics

Sample and methodological characteristics	Number of samples, number of effect sizes	Synthesized effect size in *r*, 95% CI [lower, upper]	
		Multilevel model	Robust variance estimation
Type of childhood/adolescence stress			
Socioeconomic status	$k = 87$, $es = 298$	.040 [.028, .052]*	.037 [.020, .053]*
Resources (e.g., income)	$k = 47$, $es = 107$	.049 [.029, .069]*	.050 [.033, .067]*
Prestige (e.g., education)	$k = 40$, $es = 118$	.043 [.023, .063]*	.036 [.003, .068]*
Maltreatment	$k = 56$, $es = 243$	.067 [.044, .090]*	.063 [.033, .093]*
Physical abuse/neglect	$k = 24$, $es = 88$	.056 [.018, .092]*	.071 [.000, .141]†
Emotional abuse/neglect	$k = 21$, $es = 89$	.069 [.002, .133]*	.081 [−.018, .179]†
Sexual abuse	$k = 20$, $es = 56$	.026 [−.018, .070]	.030 [−.006, .064]†
Abuse	$k = 33$, $es = 180$	.074 [.036, .112]*	.087 [.027, .146]*
Neglect	$k = 20$, $es = 85$	.054 [.027, .080]*	.050 [.015, .084]*
Interpersonal stress	$k = 44$, es=211	.051 [.026, .076]*	.042 [.011, .073]*
Cumulative adversity	$k = 30$, $es = 170$	.029 [.004, .055]*	.023 [−.000, .047]†
Developmental stage at inflammation assessment			
Childhood (< 13 years old)	$k = 46$, $es = 247$	.030 [.011, .049]*	.001 [−.031, .033]
Adolescence (13–19 years old)	$k = 40$, $es = 266$	.032 [.013, .051]*	.038 [.014, .061]*
Adulthood (> 19 years old)	$k = 88$, $es = 412$	.055 [.041, .069]*	.050 [.034, .065]*
Component of inflammation measured			
Low-grade inflammation	$k = 159$, $es = 673$	.042 [.032, .053]*	.037 [.023, .051]*
CRP	$k = 116$, $es = 273$	.038 [.026, .050]*	.024 [.007, .043]*
IL-6	$k = 73$, $es = 174$	.059 [.040, .077]*	.059 [.038, .080]*
TNF-α, sTNFRI, sTNFαII	$k = 36$, $es = 67$	.026 [.004, .049]*	.040 [.009, .071]*
Fibrinogen	$k = 15$, $es = 43$	.045 [.012, .078]*	n/a
IL-1β, IL-1α, IL-1RA	$k = 16$, $es = 20$	.049 [−.014, .112]	.060 [−.017, .130]
IL-10	$k = 14$, $es = 26$	.077 [.026, .126]*	.100 [.012, .185]*
Cytokine response to microbial challenge	$k = 16$, $es = 249$	.050 [.009, .090]*	.045 [−.023, .114]
Design, study quality, and conversion confidence			
Cross-sectional	$k = 129$, $es = 539$	.045 [.032, .058]*	.041 [.024, .059]*
Longitudinal	$k = 40$, $es = 252$	.028 [.015, .041]*	.030 [.016, .043]*
Higher quality estimates: study quality score > 6 and conversion confidence score > 4.5	$k = 94$, $es = 551$	.047 [.033, .061]*	.046 [.030, .061]*

Note. k = number of samples; es = number of effect sizes; CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor alpha; sTNFRI = soluble receptor of tumor necrosis factor receptor Type I; sTNFαII = soluble receptor of tumor necrosis factor alpha Type II; IL-1β = interleukin-1 beta; IL-1α = interleukin-1 alpha; IL-1RA = interleukin-1 receptor antagonist; IL-10 = interleukin-10. Analyses were performed in Fisher's Z units, but the results (synthesized effect sizes and their confidence intervals) were transformed back to correlation coefficients for presentation. Synthesized effect sizes based on subgroup analyses are for descriptive purposes only and are different from the predicted effect sizes reported in main text, which were based on moderation analyses. Inferences about differences in effect size magnitude by sample or methodological characteristics should only be made based on results from moderation analyses. Subgroup analyses for composites of multiple inflammatory markers and the IFN family were omitted because there were too few samples (both k's = 9). Because there were too few samples that assessed nonfamily interpersonal stress ($k = 13$), these were combined with family and household stress to represent the broader construct of interpersonal stress. Study quality score could range from 1 to 11 and conversion confidence score could range from 1 to 8. All models adjusted for study quality, conversion confidence, and effect-coded bivariate versus partial effect size (except for models examining study quality score > 6 and conversion confidence score > 4.5, which only adjusted for bivariate vs. partial effect size). Small-sample adjustment applied to robust variance estimation models when sample size was less than 50, and results were deemed unreliable and excluded when the Satterthwaite degrees of freedom were below 4 (labeled n/a). Additional subgroup analyses are presented in Supplemental Material (Table S4).
† $p < .10$. * $p < .05$.

2021). One potential explanation for such variation by developmental stage can be drawn from lifecourse and allostatic load models (e.g., Danese & McEwen, 2012; Miller et al., 2011). Inherent in and central to these models is the notion that time is necessary for the various psychosocial, behavioral, and hormonal sequelae of stress to manifest in states like low-grade chronic inflammation. For instance, childhood stress can increase exposure and sensitivity to a variety of subsequent stressors, such as social conflct, throughout the lifespan (Chiang, Taylor, & Bower, 2015; Fagundes & Way, 2014; Miller et al., 2011; Repetti et al., 2002; Stroud et al., 2020). In turn, repeated exposure to abrasive interactions and other stressors, as well as greater reactivity to them, accumulate and cumulatively affect autonomic and hormonal signaling to immune cells in ways that promote inflammatory activity (Irwin & Cole, 2011; McEwen, 1998; Miller et al., 2011). Thus, the association between childhood stress and heightened inflammation may become more stable and more apparent in later stages of the lifespan when alterations in relevant psychosocial, behavioral, and hormonal factors become more firmly established. Consistent with this proposition, one study demonstrated that the magnitude of the indirect effect from socioeconomic disadvantage on inflammation via adiposity strengthened across the lifecourse (Lam et al., 2021).

The developmental variations in effect size could also reflect normative age-related declines in biological processes that regulate inflammation. For instance, aging is associated with a progressive loss of telomeres, sequences of deoxyribonucleic acid (DNA) that cap chromosome ends and help ensure chromosomal stability (Blackburn, 1991). When cells divide, telomere sequences are not fully replicated, and when they eventually reach a certain threshold, the cell becomes senescent. Senescent cells are unable

to proliferate but are resistant to apoptosis (cell death), and importantly, they secrete pro-inflammatory cytokines (Ferrucci & Fabbri, 2018; Zhang et al., 2016). Telomere attrition and cell senescence are thought to be hallmarks of aging and key mechanisms underlying normative age-related increases in inflammation (Ferrucci & Fabbri, 2018; López-Otín et al., 2013; Zhu et al., 2019). Beyond telomere shortening, aging is also associated with greater mitochondria dysfunction and epigenetic alterations (López-Otín et al., 2013; Zhu et al., 2019), both of which can lead to cellular senescence and increases in inflammation (Ray & Yung, 2018; Sun et al., 2016). As such, across the lifespan, these age-related declines in regulatory capacity may amplify the pro-inflammatory tendencies of immune cells that have been initially shaped by childhood stress.

Although the pattern of findings observed suggests that the association between childhood stress and inflammation strengthens across the lifecourse, it is important to note that these results were derived from between-study comparisons. Additionally, the majority of studies relied on retrospective reports in adulthood; a much smaller proportion of studies assessed stress more proximal to actual exposure during childhood and/or adolescence. Recent work has highlighted the modest correlation between these two kinds of reports, and their differential associations with health outcomes (Baldwin et al., 2019; Reuben et al., 2016), raising the question of whether the developmental stage findings simply reflect differences in reporting approach between studies focusing on youth and adults. However, consistent with primary research (Danese, 2020; Reuben et al., 2016), sensitivity analyses suggested that studies with more rigorous designs, characterized by use of prospective designs and concurrent reports of childhood stress, had *larger* effect sizes than studies that utilized cross-sectional designs and retrospective reports. In light of the fact that most *adult* studies utilized retrospective reports and that current and prior findings suggest that retrospective reports should yield smaller effect sizes, that effect sizes *increased* from childhood to adulthood is likely not driven by differences in reporting approaches.

Nonetheless, to rigorously test changes across the lifecourse, we need multiwave studies with repeated assessments of childhood stress and inflammatory activity across stages of development. Only a small handful of studies have used utilized such designs (e.g., Copeland et al., 2014; Slopen et al., 2013) and they did not test for the age-related interaction that we hypothesized here. Doing so will be an important priority for subsequent research, especially in designs that measure adversity proximal in time to exposure, and consider psychosocial, behavioral, and hormonal pathways that may accentuate the impact of childhood stress. Such designs would facilitate mapping of trajectories over time in these factors, which could help answer mechanistic questions. For instance, what trajectory patterns do psychosocial, behavioral, or hormonal factors follow in normative development, and how does childhood stress modulate these trajectories? Do stress-related alterations in these trajectories in turn explain the strengthening association between childhood stress and inflammation across the lifecourse?

Type of Childhood Stress

We found no evidence to indicate the association between childhood stress and inflammation differs by adversity type or subtype. This finding could reflect methodological limitations of the primary literature—that is, adversities often co-occur in the same individuals (Kim & Drake, 2018; Lauritsen & Rezey, 2018), making it very challenging to isolate effects that are specific to certain types of stressors and to test whether dimensions of experience, such as threat versus deprivation or harshness versus unpredictability, have unique associations on development (Belsky et al., 2012; Ellis & Boyce, 2011; McLaughlin et al., 2014). These observations might lead some to conclude that our findings constitute a false negative because the primary literature does not differentiate exposures adequately to evaluate hypotheses about specificity or dimensionality.

It is, however, also plausible that the current findings are accurate reflections of how the innate immune system responds to childhood stressors. Indeed, there is considerable disagreement about the basic plausibility of specificity and dimensionality hypotheses, as well as the methodological feasibility of teasing apart the consequences of stressors that frequently co-occur (Smith & Pollak, 2020). This is not the context to wade into that debate. However, it is important to highlight that even if specificity or dimensionality exists in how the brain responds to different forms of childhood adversity, the immune system (and the downstream health problems it mediates) may not necessarily follow the brain's pattern of differential responses. Although certain brain regions and circuits can modulate the way cells of the innate immune system function (Dantzer, 2018; Irwin & Cole, 2011; Schiller et al., 2021; Sternberg, 2006), those cells are also regulated by numerous other local, regional, and systemic signals, which may plausibly wash out any specificity effects.

Definitively resolving this issue will be difficult in human studies; this may be a problem that is better suited for animal models, where random assignment to distinct stressors, and combinations of stressors, is feasible. However, future human studies can make methodological improvements to help clarify the situation, such as measuring exposures to a wide array of childhood adversities, attempting to isolate their consequences through design and statistical controls, examining experiences along dimensions theorized as determinants of stressor impact (e.g., threat, unpredictability), and testing for interactive or indirect effects among stressors.

Components of Inflammation

Results of the meta-analysis indicated that childhood stress has comparably sized associations with two different components of inflammation: chronic low-grade inflammation and cytokine responses to microbial threat. These findings help clarify some of the ambiguity in the literature about what inflammation measures reflect. As explained in the Introduction, multiple bodily tissues release inflammatory cytokines, so it is plausible that previous findings actually reflected the activity of fat, lung, and/or bone cells. The significant effect size for microbial threat studies directly implicates immune system cells in this phenomenon. It also provides insights about how childhood stressors may engender low-grade inflammation—by increasing monocyte cytokine responses to threats (Miller et al., 2011). This proposition suggests a specific temporal ordering, where childhood stress initially accentuates cytokine responses to threat, which subsequently engenders low-grade inflammation through an accumulation process. Adversity, then, may have stronger associations with cytokine responses to microbial challenge compared to low-grade inflammation early in life compared to later in life. Unfortunately, we could not test these hypotheses here because there were fewer studies assessing cytokine responses to microbial threat ($k = 16$) relative to biomarkers of

low-grade inflammation ($k = 158$), and most studies probing cytokine responses were conducted in youth (88% of microbial challenge studies; 98% of microbial challenge effect sizes). Thus, to examine the temporal ordering hypothesis, future studies will have to measure both cytokine responses to microbial threat and markers of low-grade inflammation across a broader age range. They will also have to measure sensitivity to inhibition, another key feature of inflammatory processes that was too infrequently assessed in the literature to be considered here.

There was also little evidence to suggest that the link between childhood stress and low-grade inflammation varied by specific inflammatory marker, particularly when comparing CRP to IL-6, IL-10, IL-1, TNF, and IFN families of cytokines. Overall, these findings may suggest that childhood stress has a general effect on chronic inflammatory processes irrespective of the specific cytokine marker. However, it is important to note that the vast majority of studies included in the present meta-analysis relied on CRP, IL-6, and TNF-α as markers of low-grade inflammation. Furthermore, these analyses were exploratory in nature, as there has been little theoretical work for why associations would differ by specific marker of inflammation, and individual past studies have observed differential associations with childhood stress depending on marker of inflammation (Hartwell et al., 2013; Pietras & Goodman, 2013; Schreier et al., 2014). As such, this remains an open question that warrants more empirical research.

Other Potential Sources of Heterogeneity

We also explored other potential moderators that might be expected to contribute to the heterogeneity of effect sizes. Neither gender nor race/ethnicity composition emerged as moderators, though these findings are based on between-study comparisons at the sample rather than individual level, which is a relatively crude means for testing their potential moderating role. There was, however, a significant moderation of effect sizes by BMI, such that the link between childhood stress and inflammation was stronger in samples with higher mean BMI. This is consistent with studies that have demonstrated the same phenomenon at the individual level (Chiang et al., 2017; Steptoe et al., 2019). A potential explanation for these findings is that adipocytes not only secrete pro-inflammatory cytokines but they can also activate macrophages in adipose tissue to become more pro-inflammatory (Ferrante, 2007; Weisberg et al., 2003; Xu et al., 2003). Indeed, psychosocial stress may upregulate sympathetic activity (Rohleder et al., 2004) and the resulting increase in norepinephrine can stimulate adipocytes and macrophages in adipose tissue and in circulation to release pro-inflammatory cytokines (Pirzgalska et al., 2017). As such, childhood stress in conjunction with adiposity may foster a more inflammatory phenotype. Despite known associations between adiposity and heightened inflammation, adiposity has mostly been studied as a confounding or mediating factor rather than as a moderator. Therefore, more empirical examination of adiposity's modulating role is necessary to confirm the current results.

We also tested publication year and study design as other methodological moderators. Publication year was a significant moderator, with the magnitude of the association between childhood stress and inflammation becoming smaller over time. This is consistent with a broader phenomenon in the scientific literature where effect sizes decrease over time. There are some speculations that this observation may have to do with increasing awareness about publication bias, statistical self-correction (e.g., regression to the mean), reporting of selected findings, and more rigorous methodologies in subsequent studies (Protzko & Schooler, 2017; Schooler, 2011). In addition, methodological advances in inflammation assays may have also played a role. For instance, the number of cytokines that can be assayed and the accessibility of using biomarkers in social science fields increased; the range of detection for assays has also improved, allowing inclusion of children and adolescents in samples. Together, both general and biomarker-specific factors may have contributed to the observed decrease in effect size over time.

There was no evidence that the overall effect size differed between cross-sectional and longitudinal studies. Moreover, in subgroup analyses, childhood stress was associated with inflammation in both cross-sectional ($k = 126$) and longitudinal studies ($k = 40$). Future studies that utilize longitudinal designs would valuably contribute to knowledge because of the inferential advantages they provide. However, given the difficulties and expenses of conducting research in this area, they are not always feasible to do, and cross-sectional studies can still promote hypothesis development. Areas ripe for this kind of work include examination of pathways, such as childhood stress to clinical endpoints via inflammation or childhood stress to inflammation via social relationships, as well as examination of moderating factors, such as when and for whom childhood stress may be most detrimental.

Limitations and Future Directions

The current meta-analysis is the most comprehensive quantitative synthesis of the association between childhood stress and inflammation to date. However, it is not without limitations, and some caution should be taken when interpreting results. First, as we discussed extensively above, the studies comprising this literature have observational designs, which raises concerns about causal inference. Second, to be comprehensive, we included effect sizes from both crude and adjusted analyses. We a priori prioritized effect sizes from the most fully adjusted models reported, and only extracted crude effect sizes if adjusted values were unavailable. Because adjustment for confounds typically results in attenuated links, the effect sizes reported here are likely to skew toward more conservative estimates. Studies also varied in the number of covariates and which specific covariates were adjusted for, which may have partly been specific to the study sample (e.g., smoking rates are very low in children and thus studies of children do not typically account for smoking). Some studies also accounted for confounds by design (e.g., recruit case-matching participants who have been exposed to maltreatment vs. not or exclude participants who are smokers), and thus some unadjusted effect sizes may nonetheless be accounting for potential confounds. Nonetheless, measuring and assessing a standard set of covariates in future studies would facilitate more effective comparisons across studies, as previously recommended (O'Connor et al., 2009).

Third, although numerous methods for estimating and correcting for publication bias are available, there is currently no consensus on which is optimal. Rather, a combination of method performance check and follow-up sensitivity analyses has been recommended for traditional meta-analytic frameworks (Carter et al., 2019; Kim et al., 2014). We were unable to follow this recommendation, however, as

multiple effect sizes were extracted for each study, and there are currently no means for assessing publication bias when there are dependencies among effect sizes. Thus, we adapted PET-PEESE, a metaregression approach, to assess publication bias within our multilevel framework such that dependencies can be accounted for. However, recent simulation studies suggest that this approach suffers from low power in the presence of high heterogeneity in effect sizes compared to other approaches for bias correction (Carter et al., 2019). Following previous meta-analytic studies, we also visualized publication bias using the funnel plot. However, the funnel plot relies on an unlikely assumption that the true effect size is orthogonal to the sample size, obscures any clustering of within-study effect sizes, and by nature of being a visual tool, precludes formal statistical tests. Additionally, both approaches—PET-PEESE and funnel plots—are more sensitive to small-study bias and serve only as proxies for publication bias. It will be important, then, for future work to develop and validate methods for identifying publication bias when effect sizes are not independent from one another, as in the current investigation.

Fourth, developmental stage was based on age, but given the lack of individual-level data, we assessed age at the sample level using means of age, which can reduce measurement precision. That said, the meta-analytic technique enables us to cover an age range and developmental stages that single studies typically cannot. Thus, testing moderation by developmental stage, even if based on less precise measurements of age, nevertheless provides initial insights about how the childhood stress–inflammation association might change across the lifespan. Results should be interpreted with caution until future studies can replicate the moderating effect of developmental stage using other methodologies, such as accelerated longitudinal designs and integrative data analyses (Curran & Hussong, 2009; Lam et al., 2021).

Fifth, our investigation was confined to two components of inflammation: biomarkers of low-grade inflammation and cytokine responses to microbial threat. However, as described above, the inflammatory response, regulation of it, and how it becomes chronic is a complex process, and future studies should move beyond simply measuring circulating biomarkers like CRP, IL-6, and TNF-α. More specifically, there are multiple cellular actors and signaling molecules involved in the inflammatory response, and the cytokines measured in the literature to date are quite rough proxies for them. Consequently, future studies should consider which disease outcome is of primary interest, and focus on cellular behaviors and signaling molecules that play a critical role in the pathogenesis or progression of that disease (Miller, Chen, & Cole, 2009). Future studies should also consider employing techniques that allow for direct measurement of inflammatory activity in certain tissues collected during medical procedures (Doyle et al., 2006; Keenan-Devlin et al., 2017; Kiecolt-Glaser et al., 2005), which would shed light on how childhood stress influences local inflammatory activity. With respect to regulation of inflammation, it will be important for future work to assess the sensitivity of immune cells to inhibitory signaling from anti-inflammatory cytokines like IL-10 and from the HPA axis's hormone cortisol. This is critical to examine in relation to childhood stress because it is not only an important aspect in the development of chronic inflammation, but it's also hypothesized that childhood stress has direct "programming" effects on immune cells' sensitivity to inhibitory signals (Miller et al., 2011). Another way in which studies should move beyond measuring circulating cytokines is to take a genomics approach and assess the expression of inflammatory-related genes (e.g., Chiang, Cole, et al., 2019). Such an approach would help elucidate molecular regulators of the inflammatory process, such as upregulation of NF-κB.

Sixth, we were unable to determine whether timing of exposure modulates the strength of the association between childhood stress and inflammation. Times of greater plasticity of systems have been hypothesized to be sensitive periods during which stressors have particularly profound or enduring effects (e.g., Tottenham, 2014). Times of rapid growth and development of the corticolimbic structures, such as the amygdala and prefrontal cortex, may represent particular sensitive periods given their central role in stress processes and their connections to inflammatory processes (Chiang, Taylor, & Bower, 2015; Danese & McEwen, 2012; Miller et al., 2011; Nusslock & Miller, 2016). The current investigation was not fit to test this question, as the vast majority of studies assessed childhood stress over broad windows of time that were inconsistent from study to study (e.g., 10 studies assessed age 0–18, 9 studies assessed 0–16, 6 studies assessed 5–15). Several individual studies have attempted to test this question, but findings have been inconsistent. In the Avon Longitudinal Study of Parents and Children, adversity occurring between 6 and 8 years old was associated with higher IL-6 and CRP at 10 years old whereas adversity occurring at 1.5 years old was linked to higher CRP at 15 years old (Slopen et al., 2013). In another study, lower SES in early childhood during 1–2 years of age was associated with greater IL-6; low SES at other ages through 18 were not linked to IL-6 (Carroll et al., 2011). In general, testing timing of exposure effects has proved challenging because childhood stress tends to be chronic, spanning multiple developmental stages, and because childhood stress can beget more adversity throughout the lifespan. As such, it is difficult to disentangle duration and accumulation from timing of exposure and isolate exposures to a particular defined period. Intervention studies manipulating the time of delivery, however, may shed some light on this question about timing of exposure and sensitive periods.

Lastly, we were unable to test potential buffering factors that may protect against early-adversity-related increases in inflammation. The overall effect size suggests that youth going through adversity face about 16% increased odds of developing heightened inflammation. This may suggest that more often than not, childhood stress will not produce greater levels of inflammation, which points to the important role of resilience factors. Historically, research on resilience to childhood stress has mostly focused on mental health and other psychological adjustment outcomes. However, the last several years have seen a rise in research on factors that can buffer against the physical health consequences of childhood stress. Specifically, more supportive role models, greater maternal warmth, improved parenting, psychological resources, and support in adulthood, have all been shown to buffer against the poorer physical health outcomes tied to low SES and childhood abuse (Boylan et al., 2016; Carroll et al., 2013; Chen et al., 2011, 2013; Chiang et al., 2018; Cohen et al., 2020; Evans et al., 2007; Gunnar & Hostinar, 2015; Miller et al., 2014). It will be important for future work to continue to identify factors and experiences that protect against childhood stress. Based on the current findings on the role of developmental stage, it will be particularly important to conduct research that determines whether buffering factors and their effectiveness change according to developmental stage.

Conclusions

Research has identified childhood stress as a risk factor for chronic illnesses decades later in adulthood, and inflammation has emerged as a potential mechanistic pathway underlying this vulnerability. Indeed, our meta-analytic review of the past 2 decades' worth of research on childhood stress and inflammation provides evidence of an association between various types of childhood stress and different components of inflammation across the lifespan. This suggests that inflammation may be a promising target point for interventions aiming to mitigate the health effects of childhood stress. Psychosocial rather than pharmacological interventions may be of particular interest when working with youth populations, as psychosocial interventions have been shown to modify inflammatory activity (e.g., Shields et al., 2020) and may have fewer negative side effects.

Beyond synthesizing the literature on childhood stress and inflammation, we also showed that the association varied by developmental stage, such that differences in inflammation by childhood stress widened from childhood to adolescence to adulthood. We also found stronger associations between childhood stress and inflammation in samples with higher BMI. We found no evidence that the association varied by type of stressor or by a component of inflammation. These findings suggest that the nature of the links among childhood stress, inflammation, and disease risk may depend on temporal and person characteristics, but further study is needed to confirm and extend our findings. To deepen our understanding of processes through which childhood stress translates into chronic illness in adulthood, future research may benefit from taking life-course perspectives and using prospective designs with repeated assessments. Future studies should also make methodological improvements in assessing types of adversity, expand assessments of inflammation to include cellular behaviors, different components as well as a wider range of cytokines, and examine sensitivity to anti-inflammatory signals and molecular underpinnings of inflammatory processes. To the extent that the current findings are substantiated and extended in future research, they have the potential to inform pediatric clinical practice and intervention efforts of optimal timing of intervention delivery, for whom interventions may be particularly beneficial, and whether certain stressful experiences should be targeted. Ultimately, then, they can help reduce the long-term impact of childhood stress on physical health.

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(*Appendix follows*)

Appendix

Sample and Methodological Characteristics of Studies Included in Meta-Analyses.

Authors, year	*N*	ES	Type of stress	Aspect of inflammation	Inflammation marker assessed	Age at stress assessment	Developmental stage (age) at inflammation	Design	*r*	% Female	% Non-White	Mean adiposity
Decaro et al. (2016)	88	6	Socioeconomic, family	LG	CRP	0.5	Child (0.5)	Cross	0.07 to 0.28	42	n/a	n/a
Hahn et al. (2019)	463	15	Family	MC	IL-6, TNF, IFN, IL-10, Other	0	Child (0)	Long	−0.03 to 0.08	48	23	n/a
Wright et al. (2010)	557	44	Cumulative	MC	TNF, IFN, IL-10, Other	0	Child (0)	Long	−0.13 to 0.1	49	n/a	n/a
Merrill et al. (2017)	3,866	13	Socioeconomic	LG	CRP	1.3, 1.6, 1.8, 2.5, 2.8, 3, 3.1, 3.2, 3.6	Child (1.3, 1.6, 1.8, 2.5, 2.8, 3, 3.1, 3.2, 3.6)	Cross	−0.04 to 0.1	n/a	n/a	n/a
Mansur et al. (2016)	567	2	Socioeconomic, family	LG	IL-6	10.2	Child (10.2)	Cross	0.1 to 0.11	46	42	n/a
Oshri et al. (2020)	101	2	Family	LG	CRP, IL-6	10.3	Child (10.3)	Cross	−0.11 to 0.15	52	89	Waist cir.: 71.08
Cook et al. (1999)	514	1	Socioeconomic	LG	Fibrinogen	10.5	Child (10.5)	Cross	−0.05	49	100	n/a
Gimeno et al. (2008)	2,042	1	Socioeconomic	LG	CRP	10.5	Child (10.5)	Cross	0.01	n/a	0	n/a
Schmeer and Yoon (2016a)	353	2	Socioeconomic	LG	CRP	10.9	Child (10.9)	Cross	0.1 to 0.21	47	n/a	% Obese: 22
Cook et al. (2000)	528	1	Socioeconomic	LG	CRP	10	Child (10)	Cross	0.07	48	10	n/a
Schmeer and Yoon (2016b)	13,165	1	Socioeconomic	LG	CRP	10	Child (10)	Cross	0.04	48	39	n/a
Slopen et al. (2013)	4,262	6	Socioeconomic, cumulative	LG	CRP, IL-6	0, 8	Child (10), Adol (15)	Long	0.04 to 0.07	50	5	BMI: 17.64
Broyles et al. (2012)	385	2	Socioeconomic, social	LG	CRP	11.8	Child (11.8)	Cross	0 to 0.05	51	52	% Obese: 50.9
O'Connor, Willoughby, et al. (2020)	337	10	Socioeconomic, family	LG	CRP, IL-6, TNF	1.2, 11	Child (11)	Cross, long	−0.12 to 0.15	44	36	BMI: 20.75
Goosby et al. (2015)	40	1	Socioeconomic	LG	CRP	12.3	Child (12.3)	Cross	0.09	78	100	BMI: 24.45
Kautz et al. (2020)	129	10	Cumulative	LG	CRP, IL-6, TNF, IL-10, Other	11.8	Child (12.4), Adol (13.4)	Long	−0.15 to 0.12	49	55	BMI: 24.43
Marin et al. (2009)	147	4	Family	MC	IFN, other	12.8	Child (12.8)	Long	0.02 to 0.23	38	37	n/a
Thomas et al. (2005)	101	3	Socioeconomic	LG	CRP, Fibrinogen	12.9	Child (12.9)	Cross	−0.14 to −0.04	67	0	WHR: .76
Danese et al. (2011)	174	1	Maltreat	LG	CRP	7.5	Child (12)	Long	0.01	89	0	n/a
Gallo et al. (2019)	1,343	1	Socioeconomic	LG	Composite	12	Child (12)	Cross	0.04	51	100	BMI: 22.2
Wright et al. (2004)	114	12	Family	MC	TNF, IFN, IL-10, Other	1	Child (2.4)	long	−0.2 to 0.31	39	26	n/a
Hadley and Decaro (2014)	1,387	1	Socioeconomic	LG	CRP	2.7	Child (2.7)	Cross	−0.09	51	n/a	n/a
Ramratnam et al. (2017)	419	19	Family	MC	IFN, Other	1.5	Child (3)	Other	−0.12 to 0.06	49	91	n/a
O'Connor, Ponsonby, et al. (2020)	1,156	10	Family, social	LG	CRP	0.8, 2.3, 5.5	Child (4.1, 11.9)	Long, other	−0.02 to 0.05	49	9	BMI: 15.6
Carlsson et al. (2014)	78	30	Cumulative	MC	IL-6, TNF, IFN, IL-10, Other	5	Child (5)	Cross	−0.16 to 0.18	37	n/a	n/a
Herberth et al. (2008)	162	6	Socioeconomic, family	LG	IFN, Other	6	Child (6)	Cross	−0.11 to 0.11	49	n/a	n/a
Dixon et al. (2009)	98	1	Cumulative	LG	TNF	7.9	Child (7.9)	Cross	0.22	49	100	BMI: 19.28
Fraga, Soares, et al. (2020)	4,175	1	Maltreat	LG	CRP	7	Child (7)	Cross	0.04	n/a	n/a	n/a
Kepper et al. (2016)	37	3	Socioeconomic	LG	IL-6, TNF, Other	8.1	Child (8.1)	Cross	−0.22 to 0.05	47	27	% Obese: 22
Shi et al. (2016)	793	8	Socioeconomic	LG	CRP	8.5, 14.5	Child (8.5), adol (14.5)	Cross	−0.08 to 0.06	50	26	BMI: 18.2
Amoah et al. (2014)	99	1	Socioeconomic	LG	CRP	8.9	Child (8.9)	Cross	−0.2	48	n/a	n/a
McDade et al. (2005)	536	2	Socioeconomic	LG	CRP	8	Child (8)	Cross	0.05 to 0.1	47	n/a	n/a
Bücker et al. (2015)	61	6	Maltreat	LG	IL-6, TNF, IL-10, IL-1, Other	9.2	Child (9.2)	Cross	0.13 to 0.39	40	n/a	BMI: 17.26

(*Appendix continues*)

Appendix (*continued*)

Authors, year	*N*	ES	Type of stress	Aspect of inflammation	Inflammation marker assessed	Age at stress assessment	Developmental stage (age) at inflammation	Design	*r*	% Female	% Non-White	Mean adiposity
Russell et al. (2019)	4,308	2	Cumulative	LG	CRP, IL-6	4.5	Child (9.5)	Cross	0 to 0.05	55	n/a	BMI: 17.4
Azad et al. (2012)	267	3	Socioeconomic, family	MC	IL-6	9	Child (9)	Cross	0.06 to 0.15	45	23	% Overweight: 25.8
Flouri et al. (2019)	4,583	4	Socioeconomic, family	LG	CRP, IL-6	0	Child (9)	Long	0 to 0.03	49	4	% Obese: 4.08
Flouri et al. (2020)	3,915	2	Family	LG	CRP, IL-6	0	Child (9)	Long	0.01 to 0.03	48	3	BMI: 17.56
Kokosi et al. (2020)	4,525	4	Socioeconomic	LG	CRP, IL-6	1.5, 1.7, 6	Child (9)	Long, other	0 to 0.04	49	n/a	BMI: 17.58
Lacey et al. (2020)	4,935	18	Maltreat, family	LG	CRP, IL-6	4	Child (9)	long	−0.03 to 0.02	50	n/a	n/a
Chen et al. (2006)	76	12	Socioeconomic, family	MC	IFN, Other	13.3	Adol (13.3)	Cross	0 to 0.22	58	32	n/a
Serbulent et al. (2017)	27	1	Maltreat	LG	IL-10	13.3	Adol (13.3)	Cross	0.04	74	n/a	n/a
Wolf et al. (2008)	83	2	Family	MC	Other	13.4	Adol (13.4)	Long	0.15 to 0.28	35	n/a	n/a
Morley et al. (2000)	422	1	Socioeconomic	LG	Fibrinogen	13.6	Adol (13.6)	Cross	0.14	50	n/a	BMI: 20.05
Chiang, Chen, et al. (2019)	257	1	Socioeconomic	MC	Composite	13.9	Adol (13.9)	Cross	−0.09	63	71	n/a
Finegood et al. (2020)	202	5	Socioeconomic, social	LG	Composite	13.9	Adol (13.9)	Cross	−0.14 to 0.11	66	70	n/a
Schreier and Chen (2010)	88	2	Socioeconomic	LG	CRP	13	Adol (13)	Other	0.1 to 0.1	43	49	n/a
Chen et al. (2016)	150	48	Socioeconomic	MC	IL-6, TNF, IFN, IL-10, IL-1, Other	14.1	Adol (14.1)	Cross	−0.13 to 0.2	43	51	n/a
Chen et al. (2017)	150	4	Family	MC	Composite	14.1	Adol (14.1)	Cross	0.07 to 0.18	43	51	n/a
Panter-Brick et al. (2020)	727	1	Social	LG	CRP	14.4	Adol (14.4)	Cross	−0.07	43	n/a	BMI: 21.19
Chen et al. (2013)	163	2	Socioeconomic	LG	CRP, IL-6	14.5	Adol (14.5)	Cross	0.11 to 0.37	48	53	WHR: .65
Murasko (2008)	4,602	1	Socioeconomic	LG	CRP	14.5	Adol (14.5)	Cross	0.03	49	39	% Overweight: 33.3
Peters et al. (2019)	40	2	Maltreat	LG	IL-6, IL-1	14.5	Adol (14.5)	Cross	−0.15 to 0.09	60	42	BMI: 22.36
Schreier and Chen (2017)	261	6	Family, social	LG	CRP, IL-6, IL-1	14.5	Adol (14.5)	Cross	−0.07 to 0.09	53	51	BMI: 21.37
Human et al. (2014)	116	20	Family	MC	IL-6, TNF, IL-1, Other	14.6	Adol (14.6)	Cross	−0.07 to 0.14	n/a	34	Waist cir.: 74.95
Schreier et al. (2014)	143	11	Socioeconomic, family	LG, MC	CRP, IL-6, IL-10, Composite	14.6	Adol (14.6)	Cross	−0.07 to 0.21	51	51	BMI: 21.25
Chen et al. (2003)	29	3	Socioeconomic	MC	IFN, Other	15.2	Adol (15.2)	Cross	0.17 to 0.39	40	53	n/a
do Prado et al. (2017)	57	7	Maltreat	MC	IL-6, TNF, IFN, IL-10, Other	15.4	Adol (15.4)	Cross	−0.25 to 0.31	58	n/a	BMI: 24.59
Low et al. (2013)	245	3	Socioeconomic, social, cumulative	LG	CRP	15.7	Adol (15.7)	Cross	−0.11 to 0.14	53	56	BMI: 26.09
Pietras and Goodman (2013)	941	9	Socioeconomic	LG	IL-6, TNF, Fibrinogen	15	Adol (15)	Cross	0.02 to 0.11	51	44	BMI: 23.9
Goodman et al. (2005)	758	2	Socioeconomic	LG	Fibrinogen	16.2	Adol (16.2)	Cross	0.01 to 0.08	50	43	BMI: 24.45
Jonker et al. (2017)	946	1	Maltreat	LG	CRP	15.5	Adol (16.2)	Cross	0.07	54	n/a	BMI: 20.77
Engel et al. (2020)	83	11	Maltreat	LG, MC	IL-6, TNF, IL-1	1.3	Adol (16.3)	Cross	−0.15 to 0.32	56	22	BMI Percentile: 58.43
Buchan et al. (2012)	48	1	Socioeconomic	LG	IL-6	16.4	Adol (16.4)	Cross	0.32	0	n/a	BMI: 21.77
Chiang, Bower, et al. (2015)	298	2	Socioeconomic	LG	CRP	16.4	Adol (16.4)	Cross	−0.04 to 0.12	57	71	BMI: 23.16
Walsh et al. (2016)	133	4	Maltreat	LG	CRP, IL-6	16.5	Adol (16.5)	Cross	−0.13 to 0.01	100	90	BMI: 25.67
Augustine et al. (2014)	145	3	Socioeconomic, cumulative	LG	CRP, IL-6	16.7	Adol (16.7)	Cross	0.05 to 0.22	0	n/a	Waist cir.: 64.5
Reid et al. (2020)	600	16	Socioeconomic, family	LG	CRP	1, 5.5, 10, 16.8	Adol (16.8)	Other	−0.12 to 0.35	48	n/a	Z-Scored BMI: .65
Chen et al. (2015)	122	2	Socioeconomic	LG, MC	Composite	16	Adol (16)	Cross	0.05 to 0.21	51	56	Waist cir.: 75.41

(*Appendix continues*)

Appendix (*continued*)

Authors, year	*N*	ES	Type of stress	Aspect of inflammation	Inflammation marker assessed	Age at stress assessment	Developmental stage (age) at inflammation	Design	*r*	% Female	% Non-White	Mean adiposity
de Bruine et al. (2019)	650	3	Socioeconomic, social, cumulative	LG	CRP	11.1, 13	Adol (16)	Long	−0.06 to 0.02	55	n/a	Body fat %: 28.28
Tang et al. (2020)	44	10	Cumulative	LG	CRP, IL-6	12	Adol (16)	Cross, long	−0.17 to 0.34	51	n/a	BMI: 22.07
Murphy et al. (2013)	147	4	Socioeconomic, social	LG	CRP, IL-6	17, 18.5	Adol (17, 19.6)	Cross, other	−0.06 to 0.18	100	52	BMI: 21.70
de Baumont et al. (2019)	73	1	Maltreat	LG	IL-6	12.6	Adol (17.6)	Long	0.03	60	36	n/a
Miller, Chen, Fok, et al. (2009)	103	4	Socioeconomic, social	LG, MC	CRP, IL-6	17.2	Adol (17.7)	Long	−0.1 to 0.22	100	55	WHR: .75
Fuligni, Telzer, Bower, Cole, et al. (2009)	69	1	Cumulative	LG	CRP	15.8	Adol (17.8)	Long	0.14	54	61	BMI: 25.31
Fuligni, Telzer, Bower, Irwin, et al. (2009)	64	2	Socioeconomic	LG	IL-6	17.8	Adol (17.8)	Cross	−0.08 to 0.1	56	61	BMI: 25.57
Fraga, Severo, et al. (2020)	2,942	4	Socioeconomic	LG	CRP	13	Adol (17)	Other	0.03 to 0.05	51	n/a	BMI > 95th Percentile: 17.8
Miller and Chen (2010)	135	4	Socioeconomic, family	LG, MC	IL-6	17	Adol (17)	Cross	−0.14 to 0.01	100	50	BMI: 21.61
Chiang et al. (2017)	91	1	Family	LG	IL-6	18.4	Adol (18.4)	Cross	0.07	57	62	BMI: 25.08
Cole et al. (2011)	58	1	Socioeconomic	LG	CRP	17.8	Adol (18.4)	Long	0.25	55	59	BMI: 24.8
Rasmussen et al. (2020)	1,419	3	Cumulative	LG	CRP, IL-6	8.5, 18	Adol (18.4)	Long, other	0.02 to 0.06	53	n/a	BMI: 22.9
Kuhlman, Robles, et al. (2020)	41	1	Maltreat	LG	IL-6	18.5	Adol (18.5)	Cross	0.04	73	n/a	BMI: 24.08
Baldwin et al. (2018)	1,732	1	Socioeconomic	LG	CRP	5	Adol (18)	Long	0.05	100	10	n/a
Rivenbark et al. (2020)	1,440	4	Socioeconomic	LG	CRP, IL-6	5, 12	Adol (18)	Long	0 to 0.08	51	n/a	n/a
Brody et al. (2014)	368	2	Socioeconomic, family	LG	CRP	12, 13	Adol (19.2)	Long	0.06 to 0.14	53	100	n/a
Ehrlich, Miller, Rohleder, and Adam (2016)	96	6	Socioeconomic, family, social	LG, MC	CRP, IL-6	17, 18.5	Adol (19.5)	Long, other	−0.13 to 0.08	100	46	Waist cir.: 72.5
Miller et al. (2014)	272	18	Socioeconomic, family	LG	IL-6, TNF, IFN, IL-10, IL-1, Other	11, 19	Adol (19)	Long	−0.15 to 0.24	57	100	n/a
McDade et al. (2013)	1,396	1	Family	LG	CRP	11	Adult (20.9)	Long	0.05	n/a	n/a	Waist cir.: 70.4
Copeland et al. (2014)	759	1	Social	LG	CRP	12.5	Adult (20)	Long	0.06	55	10	n/a
Nazmi et al. (2010)	1,368	4	Socioeconomic	LG	CRP	0	Adult (22.7)	Long	−0.1 to 0.07	50	25	BMI: 23.8
Brody et al. (2015)	160	2	Socioeconomic, cumulative	LG	Composite	18	Adult (22)	Long	−0.04 to 0.05	64	100	BMI: 30.63
Raposa et al. (2014)	389	2	Family	LG	CRP, TNF	7.5	Adult (23.5)	Long	−0.04 to 0.06	57	9	BMI: 24.51
Bock et al. (2020)	129	1	Maltreat	LG	IL-1	23.7	Adult (23.7)	Cross	0.14	52	25	BMI: 25.65
Counotte et al. (2019)	117	4	Maltreat	LG	CRP, IL-6, TNF, IFN	24.9	Adult (24.9)	Cross	−0.13 to 0.12	38	n/a	BMI: 23.19
Mitchell et al. (2018)	77	15	Maltreat	LG	CRP, IL-6, TNF	25.6	Adult (25.6)	Other	−0.21 to 0.34	100	49	BMI: 27.4
Moreira et al. (2018)	1,171	6	Maltreat	LG	IL-6, TNF, IL-10	25.9	Adult (25.9)	Cross	−0.03 to 0.33	n/a	n/a	n/a
Plant et al. (2016)	78	2	Maltreat, family	LG	CRP	0	Adult (25)	Long	−0.09 to 0.32	51	31	BMI: 25.47
Hepgul et al. (2012)	35	2	Maltreat	LG	CRP	26.5, 28.7	Adult (26.5, 28.7)	Cross	−0.19 to 0.19	30	66	BMI: 24.8
Carpenter et al. (2010)	69	1	Maltreat	LG	IL-6	26.8	Adult (26.8)	Cross	0.15	61	n/a	BMI: 25.57
Di Nicola et al. (2013)	24	8	Cumulative	LG	IL-6, IFN, IL-10, IL-1, Other	28.1	Adult (28.1)	Cross	0.14	33	n/a	n/a
Yang et al. (2017)	12,237	8	Socioeconomic	LG	CRP, IL-6, Fibrinogen, Other	15, 71	Adult (28.3, 54, 63.2, 66.6)	Long, other	0.01 to 0.1	54	11	n/a
Allen et al. (2018)	127	3	Socioeconomic, family	LG	IL-6	13.3, 18.2	Adult (28.5)	Long	−0.07 to 0.23	53	43	n/a
Brummett et al. (2013)	11,371	1	Socioeconomic	LG	CRP	15	Adult (28.9)	Long	0.07	54	28	BMI: 29.3
Beach et al. (2017)	413	1	Family	LG	Other	10.5	Adult (28)	Long	0.13	62	100	n/a

(*Appendix continues*)

Appendix (*continued*)

Authors, year	*N*	ES	Type of stress	Aspect of inflammation	Inflammation marker assessed	Age at stress assessment	Developmental stage (age) at inflammation	Design	*r*	% Female	% Non-White	Mean adiposity
Levandowski et al. (2014)	44	1	Maltreat	LG	TNF	29.3	Adult (29.3)	Cross	−0.24	100	n/a	BMI: 23.31
Finy and Christian (2018)	214	2	Maltreat	LG	CRP, IL-6	29.4	Adult (29.4)	Other	0.14 to 0.2	100	34	% Obese: 29
Levandowski et al. (2016)	108	4	Maltreat	LG	TNF, IFN, IL-10, Other	29	Adult (29)	Cross	−0.22 to 0.34	100	n/a	BMI: 23.15
Aas et al. (2017)	253	3	Maltreat	LG	CRP, TNF	30.5	Adult (30.5)	Cross	−0.04 to 0.23	44	n/a	BMI: 24.77
Carpenter et al. (2012)	92	2	Maltreat, cumulative	LG	CRP	30.5	Adult (30.5)	Cross	0.04 to 0.07	51	n/a	BMI: 26.1
Bublitz et al. (2017)	24	3	Maltreat	LG	IL-6, TNF, IL-1	30.6	Adult (30.6)	Cross	0.16 to 0.33	100	46	BMI: 32.54
Boeck et al. (2016)	29	1	Maltreat	LG	CRP	31.6	Adult (31.6)	Cross	−0.12	100	3	BMI: 25.3
Kivimäki et al. (2005)	1,969	2	Socioeconomic	LG	CRP	10.7, 13.7	Adult (31.7)	Long	0.03 to 0.05	55	n/a	n/a
Dennison et al. (2012)	40	3	Maltreat	LG	TNF, IL-1, Other	32.3	Adult (32.3)	Cross	−0.08 to 0.39	54	n/a	BMI: 25.92
Matthews et al. (2017)	305	2	Social	LG	CRP, IL-6	11	Adult (32.3)	Long	−0.03 to 0	0	53	BMI: 29.5
Matthews et al. (2019)	261	2	Socioeconomic	LG	CRP, IL-6	11.5	Adult (32.3)	Long	0 to 0.01	0	53	BMI: 29.5
Danese et al. (2007)	866	3	Cumulative	LG	CRP, Fibrinogen	11.2	Adult (32)	Long	0.04 to 0.17	n/a	n/a	n/a
Danese et al. (2009)	862	2	Socioeconomic, social	LG	CRP	7.5	Adult (32)	Long	0.15 to 0.16	48	n/a	n/a
Miller, Rohleder, and Cole (2009)	100	2	Socioeconomic	MC	IL-6	33.1	Adult (33.1)	Cross	0.22 to 0.26	61	32	BMI: 24.02
Moeini et al. (2020)	63	2	Maltreat	LG	CRP, Other	33.6	Adult (33.6)	Cross	−0.16 to −0.1	n/a	n/a	BMI: 22.6
Lindqvist et al. (2014)	51	12	Cumulative	LG	CRP, IL-6, TNF, IFN, IL-10, IL-1	33.7, 34.1	Adult (33.7, 34.1)	Cross	−0.2 to 0.16	0	22	BMI: 28.3
Fanning et al. (2015)	134	6	Maltreat, family	LG	CRP, IL-6	34.3	Adult (34.3)	Cross	0.12 to 0.32	51	36	BMI: 27.87
Hartwell et al. (2013)	39	3	Maltreat	LG	CRP, IL-6, IL-1	35.7	Adult (35.7)	Cross	−0.26 to 0.34	51	31	BMI: 26.8
Grosse et al. (2016)	214	4	Maltreat	LG	IL-6, TNF	36, 41	Adult (36, 41)	Cross	−0.06 to 0.03	60	n/a	BMI: 24
Hostinar, Ross, et al. (2015)	360	10	Socioeconomic, maltreat, family	LG	CRP, IL-6	36.5	Adult (36.5)	Cross	0.04 to 0.14	55	27	BMI: 25.76
John-Henderson et al. (2020)	90	2	Cumulative	LG	CRP, IL-6	37.6	Adult (37.6)	Cross	0.08 to 0.14	50	100	BMI: 30.71
Tietjen et al. (2012)	141	3	Cumulative	LG	CRP, IL-6, TNF	37	Adult (37)	Cross	0.17 to 0.24	100	9	BMI: 28.65
Quidé et al. (2019)	68	45	Maltreat	LG	CRP, IL-6, TNF	36.2, 38.1, 41.8	Adult (38.1, 41.8, 50.7)	Cross	−0.27 to 0.31	52	n/a	n/a
Grassi-Oliveira et al. (2009)	49	1	Maltreat	LG	TNF	38.5	Adult (38.5)	Cross	0.37	100	n/a	BMI: 26.6
Müller et al. (2019)	83	20	Maltreat	LG	IL-6, IL-10	38.9, 39.2	Adult (38.9, 39.2)	Cross	0.07 to 0.34	39	n/a	BMI: 23.6
Rasmussen et al. (2019)	827	6	Socioeconomic, cumulative	LG	CRP, IL-6, Fibrinogen	9	Adult (38)	Long	−0.1 to 0.06	50	7	BMI: 27.1
Frodl et al. (2012)	83	2	Maltreat	LG	CRP, IL-6	39.1	Adult (39.1)	Cross	0.19 to 0.22	59	n/a	n/a
Taylor et al. (2006)	3,248	1	Socioeconomic	LG	CRP	25.1	Adult (40.1)	Other	0.12	55	45	BMI: 28.48
Cho et al. (2012)	2,716	2	Family	LG	CRP, IL-6	40.3	Adult (40.3, 45.3)	Cross, long	0.03 to 0.06	55	43	BMI: 28.0
Lopes et al. (2012)	38	1	Maltreat	MC	IL-6	40.3	Adult (40.3)	Cross	−0.04	100	n/a	BMI: 26.3
Carroll et al. (2013)	684	3	Socioeconomic, family	LG	IL-6, Fibrinogen	40	Adult (40)	Cross	0.03 to 0.08	57	54	Waist cir.: 89.8
Kuzminskaite et al. (2020)	2,700	6	Maltreat	LG	CRP, IL-6, TNF	41.6, 45.6	Adult (41.6)	Cross, other	−0.03 to 0.01	66	n/a	BMI: 25.49
Slopen et al. (2015)	355	2	Cumulative	LG	CRP	0, 7	Adult (42.1)	Long	0.11 to 0.18	58	19	n/a
John-Henderson et al. (2016)	429	6	Socioeconomic	LG	IL-6	42.8	Adult (42.8)	Cross	0 to 0.09	53	19	BMI: 26.97
Runsten et al. (2014)	116	1	Family	LG	CRP	42.9	Adult (42.9)	Cross	−0.02	100	n/a	BMI: 25.32
Bertone-Johnson et al. (2012)	702	12	Maltreat	LG	CRP, IL-6, TNF	45.9	Adult (43.9)	Other	0 to 0.08	100	3	BMI: 25.8
Chen and Lacey (2018)	7,683	2	Cumulative	LG	CRP, Fibrinogen	11.3	Adult (44.5)	Long	0.04 to 0.05	n/a	n/a	BMI: 25.6
Phillips et al. (2009)	811	1	Socioeconomic	LG	CRP	44.8	Adult (44.8)	Cross	0.08	51	13	BMI: 27.3

(*Appendix continues*)

Appendix (*continued*)

Authors, year	*N*	ES	Type of stress	Aspect of inflammation	Inflammation marker assessed	Age at stress assessment	Developmental stage (age) at inflammation	Design	*r*	% Female	% Non-White	Mean adiposity
Lacey et al. (2013)	8,233	1	Socioeconomic	LG	CRP	16	Adult (44)	Long	0.03	54	n/a	BMI: 25.9
Lacey et al. (2014)	7,462	1	Social	LG	CRP	9	Adult (44)	Long	0.06	50	n/a	n/a
Pereira et al. (2019)	6,966	27	Socioeconomic, maltreat	LG	CRP, IL-6, Fibrinogen	45, 50.7, 57.3	Adult (45.2, 50.7, 57.3)	Cross, long	0.01 to 0.09	54	20	BMI: 29.84
Matthews et al. (2014)	326	1	Maltreat	LG	CRP	45.7	Adult (45.7)	Other	0.11	100	32	n/a
Tabassum et al. (2008)	5,951	2	Socioeconomic	LG	CRP, Fibrinogen	0.6	Adult (45)	Long	0.07 to 0.08	47	3	BMI: 27.8
Takizawa et al. (2015)	7,102	4	Social, cumulative	LG	CRP, Fibrinogen	9, 45	Adult (45)	Cross, long	0.01 to 0.03	49	n/a	BMI: 27.23
Gouin et al. (2020)	167	3	Maltreat	LG	CRP, IL-6, TNF	46.8	Adult (46.8)	Cross	0.08 to 0.16	100	26	BMI: 27.41
Munjiza et al. (2018)	64	2	Maltreat	LG	IL-6	46	Adult (46)	Cross	−0.18 to 0.38	80	n/a	n/a
Stringhini et al. (2013)	6,387	2	Socioeconomic	LG	CRP, IL-6	43.3	Adult (49.3)	Other	0.05 to 0.05	28	7	n/a
Packard et al. (2011)	666	9	Socioeconomic	LG	CRP, IL-6, Other	49.5	Adult (49.5)	Other	−0.03 to 0.08	50	n/a	BMI: 27.78
Gouin et al. (2017)	174	2	Cumulative	LG	CRP, IL-6	50.3	Adult (50.3)	Cross	−0.01 to 0.17	88	18	n/a
Lockwood et al. (2018)	94	1	Socioeconomic	LG	IL-6	50.4	Adult (50.4)	Cross	−0.07	59	10	BMI: 26.2
Brunner et al. (1999)	6,980	1	Socioeconomic	LG	Fibrinogen	45	Adult (50.5)	Long	0.02	32	n/a	n/a
Carroll et al. (2011)	112	2	Socioeconomic	LG	IL-6	50.5	Adult (50.5)	Cross	0.16 to 0.2	60	11	BMI: 26.4
Matthews et al. (2016)	1,067	2	Socioeconomic	LG	CRP, Fibrinogen	60	Adult (50.5)	Other	0.07 to 0.1	100	44	BMI: 29.8
Pedersen et al. (2018)	1,189	4	Cumulative	LG	CRP, IL-6, TNF, IL-10	0.5	Adult (50.5)	Long	0.02 to 0.09	57	n/a	BMI: 25.9
Powers et al. (2019)	55	1	Maltreat	LG	CRP	50.9	Adult (50.9)	Cross	0.08	100	100	BMI: 36.43
Crosswell et al. (2014)	152	4	Family	LG	CRP, IL-6, TNF, IL-1	51.7	Adult (51.7)	Cross	0.12 to 0.16	100	17	n/a
Almuwaqqat et al. (2020)	267	2	Cumulative	LG	CRP, IL-6	51	Adult (51)	Cross	0.1 to 0.12	50	66	n/a
Wilson et al. (1993)	2,011	1	Socioeconomic	LG	Fibrinogen	51	Adult (51)	Cross	0.02	0	n/a	BMI: 26.95
Camelo et al. (2014)	6,717	2	Socioeconomic	LG	CRP	52.2, 52.5	Adult (52.5)	Cross	−0.01 to 0	50	n/a	% Obese: 47.56
Pollitt et al. (2007)	9,043	12	Socioeconomic	LG	CRP, Fibrinogen	62.9	Adult (52.7, 53.9, 62.9)	Other	−0.02 to 0.03	n/a	50	BMI: 26.97
Castagné et al. (2016)	234	10	Socioeconomic	LG	IL-6, TNF, IFN, IL-10, IL-1, Other	53.3	Adult (53.3)	Cross	−0.01 to 0.13	72	n/a	BMI: 25.8
Davis et al. (2019)	770	1	Maltreat	LG	IL-6	53.5	Adult (53.5)	Cross	0.12	55	20	n/a
Friedman et al. (2015)	1,180	1	Cumulative	LG	Composite	54.5	Adult (54.5)	Other	0.1	57	22	n/a
Nguyen and Thurston (2020)	299	2	Maltreat	LG	CRP, IL-6	54	Adult (54)	Cross	0 to 0.08	100	27	BMI: 29.01
Hostinar et al. (2017)	1,239	3	Maltreat	LG	CRP, IL-6, Fibrinogen	55.3	Adult (55.3)	Cross	0.06 to 0.07	56	37	n/a
Janusek et al. (2013)	40	3	Maltreat	LG	IL-6	55.6	Adult (55.6)	Cross	−0.23 to 0.21	100	18	n/a
Renna et al. (2020)	157	1	Maltreat	LG	Composite	55.8	Adult (55.8)	Cross	0.23	80	17	BMI: 29
Rooks et al. (2012)	482	2	Cumulative	LG	CRP, IL-6	55	Adult (55)	Cross	0–0.02	0	n/a	BMI: 30
Ng et al. (2020)	148	2	Maltreat	LG	IL-6, IL-1	56.3	Adult (56.3)	Cross	−0.07 to 0.03	72	n/a	n/a
Hostinar, Lachman, et al. (2015)	1,180	1	Cumulative	LG	Composite	57.3	Adult (57.3)	Cross	0.07	56	25	n/a
Slopen et al. (2010)	999	5	Cumulative	LG	CRP, IL-6, Fibrinogen, Other	57.9	Adult (57.9)	Other	0.01 to 0.08	55	18	BMI: 29.89
Loucks et al. (2010)	1,513	16	Socioeconomic	LG	CRP, IL-6, TNF, Fibrinogen, Other	n/a	Adult (61.2)	Long	−0.03 to 0.04	54	5	BMI: 28.29
Steel et al. (2020)	408	6	Cumulative	LG	TNF, IFN, IL-10, IL-1, Other	62	Adult (62)	Cross	−0.05 to 0.05	36	8	n/a

(*Appendix continues*)

Appendix (*continued*)

Authors, year	*N*	ES	Type of stress	Aspect of inflammation	Inflammation marker assessed	Age at stress assessment	Developmental stage (age) at inflammation	Design	*r*	% Female	% Non-White	Mean adiposity
Gouin et al. (2012)	130	3	Maltreat	LG	CRP, IL-6, TNF	65.1	Adult (65.1)	Cross	0.07 to 0.23	82	18	BMI: 26.94
Lin et al. (2017)	864	2	Socioeconomic	LG	CRP, IL-6	65.3	Adult (65.3)	Cross	0.04 to 0.05	46	n/a	% Obese: 27.95
McFarland et al. (2020)	92	1	Family	LG	CRP	65.4	Adult (65.4)	Cross	0.1	67	13	BMI: 26.1
Pikhartova et al. (2014)	4,301	1	Socioeconomic	LG	Composite	68.9	Adult (68.9)	Cross	0.11	57	n/a	% Overweight: 48.1
Li et al. (2015)	711	4	Socioeconomic, family	LG	CRP	69.5, 70, 70.5, 71	Adult (69.5, 70, 70.5, 71)	Cross	−0.07 to 0.08	53	n/a	% Obese: 31.0
Kiecolt-Glaser et al. (2011)	132	2	Family	LG	IL-6, TNF	69.7	Adult (69.7)	Cross	0.1to 0.12	72	8	n/a
Lin et al. (2016)	11,198	1	Cumulative	LG	CRP	69	Adult (69)	Cross	0.03	61	17	BMI: 29.48
Iob et al. (2019)	4,198	4	Maltreat, family	LG	CRP	69.7	Adult (73.7)	Long	0.05 to 0.06	56	n/a	BMI: 28.21
Norton et al. (2017)	1,955	1	Family	LG	CRP	9	Adult (81.2)	Long	0.03	58	0	n/a
Smith et al. (2011)	177	1	Maltreat	LG	TNF	n/a	Adult (NA)	Cross	0.23	n/a	n/a	n/a
McCormack et al. (2021)	109	4	Maltreat, family	LG	IL-6	29.9	Adult (30)	Cross, long	−0.05 to 0.1	100	69	BMI: 26.09

Note. *N* = maximum analysis sample size; ES = total number of childhood/adolescence stress–inflammation effect sizes the study provided; LG = low-grade inflammation; CRP = C-reactive protein; MC = microbial challenge; IL-6 = interleukin-6; TNF = tumor necrosis factor; IFN = interferon; IL-10 = interleukin-10; BMI = body mass index; IL-1 = interleukin-1. n/a indicates missing data. Type of stress includes socioeconomic status (socioeconomic), maltreatment (maltreat), family or household stress (family), nonfamily interpersonal stress (social), cumulative adversity (cumulative). Aspect of inflammation assessed includes LG and cytokine responses to MC. Type of inflammation marker includes CRP, IL-6, tumor necrosis factor family, such as tumor necrosis factor alpha (TNF-α), interferon family, such as interferon gamma (IFN-γ), IL-10, IL-1 family, such as interleukin-1 beta (IL-1β) and interleukin-1 alpha (IL-1α), Fibrinogen, other inflammatory markers, such as interleukin-2 (other), and composites of multiple inflammatory markers (composite). Developmental stage at inflammation assessment includes childhood (<age 13; child), adolescence (age 13–19; adol), and adulthood (>age 19; adult). The design includes cross-sectional (cross), longitudinal (long), or other. Sample adiposity estimate was extracted based on availability in this preference order: BMI, body fat percentage (Body fat %), waist circumference (Waist cir.), waist-hip ratio (WHR), percent of sample overweight/obese.

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