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Annual Research Review: Social relationships and the immune system during development

Theodore F. Robles

Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA

A child's social relationships serve critical functions during development. The interface between a child's social world and their immune system, particularly innate immunity, which helped children survive in the face of infections, nutritional scarcity, and violence throughout human history, is the focus of this Annual Research Review. This article reviews the state of research on social relationships and innate immune inflammation during childhood. Warmth and rejection in childhood social relationships, as well as physical trauma and unpredictable social environments, were not consistently related to circulating inflammatory markers such as interleukin-6 and C-reactive protein during childhood. Instead, links between social environments and inflammation were observed in studies that focus on children with greater background risk factors, such as low family socioeconomic status, family history of mood disorders, or presence of chronic interpersonal stressors combined with acute episodic stressors. In addition, studies on worse childhood social environments and greater inflammation in adulthood were more consistent. Warmth and rejection in the social environment may be related to sensitivity of immune cells to the anti-inflammatory actions of glucocorticoids, though this is primarily observed in adolescent women at risk for depression. Additional mechanistic evidence suggests that greater warmth and less rejection are related to processes that regulate inflammation, including greater expression of the glucocorticoid receptor gene and lower expression of genes that are responsive to the pro-inflammatory transcription factor NF-kappa B. The article concludes by discussing implications of the interface between a child's social relationships and inflammation for mental health and other recent (on evolutionary timescales) health threats, as well as recommendations for future research, and recommendations for researchers interested in integrating inflammatory measures in developmental research. **Keywords:** Social factors; family functioning; parent–child relationships; peer relationships; biology.

Introduction

For 99% of human history, the chances of surviving to reproductive age were a coin flip (Kappeler, Cremer, & Nunn, 2015). Around 4 to 5 out of 10 children died prior to age 15 for virtually all of human history (Volk & Atkinson, 2013). In the most recent 1% of human history (the past 100 years), child mortality rates have drastically improved to below 0.6 in 100 in much of the world, although considerable child health inequities exist (UNICEF, 2019). The primary threats to survival during childhood include infectious diseases, nutritional scarcity, and violence (Volk & Atkinson, 2013), which influenced evolution across all the human organism's systems and functions, from digestion to skeletal muscle to reproduction. This review focuses on the interface between children's social relationships and a key system for minimizing harm: the *immune system*, which detects and defends against infectious threats from the outside world. I focus on research that started in the early 2000s and expanded over the past decade on innate *immune responses to infection*, also termed *inflammation*. Most of that work in human developmental psychoneuroimmunology (PNI) has centered around social relationships as sources of rejection and harm (Prinstein & Giletta, 2016), though some work has examined warmth in children's social relationships. The major questions addressed in the literature and in this review are as follows: (1) What are the main effect associations between support or harm in social relationships and inflammation? (2) Does support or harm in social relationships modify associations between stress exposures and inflammation; does support buffer; and does harm intensify the effects of other stress exposures on inflammation? A corollary to this question is are there groups of children, based on stress exposures, for whom support or harm in social relationships has a stronger association with inflammation.

This review begins with a guiding conceptual framework on childhood social relationships, followed by an overview of the innate immune system and inflammation. I then review recent conceptual perspectives on stress, physiology, and health that emphasize that the brain integrates information about internal states (i.e. infection) and the external social world to make determinations of safety/threat and uncertainty in the external environment and that those safety and uncertainty signals are transmitted to the immune system through neuroendocrine signaling. After those conceptual foundations, I review research on childhood social relationships and inflammation, and conclude with directions for future research, including implications

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for mental health, researchers who want to incorporate inflammatory measures in their research, and relevance for newer threats to survival in the 21st century.

Functions, development, and shared goals during childhood

A conceptual framework for social relationships

Social relationships fulfill key functions including providing safety, maintaining closeness to caregivers (attachment), supporting basic needs, helping during times of need, and forming stable systems and connections (hierarchies, reciprocity; Bugental, 2000). From infancy to middle childhood, parents/caregivers are responsible for those functions because of proximity, with peers taking on increasing importance over the course of development (Chen, Brody, & Miller, 2017; Crone & Dahl, 2012). Numerous taxonomies have characterized how parents/caregivers carry out social functions when relating to and caring for their children – that is, parenting (Skinner, Johnson, & Snyder, 2005).

To provide a framework for the review, Table 1 describes six dimensions of parenting described by Skinner et al. (2005) that are also present in other social relationships and can be approached from objective (e.g. observed behavior) and subjective perspectives (e.g. parent or child report). Figure 1A depicts overlapping dimensions on the same axis: warmth and rejection/hostility; structure/contingency and chaos/insensitivity; and autonomy support and coercion/interference. Dimensions on the same axis are not perfectly correlated; the proportion of shared variance between any two dimensions in research described by Skinner et al. (2005) did not exceed 39%, which is why each dimension is represented with different colors. A major caveat is the dimensions are informed by theory and research that primarily comes from researchers and populations from European backgrounds (Bornstein & Cheah, 2006).

Figure 1A also depicts two major risk factors for poor health, *physical trauma* and an *unpredictable environment,* derived from conceptualizations of adverse childhood experiences (Kuhlman, Chiang, Horn, & Bower, 2017; Prinstein & Giletta, 2016; Repetti, Taylor, & Seeman, 2002; Smith & Pollak, 2020). Physical trauma, defined here as exposure to physical threat, injury, or abuse (Kuhlman et al., 2017), is represented in Figure 1A as a combination of high rejection, coercion, and chaos. Unpredictable environments are defined as unmet basic needs, such as food or shelter insecurity, exposure to stressors in the local community (crime, war), or unpredictable traumatic events (natural disasters, etc.; Kuhlman et al., 2017). In this framework, even though local conditions can influence what takes place in the home, unpredictable environments are considered separately from the structure and/or chaos that exists in the home environment. For example, a family displaced by natural disaster may be experiencing food and shelter insecurity, but caregivers and other supports may still endeavor to provide structure and contingency for children in the form of routines and activities. In the other direction, a family may not be experiencing any unpredictability, but caregivers provide little structure or contingency, and may even be sources inconsistency and chaos as described in Table 1. These examples illustrate an important point, that unpredictable environments influence caregiving in complex ways (Roubinov &

Table 1 Social relationship dimensions used in the review, derived from parenting dimensions from Skinner et al. (2005)

Dimension	Definition
Warmth	...Expression of affection, love, appreciation, kindness, and regard; it includes emotional availability, support, and genuine caring...when a child seeks comfort...[and] in interactions focusing on teaching or discipline... (p. 185).
Rejection/hostility	...[when parents] actively dislike their children...aversion, hostility, harshness, overreactivity, irritability, and explosiveness...overt communication of negative feelings for the child, such as criticism, derision, or disapproval...in reaction to child bids for help and attention...[or] initiated by the parent, independent of the child's behavior...(p. 185).
Structure/contingency	...the extent to which social and physical contexts provide individuals with information about the pathways to achieving desired and avoiding undesired outcomes and provide support and guidance for following those pathways... (p. 187).
Chaos/insensitivity	...parenting behaviors that are noncontingent, inconsistent, erratic, unpredictable, undependable, arbitrary, or, in general interfere with or obscure the pathways from means to ends...a kind of environmental confusion... (p. 187).
Autonomy support	...communicating genuine respect and deference and encouraging children to actively discover, explore, and articulate their own views, goals, and preferences... (p. 188).
Coercion	...a restrictive overcontrolling intrusive autocratic style in which strict obedience is demanded... (p. 187).

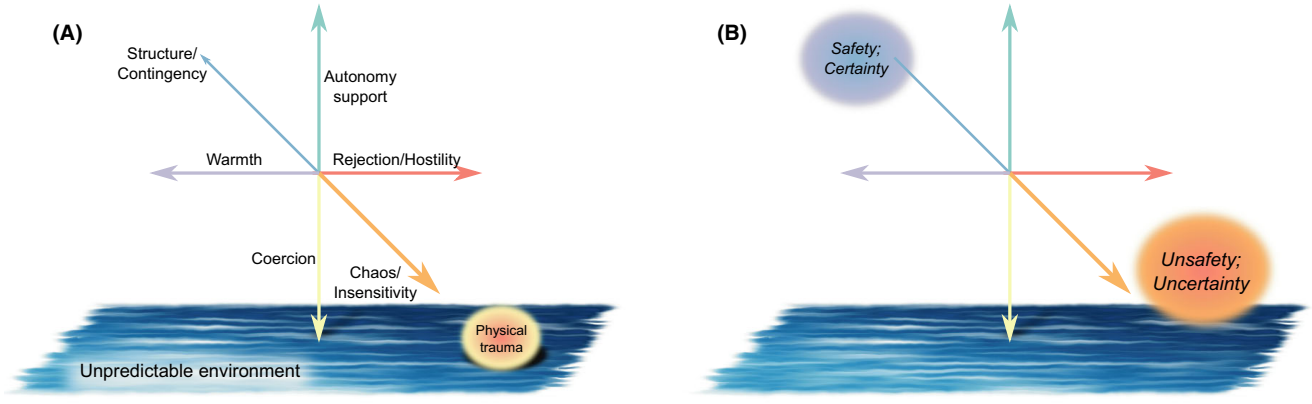

Figure 1 (A) Conceptual framework for the review based on dimensions of parenting proposed by Skinner et al. (2005). Definitions of each dimension are in Table 1. Dimensions that overlap closely, but not entirely, are on the same axis but are depicted with different colors to highlight their distinctiveness. *Physical trauma*, defined as exposure to physical threat, injury, or abuse, is depicted as a combination of high rejection, coercion, and chaos, and *unpredictable environments* are the basic needs and local conditions upon which caregiving and other social relationships 'float'. Greater unpredictability can be visualized as a 'stormier sea'. (B) Safety and certainty are superimposed upon the conceptual framework. Perceived safety and certainty are experienced in environments characterized by high warmth, structure, and autonomy support against a backdrop of high predictability in the environment. Perceived unsafety and uncertainty are experienced in environments characterized by high rejection, chaos, and coercion against a backdrop of high unpredictability in the environment [Colour figure can be viewed at wileyonlinelibrary.com]

Boyce, 2017), and accordingly are depicted in Figure 1 as the 'ocean' upon which caregiving and other relationships 'float'.

Ultimately, the Figure 1 dimensions are processed by central nervous system (CNS) nodes and networks that play key roles in thinking about and communicating with others (the social brain, represented in Figure 2A, Blakemore, 2008). Key functions of the social brain include representing the thoughts and feelings of others, simulating others' behavior, and representing social goals and motives (Lieberman, 2007; Slavich, 2020). Those functions help construct children's cognitive representations of other people, particularly caregivers, and whether they can be viewed as a secure base for exploring the world and a safe haven during times of need (Fearon, Groh, Bakermans-Kranenburg, van Ijzendoorn, & Roisman, 2016). A related construct with antecedents in early attachment experiences is *perceived social support*, the belief that support is available when needed (Thompson & Goodvin, 2016; Uchino, 2009). Children can also represent others as unpredictable, unreliable (Fearon et al., 2016), and threatening (Crick & Dodge, 1994). These representations inform affective, behavioral, and physiological responses executed by medial prefrontal and amygdala networks that promote survival (Peters, McEwen, & Friston, 2017; Slavich, 2020), including signaling to the immune system (Miller, Chen, & Parker, 2011; Slavich & Irwin, 2014).

Innate immunity and inflammation

The immune system develops in response to exposures to pathogens (Simon, Hollander, & McMichael, 2015). During childhood, interactions between a child's external environment and the immune system are mediated by exposure to infectious threats and the child's social brain communicating with the immune system. Arms of the immune system vary based on how they recognize, respond to, and remember different threats (viral, bacterial, parasite, or other stimuli; Chaplin, 2010). *Innate immunity* differentiates between threats with low specificity (bacteria with vs. without an outer membrane) and responds immediately upon exposure. *Adaptive immunity* can differentiate between threats with high specificity (e.g. the A/Brisbane/02/2018 influenza strain vs. the A/Kansas/14/2017 strain), takes days to mount a response, and 'remembers' prior exposures. Innate immunity mediates the first-line response to infection known as *inflammation*: destroying infectious pathogens, recruiting other immune cells, preventing spread to other areas, and repairing injured tissues (Calder et al., 2009; Chaplin, 2010; Turvey & Broide, 2010).

This review focuses on innate immunity for several reasons. The social world, including early life experiences (Kuhlman et al., 2017; Miller et al., 2011; Nusslock & Miller, 2016), interfaces with the innate immune system (Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2017; Slavich & Irwin, 2014). Inflammation mediates patient-reported health outcomes across a variety of conditions (Calder et al., 2009), such as upper respiratory infection symptoms (e.g. runny nose, cough; Cohen, Doyle, & Skoner, 1999). Chronic low-intensity inflammation can lead to tissue damage and dysregulated energy metabolism (i.e. insulin resistance, lipid accumulation; Calder et al., 2013) implicated in cardiovascular disease and type 2 diabetes, which often begins in adolescence (Miller et al., 2011). Finally, chemical messengers produced by the innate immune system communicate with the CNS and with immune cells in the CNS critical for brain development.

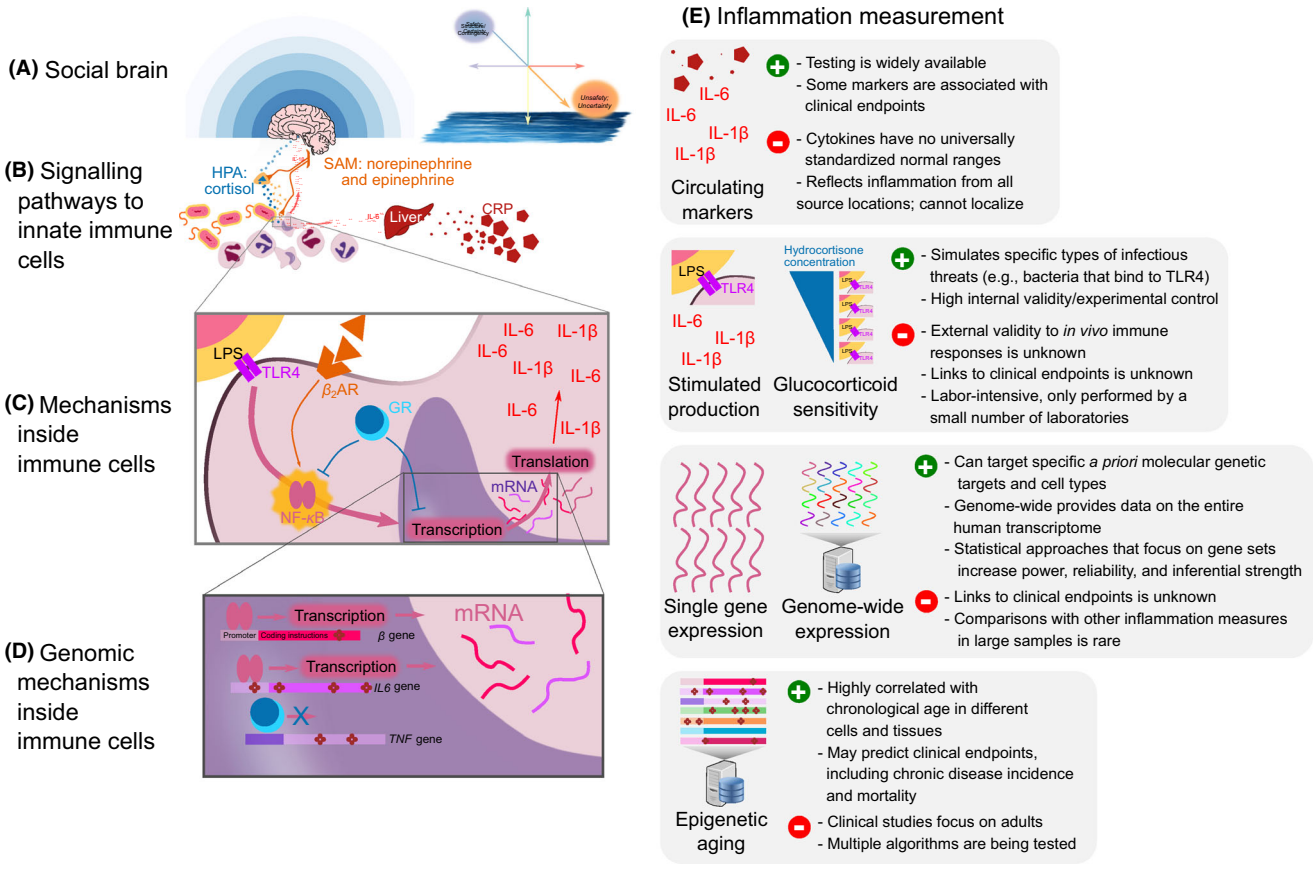

Figure 2 (A) The social brain processes features of the social environment (represented by the reproduced Figure 1B), constructing representations of other people such as perceived social support, and through medial prefrontal and amygdala networks sends signals informed by integrated assessments of safety and certainty to the periphery, including the immune system. (B) Innate immune cells respond to infectious threats, such as bacteria represented on the left side of the figure. Based on perceptions of uncertainty and lack of safety, the HPA and SAM axes send signals to immune cells in the form of the hormone cortisol, and the neurotransmitter norepinephrine (also the hormone epinephrine), respectively. In response to the pro-inflammatory cytokine IL-6, the liver produces CRP to aid inflammatory responses. (C) Inside innate immune cells, signals of infection/danger, such as LPS binding to TLR4, initiate a cascade of signals that activates the pro-inflammatory transcription factor NF-κB. Norepinephrine, through its interacting with the β_2-adrenergic receptor (β_2AR), can also activate pro-inflammatory cellular signaling, while cortisol interacting with the glucocorticoid receptor (GR) can block pro-inflammatory cellular signaling at multiple levels. Ultimately, NF-κB and other pro-inflammatory transcription factors facilitate the transcription of inflammation-related genes in the nucleus to messenger RNA (mRNA), and the translation of mRNA into proteins including pro-inflammatory cytokines (e.g. IL-1β, IL-6, but also TNF-α). (D) Inside immune cells, NF-κB binds to promoter regions on genes, which facilitates transcription of the coding regions into mRNA. Transcription factors can also block gene transcription, as shown by GR interacting with the *TNF* gene at the bottom. In addition, DNA methylation represented by the maroon clusters can modify how genes are read and transcribed, and these epigenetic changes may persist throughout the life course. (E) Inflammation-related measures include circulating pro-inflammatory markers such as IL-1β, IL-6, or CRP; stimulated cytokines produced *in vitro* after adding molecules that simulate pathogen or danger signals such as LPS; stimulating cytokines and incubating with different concentrations of glucocorticoid hormones to measure glucocorticoid hormones. Genomic measures include levels of single gene expression, such as degree of NF-κB mRNA expression; genome-wide expression which is then analyzed using bioinformatic approaches to determine inflammation-related patterns; and identifying the presence of DNA methylation and quantifying the degree of epigenetic aging [Colour figure can be viewed at wileyonlinelibrary.com]

Dysregulated peripheral inflammation and neuroinflammatory processes in the brain may negatively impact the development of reward and emotion regulation circuitry, contributing to risk for mood and substance use disorders (Kuhlman et al., 2017; Nusslock & Miller, 2016).

The inflammatory cascade

A prototypical example is the initial response to a wound. Bacteria present on the skin invade tissues beneath the surface (Figure 2B), and injured cells release molecular signals. Innate immune cells, particularly neutrophils and macrophages, have 'sensors' that detect molecular patterns associated with pathogens, such as bacterial cell walls made of lipopolysaccharides (LPS), and patterns associated with 'danger', such as proteins and DNA released by damaged or dying cells (Chaplin, 2010; Turvey & Broide, 2010). One class of sensors is 'toll-like receptors' (TLRs), such as TLR4 which detects LPS, and TLR9 which detects double-stranded DNA in viruses. Sensor activation, such as LPS binding to TLR4 (Figure 1C), starts a cascade inside immune cells, particularly activation of *transcription factors* in the Nuclear Factor (NF)-κB family (Turvey &

Broide, 2010). NF-κB binds to specific regions on genes called promoters, which leads to the *transcription* of genetic instructions in the coding region of genes into messenger RNA (mRNA; Figure 2D), and *translation* of mRNA into molecules that mediate or regulate the inflammatory response (Figure 2C, right). Those molecules include chemical messengers in the immune system – cytokines – that attract other cells to the site of infection, increase the permeability of tissue spaces to fluid movement, and enable cells to migrate between tissue spaces (Calder et al., 2013). NF-κB activation induces synthesis and release of *pro-inflammatory cytokines*, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, which have a variety of effects at the infection site, including destroying cells, increasing migration of other immune cells to the site, and activating other immune cells. In the liver, pro-inflammatory cytokines induce production of acute phase proteins including C-reactive protein (CRP), which promotes elimination of bacteria and damaged cells (Figure 2C). At the brain, high pro-inflammatory cytokine levels induce systemic and behavioral responses including sickness behaviors (e.g. social withdrawal, difficulty concentrating) and fever (Irwin & Cole, 2011).

Processes that regulate inflammation, and a caveat to interpretation

Anti-inflammatory processes help prevent excessive tissue damage (Calder et al., 2013). Cortisol produced by the hypothalamic–pituitary–adrenal (HPA) axis exerts anti-inflammatory effects by binding to the glucocorticoid receptor (GR; Figure 2C), which then prevents gene transcription by NF-κB (Irwin & Cole, 2011). Immune cells also produce anti-inflammatory cytokines (IL-10, IL-13, others). Pro-inflammatory cytokines can also act as negative feedback to downregulate inflammatory processes (Calder et al., 2013), illustrating an important caveat: inflammatory markers have many functions, some of which do not involve the prototypical pro-inflammatory response to infection. IL-6 and CRP are also involved in energy storage and facilitate dialing down inflammation and initiating tissue repair during the later phases of infection (Del Giudice & Gangestad, 2018). Thus, the inference that modest elevations in circulating inflammatory markers are *the* definition of 'low-grade inflammation' is limited; such elevations may indicate investments in growth and maintenance.

Shared goals – responding to and minimizing uncertainty and lack of safety

Contemporary stress perspectives highlight the central role of perceived *uncertainty* (Peters et al., 2017) and the presence or lack of *safety*, including social safety, in how the brain evaluates and responds to the environment (Brosschot, Verkuil, & Thayer, 2017; Slavich, 2020). Uncertainty refers to not knowing how to protect personal well-being, a lack of safety refers to perceiving that harm to personal well-being is likely, and social safety refers to social circumstances characterized by warmth and connection. Perceptions of the social environment and the presence of infections and other internal states are integrated by the brain (Irwin & Cole, 2011), and contemporary perspectives suggest that safety and certainty perceptions are based on that integration. Uncertainty or lack of safety are states that organisms then attempt to reduce by mounting physiological and behavioral responses that support coping (Peters et al., 2017). Similarly, evolutionary-developmental perspectives center around children determining the degree of external threat and uncertainty and preparing responses that promote survival, such as greater vigilance to threat and accelerated maturation (Ellis & Del Giudice, 2019).

Figure 1B adds safety/certainty onto the three-dimensional space. High rejection, chaos, coercion, and physical trauma contribute to a child's perceptions of the surrounding environment, particularly caregivers and close others, as uncertain and unsafe (Davies, Martin, & Sturge-Apple, 2016). Unpredictable environments can further amplify perceived unsafety and uncertainty. The cumulative impact of uncertain and unsafe environments, through repeated neuroendocrine stress responses communicated to the immune and other systems, may preparing individuals for future threats (Brosschot et al., 2017; Peters et al., 2017; Slavich, 2020). At the same time, moderate uncertainty that can be managed through warmth, structure, and autonomy support may be beneficial for children (Repetti & Robles, 2016; Shonkoff et al., 2012).

Indeed, social ties help reduce uncertainty and increase perceptions of safety (Slavich, 2020). Attachment theory (Fearon et al., 2016) and social baseline theory (Coan & Sbarra, 2015) highlight that social relationships increase security and distribute risk and demands across one's social network. Stress buffering, represented in Figure 1 as warmth, refers to social relationships reducing appraisals of harm, threat, and uncertainty (Rueger, Malecki, Pyun, Aycock, & Coyle, 2016). Likewise, social relationships play important roles in emotion regulation (Reeck, Ames, & Ochsner, 2016) and can serve as safety cues (Hornstein, Fanselow, & Eisenberger, 2016). Structure/contingency and autonomy support can further promote certainty for children (Skinner et al., 2005). Ultimately, increased perceived certainty and safety provided within a child's social network may act through neuroendocrine signaling pathways to lower systemic inflammation and inflammatory responses to threats (Figure 2B; Hostinar, Sullivan, & Gunnar, 2014; Slavich, 2020).

The next section reviews existing research on child social relationships and inflammation during

childhood as well as adulthood. An immune system that is prepared or programmed to respond to future threats in an amplified manner (Miller et al., 2011; Repetti, Robles, & Reynolds, 2011; Slavich & Irwin, 2014) may lead to several consequences in adulthood. *Biological embedding*, where DNA instructions are modified through epigenetic processes (Figure 2D), thereby regulating future DNA transcription (Miller et al., 2011); and faster aging of the immune system (*immunosenescence)*. Immune cells have a fixed number of replications, and as immunosenescent cell populations reach their replicative limit, they undergo changes that can promote increased inflammation later in life (Ferrucci & Fabbri, 2018).

The state of research on social relationships and inflammation in childhood

Review procedures and approaches to measurement

Search and screening strategy. While this is a narrative review, procedures were consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). Combinations of search terms (Table S1) were entered into PubMed, Web of Science, and PsycINFO during October and November 2019. After screening 17,427 titles and abstracts (Covidence, Veritas Health Innovation, Melbourne, Australia; www.covidence.org), 81 full-text articles were assessed for eligibility. Inclusion criteria were as follows: (a) neurotypical children; (b) the independent variable had to include questionnaire items or observations that measured one or more Figure 1 constructs in social networks during childhood; (c) the dependent variable was an *in vivo* or *ex vivo* inflammation or regulation of inflammation measure assessed in childhood or adulthood; (d) observational/correlational studies, as the number of intervention studies to date was too few for a truly systematic review (but are reviewed in the *Discussion* section); and (e) published in an English language journal. Of the 81 full-text articles assessed for eligibility, 43 were included in the review.

Social relationship measurement. Methods included questionnaires, daily diaries, behavioral observations in the laboratory, and semi-structured interviews. In infant samples (Table S2), the caregiver–infant relationship was operationalized through infant behavior responses during the reunion phase of the Strange Situation task. Many approaches combined multiple Figure 1 dimensions. For example, the semi-structured UCLA Life Stress Interview assesses chronic and episodic stressors in a variety of domains. Interviewers rate each domain on a 1 (exceptionally good conditions) to 5 (extreme adversity) scale. A score of 4 could be due to high rejection (regardless of warmth), low warmth (regardless of rejection), or both at the same time; warmth and rejection cannot be disentangled in the scoring system, even though social environments can be simultaneously helpful and rejecting (Holt-Lunstad & Uchino, 2019). Finally, objective exposure measures (e.g. audio recordings) are included along with measures of child attitudes and responses to parents and peers (e.g. perceived support), as both capture important facets of social relationships. Accordingly, I review studies that were not included in a recent meta-analysis on adverse childhood experience exposures and inflammation (Kuhlman, Horn, Chiang, & Bower, 2019).

Measuring inflammation and related regulatory processes. Figure 2E depicts inflammation measurement approaches, including strengths and limitations. Much like constructs and measures in the behavioral sciences, there is no 'gold standard', and measures are imperfect representations of inflammation-related constructs, such as pro-inflammatory potential. Each approach has sources of variability related to sample (plasma, serum, dried blood spot, saliva); storage and processing protocols; assay platforms (enzyme immunoassays, multiplex platforms); and biostatistical approaches. Details regarding sources of variability can be found elsewhere (Calder et al., 2013; Cole, 2016; Zhou, Fragala, McElhaney, & Kuchel, 2010).

Circulating and stimulated cytokines and markers. Circulating pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and/or the acute phase protein CRP are commonly measured in plasma, serum, and dried blood spots (Figure 2E, top, Samuelsson et al., 2015). Salivary markers are less invasive, but have disadvantages related to precision, correspondence with blood-based markers, and external validity (Riis, Byrne, Hernández, & Robles, 2020). Stimulating immune cells *ex vivo* with molecules that bind to TLRs (e.g. LPS) and measuring cytokine production may reflect the *potential* of immune cells to respond to threats. Co-incubating stimulated cells with varying concentrations of glucocorticoids can index *glucocorticoid sensitivity* (Figure 2E, second from top, Miller & Chen, 2010). If immune cells from Child A require a higher glucocorticoid concentration to achieve the same reduction in pro-inflammatory cytokine production as Child B, Child A's immune cells can be considered less sensitive to glucocorticoids.

Genomic measures. Specific gene approaches measure NF-κB (*NFKB1*), β_2-adrenergic receptor (β_2AR, *ADRB2*), and/or GR (*NR3C1*) mRNA expression (Figure 2E, second from bottom). Genome-wide approaches involve identifying patterns of relatively over- and under-expressed genes between different groups of children, and discerning meaningful

patterns of gene expression using bioinformatics, such as whether differentially expressed genes have promoter regions that bind to NF-κB and the GR (Cole, 2016). Greater *NFKB1* or *ADRB2* expression, greater expression of genes that respond to NF-κB, lower *NR3C1* expression, and lower expression of genes that respond to GR are plausible indicators of a pro-inflammatory phenotype.

Aging-related measures. Over time and exposures, methyl groups (one carbon and three hydrogen atoms) bind to DNA, known as methylation (Franceschi, Garagnani, Parini, Giuliani, & Santoro, 2018). The accumulation of methylation sites on the genome of cells and tissues tracks with chronological aging and may even predict health and lifespan (in adults, Horvath, 2013), also described as *epigenetic aging* (Figure 2E, bottom). 'Older' immune cells that have reached a point where they no longer replicate (termed replicative senescence) are implicated in the chronic, low-level inflammation associated with aging (Franceschi et al., 2018).

Covariates and mechanisms

In the studies below, researchers controlled for demographic factors including chronological age, ethnicity, gender, or biological sex; adiposity (body mass index [BMI] or waist circumference); health behaviors including smoking, alcohol use, and physical activity; family SES (O'Connor et al., 2009); and contextual factors ranging from stressful life events in the family to parent psychopathology symptoms. History of chronic conditions and medication use were often exclusion criteria. While covariates vary by study, the findings reported below controlled for potential third variables, and in a few cases, test specific mechanisms.

Organization of the review

The first section focuses on circulating inflammatory markers and is organized by developmental period (infancy and early childhood, middle childhood, and adolescence) and the Figure/Table 1 dimensions. Concurrent associations within each period are reviewed first, followed by long-term associations between childhood social relationship factors and inflammation in late adolescence or adulthood, which is relevant to biological embedding.

Circulating inflammatory markers

Infancy and early childhood

This group of studies (Table S2) focused on families with low-income (receiving federal food assistance; Measelle & Ablow, 2018; Measelle, David, & Ablow, 2017; Nelson, Bernstein, Allen, & Laurent, 2019) or prior referrals to child protective services (Bernard, Hostinar, & Dozier, 2019). Infants (between 12 and 19 months of age) who showed disorganized attachment behaviors had higher CRP (salivary or serum) compared with infants classified as secure (Bernard et al., 2019; Measelle et al., 2017), or larger increases in CRP over longitudinal follow-up (Nelson et al., 2019). Disorganized attachment behavior is characterized by 'conflicted, confused, and/or apprehensive behavior' during reunion with the caregiver in the Strange Situation Task, reflecting infant's wanting to approach and avoid the caregiver (Granqvist et al., 2017). Caregiver factors associated with increased infant disorganized behaviors include caregivers as a source of alarm and acting in frightening ways, coping with loss or trauma in ways that affect day-to-day behavior, and caregiver maltreatment. However, disorganized behavior is often observed in the absence of child maltreatment, and disorganized behavior by itself cannot be used as an indicator of maltreatment. Moreover, socioeconomic risk factors increase disorganized behavior even in high caring families (Cyr, Euser, Bakermans-Kranenburg, & Van Ijzendoorn, 2010). Thus, at best these studies suggest that unpredictable environments may be associated with elevated inflammation in infancy. Finally, secure attachment may buffer against, and insecure attachment more generally may magnify associations between maternal depressive symptoms (but not other stressors in the family) and salivary inflammatory markers (Measelle & Ablow, 2018).

Importantly, disorganized behaviors may occur because of illness or pain, that is, inflammation causing more disorganized behaviors. Longitudinal data from Nelson et al. (2019) suggest the direction is from attachment behavior to inflammation, though more work with blood-based biomarkers is needed. Finally, such elevations may persist in later childhood; infants ($N = 600$) whose mothers reported greater interpersonal stressors during infancy showed higher circulating CRP levels during adolescence (Reid et al., 2019), though this study focused on serious interpersonal stressors reported by mothers.

Middle childhood and adolescence

During this period, the importance of different social relationships and the weighting of Figure 1 dimensions for children's well-being changes. While warmth, rejection, structure, and chaos are important throughout development, warmth and rejection from peers relative to parents become increasingly important. The degree to which caregivers provide autonomy support vs. coercion takes on increasing importance as the family navigates shifts in power dynamics and household responsibilities (Chen et al., 2017). While these developmental shifts suggest studying middle childhood and adolescence separately or as moderators, wide age ranges,

sample sizes that limit testing age differences, and the preponderance of both cross-sectional studies and age-homogeneous cohort studies are the main obstacles to testing such questions. This section starts with the most frequently studied constructs of warmth and rejection, followed by structure/chaos, and finally studies that included physical trauma and unpredictable environment measures (Table S3).

Warmth. Main effects of warmth have not been associated with inflammation, as evidenced by a large cross-sectional study of Latino youth (Gallo et al., 2019). However, such associations may not emerge until adulthood. African American children reporting more perceived support from parents at age 12 showed lower circulating CRP at age 32 (Jones et al., 2017), which is consistent with research on greater perceived social support and lower circulating inflammatory markers in adults (Uchino et al., 2018).

Beyond main effects, warmth from parents may buffer against the impact of stressors. Greater depressive symptoms were related to higher circulating CRP, but only for adolescents reporting low received support from parents (Guan et al., 2016). In the same sample, received support from friends was not a moderator. In African American adolescents, parent-reported emotional support (given to the adolescent) during late adolescence was not related to epigenetic aging in immune cells during early adulthood (Brody, Miller, Yu, Beach, & Chen, 2016). At the same time, greater exposure to discrimination was related to more epigenetic aging, but only among youths whose parents reported giving low emotional support to their child.

Rejection and coercion. This cluster focused on interpersonal stressors including arguments, experienced discrimination, or being bullied. Mirroring the small, nonsignificant associations with adverse childhood experiences (Kuhlman, Horn, et al., 2019), evidence for associations between rejection and circulating markers was largely absent (Chiang et al., 2015; Fuligni, Telzer, Bower, Cole, et al., 2009; Jones, Lam, Hoffer, Chen, & Schreier, 2018; Marin, Martin, Blackwell, Stetler, & Miller, 2007; Miller, Rohleder, & Cole, 2009; Murphy, Slavich, Rohleder, & Miller, 2013; Schreier & Chen, 2017). Instead, the association between interpersonal stressors and circulating markers may depend on the presence of difficult circumstances. Across two independent samples that used semi-structured interviews, chronic interpersonal stressors and impact ratings of episodic life events were not related to circulating markers (Marin et al., 2007; Schreier & Chen, 2017); in one case, higher episodic stressor impact ratings were actually related to *lower* circulating CRP (Marin et al., 2007). Instead, higher circulating markers were only observed in adolescents exposed to chronic interpersonal stressors *and* highly impactful episodic stressors (CRP; Marin et al., 2007; IL-6, but not CRP; Schreier & Chen, 2017).

While circulating CRP increases from childhood to adolescence/young adulthood (Chiang, Park, et al., 2019; Copeland et al., 2014), longitudinal work suggests that daily interpersonal stressors were not related to circulating CRP or IL-6 over time (Chiang, Park, et al., 2019; Miller et al., 2009). However, work focused on bullying – a specific targeted rejection by peers – showed that relative to children with no perpetration or victimization history, children with a victimization history had higher CRP at ages 9–16. (Copeland et al., 2014). Greater cumulative reports of victimization were also related to increased CRP in adulthood, with a potential critical period during middle childhood. Finally, children with a perpetration history at ages 14–16 had the lowest CRP in adulthood.

Studies on rejection in childhood and adult inflammation involved predictors that were objectively coded or reported by others. Greater hostile maternal behavior during a mother–adolescent conflict discussion at age 18 (but not age 13) was related to higher circulating IL-6 at age 28 (Allen, Loeb, Tan, Narr, & Uchino, 2018). Greater harshness and less warmth reported by African American youth and parents at age 10 were related to a higher ratio of pro-inflammatory to anti-inflammatory cytokines at age 28 (Beach et al., 2017). Finally, greater parent report of bullying and child social withdrawal at ages 7 and 11 predicted higher CRP at age 44 (Lacey, Kumari, & Bartley, 2014).

Structure/chaos. Few studies measured structure and chaos. Moreover, structure-related constructs were frequently incorporated into a broader construct that included warmth and rejection, such as composite scores (Brody et al., 2016), or a single impact rating in the UCLA Life Stress Interview. Notably, in the one study that examined structure and chaos independent from warmth and rejection, greater disorganization in the home was marginally related to elevated circulating CRP (Schreier, Roy, Frimer, & Chen, 2014).

Physical trauma and unpredictable environments. A cluster of large longitudinal studies assessed exposure to physical trauma (including sexual abuse) and other adversities. These studies were also able to rule out potential confounders from early childhood, including SES and birthweight. Greater accumulation of adversities from age 1.5 to age 8 were related to higher circulating IL-6 and CRP at age 15 (Slopen, Kubzansky, McLaughlin, & Koenen, 2013) and larger increases in CRP from age 10 to age 15. Finally, accumulation of adversity during

middle childhood and adolescence was related to higher CRP in early to middle adulthood (age 44, Chen & Lacey, 2018; age 32, Danese et al., 2009).

Summary. The current evidence suggests no main effect associations between warmth or rejection and circulating markers during childhood. Instead, warmth and rejection may buffer or exacerbate links between stressors and circulating markers during childhood. In addition, children with greater environmental uncertainty show stronger associations between warmth or rejection and circulating markers, as the strongest evidence for main effects comes from under-resourced populations (e.g. families receiving food assistance). By comparison, many samples that show no association between warmth or rejection and circulating markers are characterized by low-to-moderate impact stress exposures, and/or underrepresentation of low SES families. Accordingly, accounting and selecting for chronic and acute stress exposure in future work are important because the buffering effects of warmth and exacerbating effects of rejection will not be apparent without systematic stress exposure measures.

Structure and chaos received considerably less empirical attention even though those dimensions may predict additional variance in circulating markers above and beyond warmth and rejection, even in adolescence (Schreier et al., 2014). Importantly, structure and chaos are not a direct proxy of family SES; at best, the correlations between SES and structure/chaos in the home are small (Dumas et al., 2005; Schreier et al., 2014). That said, the associations between family chaos and IL-6 (but not CRP) were stronger in low compared with high SES families (Schreier et al., 2014). Thus, future work should incorporate measures of structure and chaos, as well as autonomy support and coercion, that are treated as conceptually separate from warmth and rejection.

Unpredictable environmental conditions were related to elevated circulating markers in later, but not concurrent, developmental periods. In infants, relying on responses during the Strange Situation task limits inferences about childhood social relationships, although the highest quality study included infants referred to childhood protective services (Bernard et al., 2019), which clearly indicates social disruption. Unfortunately, large longitudinal cohort studies thus far did not assess inflammation in childhood, though newer longitudinal cohort studies will fill this knowledge gap. Meanwhile, unpredictable environments and physical trauma in childhood are related to circulating inflammation in *adulthood*. Normative changes during adulthood such as accumulating unhealthy behaviors, stress exposures, adiposity, and less supervision by caregivers may lead a biologically embedded pro-inflammatory phenotype to emerge later in life (Kuhlman, Horn, et al., 2019). Ultimately, stronger designs that include longitudinal inflammation measures throughout childhood and into adulthood are needed.

Mechanisms linking social relationships to inflammation

Neuroendocrine signaling initiated by the social brain (Hostinar et al., 2014) acts on the biology of the inflammatory cascade (for more detailed reviews, see Miller et al., 2011; Slavich & Irwin, 2014). Figure 2B depicts rapid norepinephrine signaling by the sympathetic–adrenal–medullary (SAM) axis and the slower glucocorticoid (cortisol) signaling from the HPA axis. Signaling molecules (norepinephrine, cortisol) bind to their respective receptors on or inside innate immune cells (Figure 2C; β_2AR, GR), which activates factors that regulate DNA transcription into RNA, followed by translation of the RNA instructions into proteins (including IL-1β, IL-6, and IL-10; Figure 2C), which travel throughout tissues and organs and produce effects within cells. Notably, norepinephrine is a potent pro-inflammatory signal even in the absence of pathogen exposure (Irwin & Cole, 2011).

Glucocorticoid sensitivity

One mechanism involves how stimulated immune cells respond to anti-inflammatory signaling via cortisol binding with the GR (Figure 2C). In adolescent women at high risk for depression based on family history and/or cognitive vulnerability (Table S4), greater adverse childhood experiences were related to decreasing glucocorticoid sensitivity over four timepoints from study entry to 18-month follow-up (Miller & Chen, 2010). Exposure to unpredictable environments was also related to lower glucocorticoid sensitivity (Ehrlich, Ross, Chen, & Miller, 2016). Because these findings come from a single sample, additional replications are needed.

Genomic mechanisms

Another mechanism involves transcription factors that regulate inflammation (Figure 2D and E, second from bottom, Table S5). Lower glucocorticoid sensitivity may be due to lower *NR3C1* mRNA expression in immune cells. In youth with asthma, greater youth-rated maternal warmth (Stanton et al., 2017) and higher daily self-disclosure to highly responsive social interaction partners (Imami et al., 2019) were related to higher *NR3C1* expression. However, in the same sample observed positive emotion expressions in families were not related to *NR3C1* expression (Farrell et al., 2018). Moreover, in generally healthy children, family warmth was not related to the expression of genes bearing response elements to GR (Robles et al., 2018).

For rejection, while chronic interpersonal stressor exposure was related to lower *NR3C1* expression in adolescent women at high risk for depression (Marin et al., 2007), main effects were not found in children with asthma (Imami et al., 2019; Miller & Chen, 2006). Higher family conflict was not related to expression of genes bearing GR response elements (Robles et al., 2018). However, chronic family stressors were related to lower *NR3C1* expression if children with asthma also experienced a highly impactful episodic stressor in the last 6 months (Miller & Chen, 2006). Lower *NR3C1* expression was also related to greater rejection in more focused coding of targeted rejection in life event interviews (overt, intentional rejection by others, Murphy, Slavich, Chen, & Miller, 2015); harsh conflict behaviors during an 8-min disagreement between parents and children (Ehrlich, Miller, & Chen, 2015); and family negative emotion expression in audio recordings (Farrell et al., 2018).

Longitudinal studies have shed light on dynamics over time and within the GR signaling cascade. Over 2.5 years, during periods when youth with asthma experienced a targeted rejection in the previous 6 months, they showed lower *NR3C1* expression (Murphy et al., 2015). The GR exists in multiple isoforms (Timmermans, Souffriau, & Libert, 2019), and the GRα isoform acts in an anti-inflammatory manner by inhibiting NF-κB actions (Bekhbat, Rowson, & Neigh, 2017). The GRβ isoform acts in a pro-inflammatory manner, promoting reduced glucocorticoid sensitivity by blocking GRα. In adolescent women at high risk for depression, greater chronic interpersonal stress was related to larger increases in GRβ (and not GRα) gene expression from study entry to 6 months later (Miller et al., 2009), consistent with the concept that rejection is related to reduced glucocorticoid sensitivity. No other studies have explored these GR dynamics in children, which should be revisited in future work.

Another pathway involves norepinephrine binding to the β_2AR on immune cells, which increases transcription of pro-inflammatory genes (Cole et al., 2010; Grebe et al., 2010). In children with asthma, warmth-related measures were not related to *ADRB2* expression (Ehrlich et al., 2015). For rejection, greater chronic family stressors in youth who experienced an impactful episodic stressor (Miller & Chen, 2006), targeted rejection (Murphy et al., 2015), and observed harsh conflict behaviors were related to lower *ADRB2* expression (Ehrlich et al., 2015). In contrast, greater chronic family stress was related to greater *ADRB2* expression in healthy children (Miller & Chen, 2006). Thus, in children with asthma, rejection may lower immune cell sensitivity to β_2AR signaling. The asthma context is critical, because medications that bind to the β_2AR facilitate airway expansion and reduce allergic inflammation (a different set of cells and cytokines compared with innate immune inflammation). Certain polymorphisms in the *ADRB2* gene impair β_2AR signaling, reducing the effectiveness of controller medications (Turner et al., 2016); reduced *ADRB2* expression may have a similar effect.

A final mechanism is NF-κB activity (Figure 2C, right). Greater warmth was related to lower expression of NF-κB-responsive genes during middle childhood (Robles et al., 2018). For rejection, in cross-sectional studies greater family conflict in middle childhood (Robles et al., 2018) and daily interpersonal stressors in adolescents were related to greater expression of genes bearing response elements to NF-κB (Chiang, Cole, et al., 2019). In adolescent women at risk for depression, chronic interpersonal stressors were related to increased *NFKB1* expression over 6 months (Miller et al., 2009), and over 2.5 years, experiencing targeted rejection in the past 6 months was related to greater *NFKB1* expression compared to periods with no targeted rejection (Murphy et al., 2013). While these findings show promise, the degree to which variations in gene expression related to social environments reflect brief, time-limited changes vs. biological embedding is unclear and more longitudinal data in developing children are needed.

Stimulated pro-inflammatory cytokine production

In the abstract, lower glucocorticoid sensitivity and higher *NFKB1* expression should be related to greater stimulated pro-inflammatory cytokine production (Figure 2E, second from top). However, in adolescent women at risk for depression glucocorticoid sensitivity measures showed modest, positive correlations with stimulated cytokine production in only *one* out of six visits over a 2.5-year period (Ehrlich, Miller, Rohleder, & Adam, 2016). Counterintuitively, GRα gene expression was positively correlated with stimulated IL-6 production, and *NFKB1* expression was not related to stimulated IL-6 production (Miller et al., 2009). These multimethod correlations come from one sample and need further replication, though expecting strong correlations between different methods may not be reasonable. Gene expression in cells obtained *in vivo* reflects multiple influences ranging from infectious burden, stress exposure, adiposity (described below), and signals from other tissues and cells, whereas stimulated cytokine production takes place in a highly controlled system that is outside the body. Ultimately, just like relationships between measures and constructs, each inflammation measure is an imperfect and independent representation of pro-inflammatory potential.

The studies below (Table S4) are discussed in order of increasing number of Figure 1 dimensions. Starting with warmth and structure, increased consistency of leisure-related parent–child interactions across time was related to lower stimulated cytokine production, whereas increased variability in the

quality of parent–child interactions was related to higher stimulated cytokine production (Manczak, Leigh, Chin, & Chen, 2018). Regarding warmth and rejection, in adolescent women at risk for depression, greater chronic interpersonal stressors were related to an increase in stimulated IL-6 at 6-month follow-up (Miller et al., 2009). However, chronic interpersonal stress was not related to stimulated cytokine production over subsequent timepoints across 2.5 years in the same sample (Ehrlich, Ross, et al., 2016). Chronic peer stress was related to greater stimulated IL-6 across multiple timepoints, but only for women from European backgrounds (vs. Asian backgrounds, Ehrlich, Miller, et al., 2016). Regarding structure and chaos, greater home disorganization was related to greater stimulated cytokine production even after including warmth- and rejection-related covariates (Schreier et al., 2014). Finally, exposure to unpredictable environments (Ehrlich, Ross, et al., 2016) and physical trauma (Miller & Chen, 2010) earlier in childhood were related to greater stimulated IL-6.

Finally, acute stressors can also stimulate inflammatory responses (Marsland, Walsh, Lockwood, & John-Henderson, 2017), and thus, the quality of social relationships in childhood may be related to immune responses to stress exposures (events). In a different sample of adolescent women at high risk for mood disorders, participants whose friends reported their being socially victimized by others showed larger salivary IL-1β and IL-6 responses to a brief laboratory stressor (Trier Social Stress Test, Giletta et al., 2018). Despite the findings described in this section, the clinical relevance of stimulated cytokine or stress-induced salivary cytokine production for later health outcomes is unknown.

Health behaviors

Diet and physical activity play a mechanistic role linking social environments to inflammation but are frequently treated as a covariate. Adiposity (excess body fat; Cornier et al., 2011) is a mechanism linking psychosocial factors and inflammation for several reasons. First, consuming food with high sugar and saturated fat is related to greater circulating inflammatory markers, due in part to their ability to stimulate inflammation (Gregor & Hotamisligil, 2011). Such diets are low in plant-based foods, which have antioxidant and anti-inflammatory properties (Calder et al., 2009). Second, poor family functioning is associated with greater adiposity in children and adolescents (Halliday, Palma, Mellor, Green, & Renzaho, 2014), and warmth, structure, and autonomy support from caregivers are related to psychological aspects of eating such as emotional eating and self-regulation (Harrist, Topham, Hubbs-Tait, Shriver, & Swindle, 2017) as well as physical activity (Yao & Rhodes, 2015). Finally, stored fat is a major source of pro-inflammatory immune cells and cytokines (Calder et al., 2009; Gregor & Hotamisligil, 2011), which in the absence of acute infection contribute to energy storage (including stored fat; Del Giudice & Gangestad, 2018). Accordingly, inflammation in early childhood may predict adiposity years later (Bernard et al., 2019). In several large studies, BMI emerges as a partial (Chen & Lacey, 2018; Lacey et al., 2014; Slopen et al., 2013) or even full mediator (Reid et al., 2019) of prospective associations between unpredictable environments and later inflammation.

Moderators of links between social relationships and inflammation

The associations between social relationships and inflammation may be conditioned on interconnected factors at the level of culture, family, and children. For example, greater chronic peer stress was related to lower glucocorticoid sensitivity and greater stimulated IL-6 production among adolescent women from European but not Asian backgrounds, even though peer stress did not vary between the two cultural groups (Table S4, Ehrlich, Miller, et al., 2016). The authors noted this may be due to cultural differences in health behaviors (such as alcohol or oral contraceptive use); immune responses, as adolescent women from Asian backgrounds had lower stimulated cytokine responses; responses to social stressors; or how research teams code the impact of stress exposures relative to how they are experienced by members of a cultural group.

Cultural values related to warmth and structure include the importance of family closeness, obligations, and interdependence. One example is familism, which varies both between and within cultural groups (e.g. persons from Latino backgrounds endorse more familism values vs. persons from European backgrounds). Individual differences in endorsing familism values may be more relevant in some groups but not others. For example, endorsing more familism values was related to greater sensitivity to the anti-inflammatory effects of IL-10 among Latino American and African American adolescents, but not European American adolescents (Chiang, Chen, et al., 2019). In addition, more time spent helping and with family was related to lower stimulated IL-6 production and greater GC sensitivity, but only among African American adolescents. The degree to which familism values become internalized by children may also play a role, as providing assistance to families was related to greater circulating CRP (but not IL-6), but adolescents that reported feeling like a good family member when providing assistance showed lower circulating CRP compared with adolescents who did not report similar role fulfillment (Fuligni, Telzer, Bower, Irwin, et al., 2009).

Both objective and subjective social statuses may also modify links between social relationship

functioning and inflammation, though evidence is preliminary and focused on chaos and rejection. At lower family income, greater disorganization in the home was related to higher circulating IL-6 (but not CRP) and greater stimulated IL-6 production (Schreier et al., 2014). Higher perceived social status was related to stronger associations between experiencing targeted rejection and NF-κB and IκB gene expression in adolescent women at risk for depression (Murphy et al., 2013), and stronger associations between targeted rejection and lower *NR3C1* and *ADRB1* gene expression among youth with asthma (Murphy et al., 2015).

In addition to cultural and socioeconomic contexts, parent capacity to engage in warmth or provide structure are also plausible moderators, though they were not specifically tested as moderators in the work described below. Adolescents whose parents self-reported greater empathic concern and perspective-taking had lower circulating CRP levels (but not IL-6; Manczak, DeLongis, & Chen, 2016). In addition, children with asthma whose parents showed more spontaneous perspective-taking when recalling personal challenges and struggles showed smaller pro-inflammatory cytokine responses during TLR3 (but not TLR4 or TLR9) stimulation (Manczak et al., 2017).

Finally, health conditions may moderate associations between social relationships and inflammation in childhood. While adolescent women at high risk for depression were a population of interest, studies did not include direct comparisons with children with low risk. Regarding physical health, only one paper directly compared children with and without asthma, noting between-group differences in the direction of associations between exposure to interpersonal stressors and *NR3C1* and *ADRB2* expression (Miller & Chen, 2006). However, the small sample size precludes drawing generalizable conclusions. Instead, the findings suggest that the pathophysiology of some chronic illnesses interacts with processes that exacerbate and regulate inflammation, and for children with chronic conditions, the social environment may play an important role in disease management and progression because of inflammatory pathways.

Discussion

Research connecting children's social relationships to inflammation emerged over the past decade from 23 independent samples across the studies and were reviewed through the lens of Figure 1A. The major questions posed at the beginning of this review were as follows: (1) What are the main effect associations between support or harm in social relationships and inflammation? (2) Does support or harm in social relationships modify associations between stress exposures and inflammation, with the corollary of are there groups of children, based on stress exposures, for whom support or harm in social relationships has a stronger association with inflammation? While warmth and structure contribute to perceptions of safety and certainty, main effect associations between warmth and circulating markers were not found. Several studies suggested links between warmth and genomic mechanisms, such as lower *NR3C1* expression (in children with asthma) or downregulation of genes that bind to NF-κB. Structure was rarely measured or considered separate from other dimensions, but cross-sectional findings from the same sample suggest plausible links with inflammation.

Rejection, physical trauma, and unpredictable environments contribute to perceptions of uncertainty and lack of safety and constitute most of the reviewed studies. Main effect associations between rejection and several inflammation measures were equivocal. Links between rejection and genomic mechanisms were more consistent across multiple populations (healthy children, children with asthma, and adolescent women at risk for depression) and rejection measures, but most of that work is cross-sectional, and implications for health remain unclear. For physical trauma and unpredictable environments, the current evidence suggests effects that may manifest later in development, and certainly in adulthood (Kuhlman, Horn, et al., 2019). At best, concurrent associations between adverse childhood experiences and inflammation may be specific for children in vulnerable groups, such as children at risk for depression based on family history.

One major takeaway is that many links between social relationships and inflammation during childhood were conditional on characteristics of the sample (presence of chronic illness, risk for psychopathology, economic hardship) or the presence of chronic and/or episodic interpersonal stressors. That is, there are groups of children for whom social relationships may have stronger associations with inflammation. While most work has focused on measuring warmth and rejection, structure and chaos are clearly relevant for appraising safety and certainty in one's environment, and autonomy vs. being controlling may impact a child's perceptions of safety and certainty. Ultimately, integration and evaluation of social relationships within the social brain shapes the safety and certainty signals that are transmitted to the immune system, but we know comparatively little about implications of that integration for inflammation. An ideal outcome in the next decade is assessing multiple dimensions of social relationships and consider how they interact with one another (e.g. can warmth from peers protect against a chaotic home?), which would allow for making meaningful inferences about inflammatory processes for children at different points in the three-dimensional space in Figure 1.

Implications for mental health

Children with particular combinations of social relationship conditions (i.e. high uncertainty), personality characteristics, and genetic factors may develop a pro-inflammatory phenotype in response to both psychological and infectious threat that increases risk for later depression or anxiety disorders (Slavich & Irwin, 2014). As noted earlier, pro-inflammatory cytokines mediate communication between the periphery and the brain. Reduced glucocorticoid sensitivity and increased pro-inflammatory cytokine production may impact reward and emotion regulation circuitry. For example, depression is a highly heterogeneous condition that can be deconstructed into different endophenotypes (measurable intermediate components), and experimental work suggests dysregulated inflammation is implicated in several endophenotypes (Dooley et al., 2018). In these studies, inflammation is manipulated through medical treatments for a chronic illness (interferon-α treatment), vaccination (typhoid, influenza virus), or low doses of LPS administered to healthy volunteers. The evidence to date suggests that inducing inflammation can increase neural reactivity to negative information, blunt reactivity to reward, heighten neural reactivity to stimuli depicting close others, increase fatigue and psychomotor slowing, and disrupt sleep (Dooley et al., 2018). Moreover, depressed patients and healthy controls show differences in some glucocorticoid sensitivity measures (Perrin, Horowitz, Roelofs, Zunszain, & Pariante, 2019), and developmental PNI research may help determine whether reduced glucocorticoid sensitivity is a risk factor for later depression.

Key directions for future research

Measuring perceptions of safety

This review and others have proposed safety, certainty, and the lack thereof as a key signal that is communicated to the innate immune system (Peters et al., 2017; Slavich, 2020). In addition to measuring social relationship dimensions in Figure 1, just as stress research distinguishes between exposures (events that happen to people) and stress responses (cognitive, affective, behavioral responses to those events, Harkness & Monroe, 2016), more work is needed to identify multimethod approaches to measuring perceptions of safety and certainty in children. Work informed by theories that focus on children's perceptions of security in caregiver–caregiver and caregiver–child relationships (Davies & Martin, 2013; Fearon et al., 2016) suggests attachment behaviors during infancy and emotional reactivity to the social environment during childhood as possible safety-related measures.

Sleep as a mechanism

Children spend approximately 40% of their childhood asleep, and developmental researchers have noted that safety and certainty are important prerequisites for sleep (Dahl, 1996). Sleep duration, how long a child is asleep during the night, decreases normally throughout development (Galland, Taylor, Elder, & Herbison, 2012; Park et al., 2019). Current guidelines recommend 12–16 hr of sleep in infancy, ultimately decreasing to 8–10 hr/night during adolescence (Matricciani, Olds, Blunden, Rigney, & Williams, 2012).

Several Figure 1 dimensions are related to sleep duration and disturbance in children. In a large cross-sectional, nationally representative sample of children, greater parental warmth (rather than reports of family conflict) predicted longer sleep duration for children between ages 5–12, but not children older than age 12 (Adam, Snell, & Pendry, 2007). Uncertain environments characterized by greater family disorganization (Billows et al., 2009) and greater marital conflict (El-Sheikh, Buckhalt, Mize, & Acebo, 2006) are related to sleep disturbance in childhood. Moreover, greater family conflict accumulated during childhood predicted insomnia symptoms at age 18 (Gregory, Caspi, Moffitt, & Poulton, 2006). Associations between family environments and sleep may be conditional; for example, in a sample of diverse adolescents, reports of perceived support from parents were not related to actigraphy-based sleep measures. However, for adolescents whose parents reported more stressful life events, greater perceived support from parents was related to more consistent sleep duration across the week and fewer awakenings during the night (Tsai et al., 2018).

To date, we know much more about sleep disruption and inflammation from research in adolescents and adults. Shortened sleep duration in adults is related to increased pro-inflammatory gene expression and cytokine levels following TLR4 stimulation (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006; Irwin et al., 2008). Shorter sleep duration is also related to higher circulating inflammatory markers in adolescent samples (Hall, Lee, & Matthews, 2015; Larkin et al., 2005; Martinez-Gomez et al., 2011; Park et al., 2016). Moreover, short sleep duration may amplify pro-inflammatory phenotypes related to social rejection. In adolescents, reporting more daily negative social interactions was related to greater expression of NF-κB-responsive genes, with larger effects for children with shorter objectively assessed sleep duration (Chiang, Cole, et al., 2019). The interplay among social relationships, sleep, and inflammation in adults and adolescents suggests the need for research in earlier developmental periods.

Electronically mediated social rejection

Social rejection and threat are potent stimulators of innate immune inflammation, even in the absence of actual infection (Slavich & Irwin, 2014), and children and adolescents are now subject to heightened social contexts and experiences that were not present for 99% of human history. Children use electronic platforms more than ever before, for individual- and group-level video gaming, viewing videos, and connecting with other peers through messaging and social media (Pew Research Center, 2018a, 2018b). Electronic platforms transform social experiences in several ways (Nesi, Choukas-Bradley, & Prinstein, 2018a, 2018b): increasing frequency and immediacy, amplifying intensity, and creating new opportunities for compensatory behaviors or even new types of social experiences (e.g. likes, getting canceled, posting demeaning videos, doxing). When those interactions involve frequent and/or intense peer victimization, inequities in peer status, or efforts to influence other peers, the potential for amplified social rejection is considerably high. Accordingly, the immunological and health impact of such exposures is a critically important area for future research.

Testing interventions

The few intervention studies with inflammation outcomes thus far are encouraging, and observational studies suggest additional intervention targets. A promising direction is engaging in prosocial behavior (Schreier, Schonert-Reichl, & Chen, 2013). In a small trial, 10th grade students randomly assigned to weekly volunteering with elementary school-aged children for two months showed lower circulating IL-6 levels at the end of the intervention compared with a waitlist control group. Moreover, students who reported increases in self-reported empathy and altruistic behaviors toward others showed lower IL-6 levels. Observational research suggests interpersonal skills as a potential target, as children who showed greater ability to defuse conflict in adolescence (rated by others) showed lower circulating IL-6 at age 28 (Allen et al., 2018).

Interventions that target families and children may also reduce inflammation in early adulthood (Miller, Brody, Yu, & Chen, 2014). The Strong African American Families (SAAF) Program recruited African American children between 10 and 14 years of age from nine rural counties in Georgia, who were randomly assigned at the county level to either a control group that received informational leaflets. Briefly, families in the SAAF intervention attended seven weekly meetings led by trained community members. In this study, warmth, structure, and autonomy support were targeted in the form of teaching involved parenting, encouraging open discussions around racism and substance use, and participating in activities together. Circulating pro-inflammatory cytokines from an age 19 follow-up were analyzed for 40% of the original sample. Children in the SAAF intervention showed lower circulating inflammatory markers (around −0.7 to −0.9 *SD* lower) compared with the control group, which was partially mediated by improvements in parenting quality during the trial, but not changes in adiposity or smoking, and the treatment effect was larger for families living in lower SES neighborhoods. Other targets for future intervention studies include increasing structure, which was related to lower circulating IL-6 in models examining links between parental depression and inflammation (Manczak et al., 2018). Ultimately, inflammatory measures will need to be incorporated into intervention studies in childhood to test causal questions and mechanisms, and the next section provides some discussion of how.

Incorporating inflammatory measures into developmental research

Before including inflammation measures into research, researchers should consider concerns of the populations of interest, particularly when working with groups that are underrepresented in research (Kuhlman, Urizar, Robles, Yim, & Dunkel Schetter, 2019). Circulating inflammatory markers are widely used and accessible. Where such measures have added utility is testing models and questions related to risk for cardiometabolic conditions (type 2 diabetes, obesity, metabolic syndrome, cardiovascular disease), including populations at increased risk for cardiometabolic disease (Ferrucci & Fabbri, 2018). A similar case can be made for risk for mood and anxiety disorders. When collecting circulating markers in children, be mindful that IL-6 and CRP may be linked to growth and maintenance, and incorporating what Del Giudice and Gangestad (2018) term 'unambiguous' inflammatory markers such as IL-1β and TNF-α will be critical for inferences about links between social relationships and inflammatory processes.

Despite their value thus far, the clinical relevance of stimulated cytokine production for health remains to be determined, and relatively few laboratories have the expertise and resources to regularly conduct those protocols. However, theoretical frameworks suggest that heightened immune responses to infectious challenge in childhood may presage poor health in adulthood (Miller et al., 2011; Repetti et al., 2011). *In vivo* stimulation methods such as typhoid vaccine or endotoxin injection are one way to examine immune responses to challenge but are less appropriate for children. We recently piloted measuring circulating IL-6 in response to influenza virus vaccination in a young adult sample (Kuhlman et al., 2018), and this paradigm can be extended to children and adolescents (in the 2018-2019 flu season, 6 out of 10 children were vaccinated, Centers for

Disease Control & Prevention, 2019). For example, we used this paradigm to examine links among adverse childhood experiences, inflammatory responses to vaccination, and mood symptoms post-vaccination (Kuhlman et al., 2020). Future work in children and adolescents could consider incorporating circulating IL-6 responses to influenza virus vaccination as a potentially health-relevant measure of *in vivo* innate immune reactivity.

Finally, gene expression and epigenetic age markers will become increasingly incorporated into psychoneuroimmunology research. An accumulating empirical literature and the continually decreasing price of collecting and sequencing DNA and RNA suggest continued adoption of these methods over the next decade. Two major unknowns for measures of gene expression are the degree to which they are stable or unstable over time, and whether such measures are associated with health outcomes. Answering these questions requires more longitudinal data and increased inclusion of genomic measures.

Conclusion: Threats to survival in the 21st century

Infectious diseases, nutritional scarcity, and violence persist to this day. Infection and malnutrition remain major threats to survival for children in low- and middle-income countries, and have been drastically reduced in high-income countries (United Nations Inter-agency Group for Child Mortality Estimation, 2019). Sadly, 1 in 2 children worldwide are exposed to physical, sexual, emotional, or other types of violence regardless of country-level wealth (Hillis, Mercy, Amobi, & Kress, 2016). Anticipating and preparing for survival threats, and protection conferred the safety and certainty from social relationships remain critical adaptations. For example, greater family warmth and structure can buffer against the harmful psychological consequences of exposure to violence (Yule, Houston, & Grych, 2019).

Modern civilization has added new threats that impact children's health through inflammatory pathways and cause health inequities; a child's social world may be a key amplifier or buffer of inflammatory responses to those threats. One example is environmental pollution (Trentacosta, Davis-Kean, Mitchell, Hyde, & Dolinoy, 2016), and outdoor air pollution in particular that acts on innate inflammatory processes in the airway, making it possible that harmful effects may be magnified by stressful social environments (Clougherty & Kubzansky, 2009; Olvera Alvarez, Kubzansky, Carnpen, & Slavich, 2018). Global climate change will bring additional exposures (wildfires, temperature-related synthesis of pollutants), and social disruptions because of higher temperatures, increased frequency of impactful weather events, and displacement from fire, flooding, and drought (Evans, 2019).

The newest threat is the ongoing COVID-19 pandemic. Research from upper respiratory infection viral challenge studies in adults suggests that interpersonal stressors can exacerbate upper respiratory infection symptoms and that greater social integration, perceived social support, and frequency of receiving hugs are related to less severe symptoms (Cohen, 2020). Importantly, innate immune inflammation across multiple organ systems including the lung, heart, vasculature, and CNS is implicated in the pathophysiology of COVID-19 (Sokolowska et al., 2020). Although children have been less impacted by COVID-19, asymptomatic children and children with symptoms can still spread the novel coronavirus. Notably, innate immune inflammation mediates virus-transmitting symptoms such as coughing and sneezing (Cohen et al., 1999). The mechanistic evidence in this paper suggests that warmth may downregulate inflammatory processes, and very preliminary correlational data suggest that greater family warmth may be related to less severe symptoms of active upper respiratory infection in children (Robles et al., 2018). Ultimately, the long-term impacts of COVID-19 on children may come from harmful side effects of physical distancing measures needed to contain the virus on children's social environments and sense of safety and certainty – reducing sources of warmth, structure, and autonomy support from peers and schools, and prolonging exposure for children in rejecting, chaotic, coercive, and abusive environments. Clearly, the impact of these social changes for children's social and immune development is an important direction for research in this new and uncertain time.

This paper reviewed research on social relationships and innate immune inflammation because of its wide-ranging consequences for physical and mental health. Greater attention to assessing multiple dimensions of the childhood social environment (particularly structure/chaos and autonomy support/coercion); assessing perceptions of safety; considering cultural, family, and individual moderators; exploring the role of sleep and electronically mediated social rejection; identifying the clinical relevance of inflammation-related measures; and incorporating inflammatory measures in intervention research will be key areas for growth. Ultimately, the ability to make strong inferences about social relationships and inflammation will help inform efforts by practitioners and policymakers to promote healthy social relationships that benefit health (Berger & Carlson, 2020; Holt-Lunstad, Robles, & Sbarra, 2017).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Search terms used in database searches.
Table S2. Infant samples with circulating inflammatory markers.
Table S3. Middle childhood and adolescent samples with circulating inflammatory markers, organized by clusters of Figure 1 categories.
Table S4. Middle childhood and adolescent samples with stimulated or stress-responsive cytokines, including glucocorticoid sensitivity.
Table S5. Middle childhood and adolescent samples with genomic mechanisms organized by clusters of Figure 1 categories.
Table S6. Studies that examined plausible psychosocial moderators.

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Correspondence
Theodore F. Robles, Department of Psychology, University of California, Los Angeles, 1285 Psychology Building, Box 951563, Los Angeles, CA 90095-1563, USA; Email: robles@psych.ucla.edu

Key points

- Multiple dimensions of a child's social relationships are processed by a child's social brain, and evaluations of the degree of safety and certainty in the social environment inform signals relayed via the neuroendocrine system to the immune system.
- The innate immune system is implicated in health in the short term and in the long term, including risk for future mental and physical health problems, and can be measured in multiple ways.
- Warmth and rejection in the social environment are not related to circulating inflammatory markers in a 'main effects' manner during childhood; instead, stronger and more consistent associations are found for children in higher-risk circumstances
- Warmth, rejection, and other features of children's social environments are related to inflammation in adulthood.
- Key directions for future research on social relationships and inflammation in childhood include measuring perceptions of safety, incorporating sleep as a mechanism, studying new threat contexts (electronically mediated social rejection), and testing interventions. Implications of this work extend to current health inequities including pollution exposure and COVID-19.

References
Adam, E.K., Snell, E.K., & Pendry, P. (2007). Sleep timing and quantity in ecological and family context: A nationally representative time-diary study. *Journal of Family Psychology*, *21*, 4–19.

Allen, J.P., Loeb, E.L., Tan, J.S., Narr, R.K., & Uchino, B.N. (2018). The body remembers: Adolescent conflict struggles predict adult interleukin-6 levels. *Development and Psychopathology*, *30*, 1435–1445.

Beach, S.R.H., Lei, M.K., Simons, R.L., Barr, A.B., Simons, L.G., Ehrlich, K., … & Philibert, R.A. (2017). When inflammation and depression go together: The longitudinal effects of parent-child relationships. *Development and Psychopathology*, *29*, 1969–1986.

Bekhbat, M., Rowson, S.A., & Neigh, G.N. (2017). Checks and balances: The glucocorticoid receptor and NFκB in good times and bad. *Frontiers in Neuroendocrinology*, *46*, 15–31.

Berger, L.M., & Carlson, M.J. (2020). Family policy and complex contemporary families: A decade in review and implications for the next decade of research and policy practice. *Journal of Marriage and Family*, *82*, 478–507.

Bernard, K., Hostinar, C.E., & Dozier, M. (2019). Longitudinal associations between attachment quality in infancy, C-reactive protein in early childhood, and BMI in middle childhood: preliminary evidence from a CPS-referred sample. *Attachment & Human Development*, *21*, 5–22.

Billows, M., Gradisar, M., Dohnt, H., Johnston, A., McCappin, S., & Hudson, J. (2009). Family disorganization, sleep hygiene, and adolescent sleep disturbance. *Journal of Clinical Child and Adolescent Psychology*, *38*, 745–752.

Blakemore, S. (2008). The social brain in adolescence. *Nature Reviews Neuroscience*, *9*, 267–277.

Brody, G.H., Miller, G.E., Yu, T.Y., Beach, S.R.H., & Chen, E. (2016). Supportive family environments ameliorate the link between racial discrimination and epigenetic aging: a replication across two longitudinal cohorts. *Psychological Science*, *27*, 530–541.

Brosschot, J.F., Verkuil, B., & Thayer, J.F. (2017). Exposed to events that never happen: Generalized unsafety, the default stress response, and prolonged autonomic activity. *Neuroscience and Biobehavioral Reviews*, *74*, 287–296.

Bugental, D.B. (2000). Acquisition of the algorithms of social life: A domain-based approach. *Psychological Bulletin*, *126*, 187–219.

Bornstein, M. H., & Cheah, C. S. L. (2006). The Place of "Culture and Parenting" in the Ecological Contextual Perspective on Developmental Science. In K. H. Rubin & O. B. Chung (Eds.), *Parenting beliefs, behaviors, and parent-child relations: A crosscultural perspective* (pp. 3–33). Psychology Press.

Calder, P.C., Ahluwalia, N., Albers, R., Bosco, N., Bourdet-Sicard, R., Haller, D., … & Zhao, J. (2013). A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. *British Journal of Nutrition*, *109*, S1–S34.

Calder, P.C., Albers, R., Antoine, J.M., Blum, S., Bourdet-Sicard, R., Ferns, G.A., … & Zhao, J. (2009). Inflammatory disease processes and interactions with nutrition. *British Journal of Nutrition*, *101*, S1–S45.

Centers for Disease Control and Prevention (2019). *Flu vaccination coverage, United States, 2018–19 influenza season*. Available from https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm

Chaplin, D.D. (2010). Overview of the immune response. *Journal of Allergy and Clinical Immunology*, *125*, S3–S23.

Chen, E., Brody, G.H., & Miller, G.E. (2017). Childhood close family relationships and health. *American Psychologist*, *72*, 555–566.

Chen, M.Y., & Lacey, R.E. (2018). Adverse childhood experiences and adult inflammation: Findings from the 1958 British birth cohort. *Brain, Behavior, and Immunity*, *69*, 582–590.

Chiang, J.J., Bower, J.E., Almeida, D.M., Irwin, M.R., Seeman, T.E., & Fuligni, A.J. (2015). Socioeconomic status, daily affective and social experiences, and inflammation during adolescence. *Psychosomatic Medicine*, *77*, 256–266.

Chiang, J.J., Chen, E., Leigh, A.K.K., Hoffer, L.C., Lam, P.H., & Miller, G.E. (2019). Familism and inflammatory processes in African American, Latino, and White youth. *Health Psychology*, *38*, 306–317.

Chiang, J.J., Cole, S.W., Bower, J.E., Irwin, M.R., Taylor, S.E., Arevalo, J., … & Fuligni, A.J. (2019). Daily interpersonal stress, sleep duration, and gene regulation during late adolescence. *Psychoneuroendocrinology*, *103*, 147–155.

Chiang, J.J., Park, H., Almeida, D.M., Bower, J.E., Cole, S.W., Irwin, M.R., … & Fuligni, A.J. (2019). Psychosocial stress and C-reactive protein from mid-adolescence to young adulthood. *Health Psychology*, *38*, 259–267.

Clougherty, J.E., & Kubzansky, L.D. (2009). A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environmental Health Perspectives*, *117*, 1351–1358.

Coan, J.A., & Sbarra, D.A. (2015). Social Baseline Theory: the social regulation of risk and effort. *Current Opinion in Psychology*, *1*, 87–91.

Cohen, S. (2020). Psychosocial vulnerabilities to upper respiratory infectious illness: implications for susceptibility to Coronavirus Disease 2019 (COVID-19). *Perspectives on Psychological Science*. https://doi.org/10.1177/1745691620942516

Cohen, S., Doyle, W.J., & Skoner, D.P. (1999). Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosomatic Medicine*, *61*, 175–180.

Cole, S.W. (2016). Functional genomic approaches to psychophysiology. In G.G. Berntson, J.T. Cacioppo & L.G. Tassinary (Eds.), *Handbook of psychophysiology* (4th edn, pp. 354–376). Cambridge, UK: Cambridge University Press.

Cole, S.W., Arevalo, J.M.G., Takahashi, R., Sloan, E.K., Lutgendorf, S.K., Sood, A.K., … & Seeman, T.E. (2010). Computational identification of gene-social environment interaction at the human IL6 locus. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 5681–5686.

Copeland, W.E., Wolke, D., Lereya, S.T., Shanahan, L., Worthman, C., & Costello, E.J. (2014). Childhood bullying involvement predicts low-grade systemic inflammation into adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, *111*, 7570–7575.

Cornier, M.A., Despres, J.P., Davis, N., Grossniklaus, D.A., Klein, S., Lamarche, B., … & Poirier, P. (2011). Assessing adiposity: a scientific statement from the American Heart Association. *Circulation*, *124*, 1996–2019.

Crick, N.R., & Dodge, K.A. (1994). A review and reformulation of social information-processing mechanisms in children's social adjustment. *Psychological Bulletin*, *115*, 74–101.

Crone, E.A., & Dahl, R.E. (2012). Understanding adolescence as a period of social-affective engagement and goal flexibility. *Nature Reviews Neuroscience*, *13*, 636–650.

Cyr, C., Euser, E.M., Bakermans-Kranenburg, M.J., & Van Ijzendoorn, M.H. (2010). Attachment security and disorganization in maltreating and high-risk families: A series of meta-analyses. *Development and Psychopathology*, *22*, 87–108.

Dahl, R.E. (1996). The regulation of sleep and arousal: Development and psychopathology. *Development and Psychopathology*, *8*, 3–27.

Danese, A., Moffitt, T.E., Harrington, H., Milne, B.J., Polanczyk, G., Pariante, C.M., … & Caspi, A. (2009). Adverse childhood experiences and adult risk factors for age-related disease depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatrics & Adolescent Medicine*, *163*, 1135–1143.

Davies, P.T., & Martin, M.J. (2013). The reformulation of emotional security theory: The role of children's social defense in developmental psychopathology. *Development and Psychopathology*, *25*, 1435–1454.

Davies, P.T., Martin, M.J., & Sturge-Apple, M.L. (2016). Emotional security theory and developmental psychopathology. In D. Cicchetti (Ed.), *Developmental psychopathology* (pp. 1–66). Hoboken, NJ: John Wiley & Sons.

Del Giudice, M., & Gangestad, S.W. (2018). Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain Behavior and Immunity*, *70*, 61–75.

Dooley, L.N., Kuhlman, K.R., Robles, T.F., Eisenberger, N.I., Craske, M.G., & Bower, J.E. (2018). The role of inflammation in core features of depression: Insights from paradigms using exogenously-induced inflammation. *Neuroscience and Biobehavioral Reviews*, *94*, 219–237.

Dumas, J.E., Nissley, J., Nordstrom, A., Smith, E.P., Prinz, R.J., & Levine, D.W. (2005). Home chaos: Sociodemographic, parenting, interactional, and child correlates. *Journal of Clinical Child and Adolescent Psychology*, *34*, 93–104.

Ehrlich, K.B., Miller, G.E., & Chen, E. (2015). Harsh parent-child conflict is associated with decreased anti-inflammatory gene expression and increased symptom severity in children with asthma. *Development and Psychopathology*, *27*, 1547–1554.

Ehrlich, K.B., Miller, G.E., Rohleder, N., & Adam, E.K. (2016). Trajectories of relationship stress and inflammatory processes in adolescence. *Development and Psychopathology*, *28*, 127–138.

Ehrlich, K.B., Ross, K.M., Chen, E., & Miller, G.E. (2016). Testing the biological embedding hypothesis: Is early life adversity associated with a later proinflammatory phenotype? *Development and Psychopathology*, *28*, 1273–1283.

Eisenberger, N.I., Moieni, M., Inagaki, T.K., Muscatell, K.A., & Irwin, M.R. (2017). In sickness and in health: The co-regulation of inflammation and social behavior. *Neuropsychopharmacology*, *42*, 242–253.

Ellis, B.J., & Del Giudice, M. (2019). Developmental adaptation to stress: An evolutionary perspective. *Annual Review of Psychology*, *70*, 111–139.

El-Sheikh, M., Buckhalt, J.A., Mize, J., & Acebo, C. (2006). Marital conflict and disruption of children's sleep. *Child Development*, *77*, 31–43.

Evans, G.W. (2019). Projected behavioral impacts of global climate change. *Annual Review of Psychology*, *70*, 449–474.

Farrell, A.K., Slatcher, R.B., Tobin, E.T., Imami, L., Wildman, D.E., Luca, F., & Zilioli, S. (2018). Socioeconomic status, family negative emotional climate, and anti-inflammatory gene expression among youth with asthma. *Psychoneuroendocrinology*, *91*, 62–67.

Fearon, R.M.P., Groh, A.M., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., & Roisman, G.I. (2016). Attachment and developmental psychopathology. In D. Cichetti (Ed.), *Developmental psychopathology*, *1*, 3rd edn, pp. 325–384). Hoboken, NJ: John Wiley & Sons.

Ferrucci, L., & Fabbri, E. (2018). Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nature Reviews Cardiology*, *15*, 505–522.

Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., & Santoro, A. (2018). Inflammaging: A new immune-metabolic viewpoint for age-related diseases. *Nature Reviews Endocrinology*, *14*, 576–590.

Fuligni, A.J., Telzer, E.H., Bower, J., Cole, S.W., Kiang, L., & Irwin, M.R. (2009). A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. *Psychosomatic Medicine*, *71*, 329–333.

Fuligni, A.J., Telzer, E.H., Bower, J., Irwin, M.R., Kiang, L., & Cole, S.W. (2009). Daily family assistance and inflammation among adolescents from Latin American and European backgrounds. *Brain, Behavior, and Immunity*, *23*, 803–809.

Galland, B.C., Taylor, B.J., Elder, D.E., & Herbison, P. (2012). Normal sleep patterns in infants and children: A systematic review of observational studies. *Sleep Medicine Reviews*, *16*, 213–222.

Gallo, L.C., Roesch, S.C., Bravin, J.I., Savin, K.L., Perreira, K.M., Carnethon, M.R., … & Isasi, C.R. (2019). Socioeconomic adversity, social resources, and allostatic load among Hispanic/Latino Youth: The Study of Latino Youth. *Psychosomatic Medicine*, *81*, 305–312.

Giletta, M., Slavich, G.M., Rudolph, K.D., Hastings, P.D., Nock, M.K., & Prinstein, M.J. (2018). Peer victimization predicts heightened inflammatory reactivity to social stress in cognitively vulnerable adolescents. *Journal of Child Psychology and Psychiatry*, *59*, 129–139.

Granqvist, P., Sroufe, L.A., Dozier, M., Hesse, E., Steele, M., van Ijzendoorn, M., … & Duschinsky, R. (2017). Disorganized attachment in infancy: A review of the phenomenon and its implications for clinicians and policy-makers. *Attachment & Human Development*, *19*, 534–558.

Grebe, K.M., Takeda, K., Hickman, H.D., Bailey, A.M., Embryo, A.C., Bennink, J.R., & Yewdell, J.W. (2010). Cutting edge: Sympathetic nervous system increases proinflammatory cytokines and exacerbates influenza A Virus pathogenesis. *Journal of Immunology*, *184*, 540–544.

Gregor, M.F., & Hotamisligil, G.S. (2011). Inflammatory mechanisms in obesity. *Annual Review of Immunology*, *29*, 415–445.

Gregory, A.M., Caspi, A., Moffitt, T.E., & Poulton, R. (2006). Family conflict in childhood: A predictor of later insomnia. *Sleep*, *29*, 1063–1067.

Guan, S.S.A., Bower, J.E., Almeida, D.M., Cole, S.W., Dahl, R.E., Irwin, M.R., & Fuligni, A.J. (2016). Parental support buffers the association of depressive symptoms with cortisol and C-reactive protein during adolescence. *Brain, Behavior, and Immunity*, *57*, 134–143.

Hall, M.H., Lee, L., & Matthews, K.A. (2015). Sleep duration during the school week is associated with C-reactive protein risk groups in healthy adolescents. *Sleep Medicine*, *16*, 73–78.

Halliday, J.A., Palma, C.L., Mellor, D., Green, J., & Renzaho, A.M.N. (2014). The relationship between family functioning and child and adolescent overweight and obesity: A systematic review. *International Journal of Obesity*, *38*, 480–493.

Harkness, K.L., & Monroe, S.M. (2016). The assessment and measurement of adult life stress: basic premises, operational principles, and design requirements. *Journal of Abnormal Psychology*, *125*, 727–745.

Harrist, A.W., Topham, G.L., Hubbs-Tait, L., Shriver, L.H., & Swindle, T.M. (2017). Psychosocial factors in children's obesity: Examples from an innovative line of inquiry. *Child Development Perspectives*, *11*, 275–281.

Hillis, S., Mercy, J., Amobi, A., & Kress, H. (2016). Global prevalence of past-year violence against children: A systematic review and minimum estimates. *Pediatrics*, *137*, e20154079.

Holt-Lunstad, J., Robles, T.F., & Sbarra, D.A. (2017). Advancing social connection as a public health priority in the United States. *American Psychologist*, *72*, 517–530.

Holt-Lunstad, J., & Uchino, B.N. (2019). Social ambivalence and disease (SAD): A theoretical model aimed at understanding the health implications of ambivalent relationships. *Perspectives on Psychological Science*, *14*, 941–966.

Hornstein, E.A., Fanselow, M.S., & Eisenberger, N.I. (2016). A safe haven: investigating social-support figures as prepared safety stimuli. *Psychological Science*, *27*, 1051–1060.

Horvath, S. (2013). DNA methylation age of human tissues and cell types. *Genome Biology*, *14*, R115.

Hostinar, C.E., Sullivan, R.M., & Gunnar, M.R. (2014). Psychobiological mechanisms underlying the social buffering of the hypothalamic–pituitary–adrenocortical axis: A review of animal models and human studies across development. *Psychological Bulletin*, *140*, 256–282.

Imami, L., Stanton, S.C.E., Zilioli, S., Tobin, E.T., Farrell, A.K., Luca, F., & Slatcher, R.B. (2019). Self-disclosure and perceived responsiveness among youth with asthma: Links to affect and anti-inflammatory gene expression. *Personality and Social Psychology Bulletin*, *45*, 1155–1169.

Irwin, M.R., & Cole, S.W. (2011). Reciprocal regulation of the neural and innate immune systems. *Nature Reviews Immunology*, *11*, 625–632.

Irwin, M.R., Wang, M.G., Campomayor, C.O., Collado-Hidalgo, A., & Cole, S. (2006). Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Archives of Internal Medicine*, *166*, 1756–1762.

Irwin, M.R., Wang, M., Ribeiro, D., Cho, H.J., Olmstead, R., Breen, E.C., … & Cole, S. (2008). Sleep loss activates cellular inflammatory signaling. *Biological Psychiatry*, *64*, 538–540.

Jones, E.J., Lam, P.H., Hoffer, L.C., Chen, E., & Schreier, H.M.C. (2018). Chronic family stress and adolescent health: the moderating role of emotion regulation. *Psychosomatic Medicine*, *80*, 764–773.

Jones, J.D., Ehrlich, K.B., Brett, B.E., Gross, J.T., Mohr, J.J., Hopper, E.A., … & Cassidy, J. (2017). Perceptions of parental secure base support in African American adolescents and young adults: A preliminary study of predictive links to adult C-reactive protein. *Journal of Social and Personal Relationships*, *34*, 1168–1185.

Kappeler, P.M., Cremer, S., & Nunn, C.L. (2015). Sociality and health: Impacts of sociality on disease susceptibility and transmission in animal and human societies Introduction. *Philosophical Transactions of the Royal Society B-Biological Sciences*, *370*, 20140116.

Kuhlman, K.R., Chiang, J.J., Horn, S., & Bower, J.E. (2017). Developmental psychoneuroendocrine and psychoneuroimmune pathways from childhood adversity to disease. *Neuroscience and Biobehavioral Reviews*, *80*, 166–184.

Kuhlman, K.R., Horn, S.R., Chiang, J.J., & Bower, J.E. (2019). Early life adversity exposure and circulating markers of inflammation in children and adolescents: A systematic review and meta-analysis. *Brain, Behavior, and Immunity*, *86*, 30–42.

Kuhlman, K.R., Robles, T.F., Dooley, L.N., Boyle, C.C., Haydon, M.D., & Bower, J.E. (2018). Within-subject associations between inflammation and features of depression: Using the flu vaccine as a mild inflammatory stimulus. *Brain, Behavior, and Immunity*, *69*, 540–547.

Kuhlman, K.R., Robles, T.F., Haydon, M.D., Dooley, L., Boyle, C.C., & Bower, J.E. (2020). Early life stress sensitizes individuals to the psychological correlates of mild fluctuations in inflammation. *Developmental Psychobiology*, *62*, 400–408.

Kuhlman, K.R., Urizar, G.G., Robles, T.F., Yim, I.S., & Dunkel Schetter, C. (2019). Testing plausible biopsychosocial models in diverse community samples: Common pitfalls and strategies. *Psychoneuroendocrinology*, *107*, 191–200.

Lacey, R.E., Kumari, M., & Bartley, M. (2014). Social isolation in childhood and adult inflammation: Evidence from the National Child Development Study. *Psychoneuroendocrinology*, *50*, 85–94.

Larkin, E.K., Rosen, C.L., Kirchner, H.L., Storfer-Isser, A., Emancipator, J.L., Johnson, N.L., … & Redline, S. (2005). Variation of C-reactive protein levels in adolescents – Association with sleep-disordered breathing and sleep duration. *Circulation*, *111*, 1978–1984.

Lieberman, M.D. (2007). Social cognitive neuroscience: A review of core processes. *Annual Review of Psychology*, *58*, 259–289.

Manczak, E.M., DeLongis, A., & Chen, E. (2016). Does empathy have a cost? Diverging psychological and physiological effects within families. *Health Psychology*, *35*, 211–218.

Manczak, E.M., Leigh, A.K.K., Chin, C., & Chen, E. (2018). Consistency matters: Consistency in the timing and quality of daily interactions between parents and adolescents predicts production of proinflammatory cytokines in youths. *Development and Psychopathology*, *30*, 373–382.

Manczak, E.M., Levine, C.S., Ehrlich, K.B., Basu, D., McAdams, D.P., & Chen, E. (2017). Associations between spontaneous parental perspective-taking and stimulated cytokine responses in children with asthma. *Health Psychology*, *36*, 652–661.

Marin, T.J., Martin, T.M., Blackwell, E., Stetler, C., & Miller, G.E. (2007). Differentiating the impact of episodic and chronic stressors on hypothalamic-pituitary-adrenocortical axis regulation in young women. *Health Psychology*, *26*, 447–455.

Marsland, A.L., Walsh, C., Lockwood, K., & John-Henderson, N.A. (2017). The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis. *Brain, Behavior, and Immunity*, *64*, 208–219.

Martinez-Gomez, D., Eisenmann, J.C., Gomez-Martinez, S., Hill, E.E., Zapatera, B., Veiga, O.L., & Marcos, A. (2011). Sleep duration and emerging cardiometabolic risk markers in adolescents. The AFINOS study. *Sleep Medicine*, *12*, 997–1002.

Matricciani, L.A., Olds, T.S., Blunden, S., Rigney, G., & Williams, M.T. (2012). Never enough sleep: A brief history of sleep recommendations for children. *Pediatrics*, *129*, 548–556.

Measelle, J.R., & Ablow, J.C. (2018). Contributions of early adversity to pro-inflammatory phenotype in infancy: the buffer provided by attachment security. *Attachment & Human Development*, *20*, 1–23.

Measelle, J.R., David, J., & Ablow, J.C. (2017). Increased levels of inflammation among infants with disorganized histories of attachment. *Behavioural Brain Research*, *325*, 260–267.

Miller, G.E., Brody, G.H., Yu, T.Y., & Chen, E. (2014). A family-oriented psychosocial intervention reduces inflammation in low-SES African American youth. *Proceedings of the National Academy of Sciences of the United States of America*, *111*, 11287–11292.

Miller, G.E., & Chen, E. (2006). Life stress and diminished expression of genes encoding glucocorticoid receptor and beta(2)-adrenergic receptor in children with asthma. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 5496–5501.

Miller, G.E., & Chen, E. (2010). Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. *Psychological Science*, *21*, 848–856.

Miller, G.E., Chen, E., & Parker, K.J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychological Bulletin*, *137*, 959–997.

Miller, G.E., Rohleder, N., & Cole, S.W. (2009). Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later. *Psychosomatic Medicine*, *71*, 57–62.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., & The PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*, e1000097.

Murphy, M.L.M., Slavich, G.M., Chen, E., & Miller, G.E. (2015). Targeted rejection predicts decreased anti-inflammatory gene expression and increased symptom severity in youth with asthma. *Psychological Science*, *26*, 111–121.

Murphy, M.L.M., Slavich, G.M., Rohleder, N., & Miller, G.E. (2013). Targeted rejection triggers differential pro-and anti-inflammatory gene expression in adolescents as a function of social status. *Clinical Psychological Science*, *1*, 30–40.

Nelson, B.W., Bernstein, R., Allen, N.B., & Laurent, H.K. (2019). The quality of early infant-caregiver relational attachment and longitudinal changes in infant inflammation across 6 months. *Developmental Psychobiology*, *62*, 674–683.

Nesi, J., Choukas-Bradley, S., & Prinstein, M.J. (2018a). Transformation of adolescent peer relations in the social media context: Part 1-A theoretical framework and application to dyadic peer relationships. *Clinical Child and Family Psychology Review*, *21*, 267–294.

Nesi, J., Choukas-Bradley, S., & Prinstein, M.J. (2018b). Transformation of adolescent peer relations in the social media context: Part 2-application to peer group processes and future directions for research. *Clinical Child and Family Psychology Review*, *21*, 295–319.

Nusslock, R., & Miller, G.E. (2016). Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. *Biological Psychiatry*, *80*, 23–32.

O'Connor, M.F., Bower, J.E., Cho, H.J., Creswell, J.D., Dimitrov, S., Hamby, M.E., … & Irwin, M.R. (2009). To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. *Brain, Behavior, and Immunity*, *23*, 887–897.

Olvera Alvarez, H.A., Kubzansky, L.D., Carnpen, M.J., & Slavich, G.M. (2018). Early life stress, air pollution, inflammation, and disease: An integrative review and immunologic model of social-environmental adversity and lifespan health. *Neuroscience and Biobehavioral Reviews*, *92*, 226–242.

Park, H., Chiang, J.J., Irwin, M.R., Bower, J.E., McCreath, H., & Fuligni, A.J. (2019). Developmental trends in sleep during adolescents' transition to young adulthood. *Sleep Medicine*, *60*, 202–210.

Park, H., Tsai, K.M., Dahl, R.E., Irwin, M.R., McCreath, H., Seeman, T.E. & Fuligni, A.J. (2016). Sleep and inflammation during adolescence. *Psychosomatic Medicine*, *78*, 677–685.

Perrin, A.J., Horowitz, M.A., Roelofs, J., Zunszain, P.A., & Pariante, C.M. (2019). Glucocorticoid resistance: is it a requisite for increased cytokine production in depression? A systematic review and meta-analysis. *Frontiers in Psychiatry*, *10*, 423.

Peters, A., McEwen, B.S., & Friston, K. (2017). Uncertainty and stress: Why it causes diseases and how it is mastered by the brain. *Progress in Neurobiology*, *156*, 164–188.

Pew Research Center (2018). Teens, social media, & technology 2018. Available from https://www.pewresearch.org/internet/2018/05/31/teens-social-media-technology-2018/

Pew Research Center (2018). How teens and parents navigate screen time and device distractions. Available from https://www.pewresearch.org/internet/2018/08/22/how-teens-and-parents-navigate-screen-time-and-device-distractions/

Prinstein, M.J., & Giletta, M. (2016). Peer relations and developmental psychopathology. In D. Cicchetti (Ed.), *Developmental psychopathology* (*1*, 3rd edn, pp. 527–579). Hoboken, NJ: John Wiley & Sons.

Reeck, C., Ames, D.R., & Ochsner, K.N. (2016). The social regulation of emotion: An integrative, cross-disciplinary model. *Trends in Cognitive Sciences*, *20*, 47–63.

Reid, B.M., Doom, J.R., Argote, R.B., Correa-Burrows, P., Lozoff, B., Blanco, E., & Gahagan, S. (2019). Pathways to inflammation in adolescence through early adversity, childhood depressive symptoms, and body mass index: A prospective longitudinal study of Chilean infants. *Brain, Behavior, and Immunity*, *86*, 4–13.

Repetti, R.L., & Robles, T.F. (2016). Nontoxic family stress: potential benefits and underlying biology. *Family Relations*, *65*, 163–175.

Repetti, R.L., Robles, T.F., & Reynolds, B. (2011). Allostatic processes in the family. *Development and Psychopathology*, *23*, 921–938.

Repetti, R.L., Taylor, S.E., & Seeman, T.E. (2002). Risky families: Family social environments and the mental and physical health of offspring. *Psychological Bulletin*, *128*, 330–366.

Riis, J.L., Byrne, M.L., Hernández, L.M., & Robles, T.F. (2020). Salivary bioscience, immunity, and inflammation. In D.A. Granger & M.K. Taylor (Eds.), *Salivary bioscience: Foundations of interdisciplinary saliva research and applications* (pp. 177–213). Cham, Switzerland: Springer International Publishing.

Robles, T.F., Repetti, R.L., Reynolds, B.M., Chung, P.J., Arevalo, J.M.G., & Cole, S.W. (2018). Family environments and the leukocyte transcriptome in children and parents. *Development and Psychopathology*, *30*, 235–253.

Roubinov, D.S., & Boyce, W.T. (2017). Parenting and SES: Relative values or enduring principles? *Current Opinion in Psychology*, *15*, 162–167.

Rueger, S.Y., Malecki, C.K., Pyun, Y., Aycock, C., & Coyle, S. (2016). A meta-analytic review of the association between perceived social support and depression in childhood and adolescence. *Psychological Bulletin*, *142*, 1017–1067.

Samuelsson, L.B., Hall, M.H., McLean, S., Porter, J.H., Berkman, L., Marino, M., … & Buxton, O.M. (2015). Validation of biomarkers of CVD Risk from dried blood spots in community-based research: Methodologies and study-specific serum equivalencies. *Biodemography and Social Biology*, *61*, 285–297.

Schreier, H.M.C., & Chen, E. (2017). Low-grade inflammation and ambulatory cortisol in adolescents: interaction between interviewer-rated versus self-rated acute stress and chronic stress. *Psychosomatic Medicine*, *79*, 133–142.

Schreier, H.M.C., Roy, L.B., Frimer, L.T., & Chen, E. (2014). Family chaos and adolescent inflammatory profiles: the moderating role of socioeconomic status. *Psychosomatic Medicine*, *76*, 460–467.

Schreier, H.M.C., Schonert-Reichl, K.A., & Chen, E. (2013). Effect of volunteering on risk factors for cardiovascular disease in adolescents: a randomized controlled trial. *JAMA Pediatrics*, *167*, 327–332.

Shonkoff, J.P., Garner, A.S., Siegel, B.S., Dobbins, M.I., Earls, M.F., McGuinn, L., … & Wood, D.L. (2012). The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*, *129*, E232–E246.

Simon, A.K., Hollander, G.A., & McMichael, A. (2015). Evolution of the immune system in humans from infancy to old age. *Proceedings of the Royal Society B: Biological Sciences*, *282*, 20143085.

Skinner, E., Johnson, S., & Snyder, T. (2005). Six dimensions of parenting: A motivational model. *Parenting: Science and Practice*, *5*, 175–235.

Slavich, G.M. (2020). Social Safety Theory: A biologically based evolutionary perspective on life stress, health, and behavior. *Annual Review of Clinical Psychology*, *16*, 265–295.

Slavich, G.M., & Irwin, M.R. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*, *140*, 774–815.

Slopen, N., Kubzansky, L.D., McLaughlin, K.A., & Koenen, K.C. (2013). Childhood adversity and inflammatory processes in youth: A prospective study. *Psychoneuroendocrinology*, *38*, 188–200.

Smith, K.E., & Pollak, S.D. (2020). Rethinking concepts and categories for understanding the neurodevelopmental effects of childhood adversity. *Perspectives on Psychological Science*. https://doi.org/10.1177/1745691620920725

Sokolowska, M., Lukasik, Z., Agache, I., Akdis, C.A., Akdis, D., Akdis, M., & Untersmayr, E. (2020). Immunology of COVID-19: Mechanisms, clinical outcome, diagnostics and perspectives – a report of the European Academy of Allergy and Clinical Immunology (EAACI). *Allergy*, *75*, 2445–2476.

Stanton, S.C.E., Zilioli, S., Briskin, J.L., Imami, L., Tobin, E.T., Wildman, D.E., … & Slatcher, R.B. (2017). Mothers' attachment is linked to their children's anti-inflammatory gene expression via maternal warmth. *Social Psychological and Personality Science*, *8*, 796–805.

Thompson, R.A., & Goodvin, R. (2016). Social support and developmental psychopathology. In D. Cichetti (Ed.), *Developmental psychopathology* (*4*, 3rd edn, pp. 86–135). Hoboken, NJ: John Wiley & Sons.

Timmermans, S., Souffriau, J., & Libert, C. (2019). A general introduction to glucocorticoid biology. *Frontiers in Immunology*, *10*, 1545.

Trentacosta, C.J., Davis-Kean, P., Mitchell, C., Hyde, L., & Dolinoy, D. (2016). Environmental contaminants and child development. *Child Development Perspectives*, *10*, 228–233.

Tsai, K.M., Dahl, R.E., Irwin, M.R., Bower, J.E., McCreath, H., Seeman, T.E., … & Fuligni, A.J. (2018). The roles of parental support and family stress in adolescent sleep. *Child Development*, *89*, 1577–1588.

Turner, S., Francis, B., Vijverberg, S., Pino-Yanes, M., Maitland-van der Zee, A.H., Basu, K., … & Lipworth, B. (2016). Childhood asthma exacerbations and the Arg16 beta(2)-receptor polymorphism: A meta-analysis stratified by treatment. *Journal of Allergy and Clinical Immunology*, *138*, 107–113.e5.

Turvey, S.E., & Broide, D.H. (2010). Innate immunity. *Journal of Allergy and Clinical Immunology*, *125*, S24–S32.

Uchino, B.N. (2009). Understanding the links between social support and physical health: A life-span perspective with emphasis on the separability of perceived and received support. *Perspectives on Psychological Science*, *4*, 236–255.

Uchino, B.N., Trettevik, R., de Grey, R.G.K., Cronan, S., Hogan, J., & Baucom, B.R.W. (2018). Social support, social integration, and inflammatory cytokines: A meta-analysis. *Health Psychology*, *37*, 462–471.

UNICEF (2019). Child mortality age 5–14. Available from https://data.unicef.org/topic/child-survival/child-mortality-aged-5-14/

United Nations Inter-agency Group for Child Mortality Estimation (2019). Levels and trends in child mortality: Report 2019. New York, NY.

Volk, A.A., & Atkinson, J.A. (2013). Infant and child death in the human environment of evolutionary adaptation. *Evolution and Human Behavior*, *34*, 182–192.

Yao, C.A., & Rhodes, R.E. (2015). Parental correlates in child and adolescent physical activity: A meta-analysis. *International Journal of Behavioral Nutrition and Physical Activity*, *12*, 10.

Yule, K., Houston, J., & Grych, J. (2019). Resilience in children exposed to violence: A meta-analysis of protective factors across ecological contexts. *Clinical Child and Family Psychology Review*, *22*, 406–431.

Zhou, X., Fragala, M.S., McElhaney, J.E., & Kuchel, G.A. (2010). Conceptual and methodological issues relevant to cytokine and inflammatory marker measurements in clinical research. *Current Opinion in Clinical Nutrition and Metabolic Care*, *13*, 541–547.

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