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Biological Aging in Childhood and Adolescence Following Experiences of Threat and Deprivation: A Systematic Review and Meta-Analysis

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Life history theory argues that exposure to early life adversity (ELA) accelerates development, although existing evidence for this varies. We present a meta-analysis and systematic review testing the hypothesis that ELA involving threat (e.g., violence exposure) will be associated with accelerated biological aging across multiple metrics, whereas exposure to deprivation (e.g., neglect, institutional rearing) and low-socioeconomic status (SES) will not. We meta-analyze 54 studies (n = 116,010) examining associations of ELA with pubertal timing and cellular aging (telomere length and DNA methylation age), systematically review 25 studies (n = 3,253) examining ELA and neural markers of accelerated development (cortical thickness and amygdala-prefrontal cortex functional connectivity) and evaluate whether associations of ELA with biological aging vary according to the nature of adversity experienced. ELA overall was associated with accelerated pubertal timing (d = −0.10) and cellular aging (d = −0.21), but these associations varied by adversity type. Moderator analysis revealed that ELA characterized by threat was associated with accelerated pubertal development (d = −0.26) and accelerated cellular aging (d = −0.43), but deprivation and SES were unrelated to accelerated development. Systematic review revealed associations between ELA and accelerated cortical thinning, with threat-related ELA consistently associated with thinning in ventromedial prefrontal cortex, and deprivation and SES associated with thinning in frontoparietal, default, and visual networks. There was no consistent association of ELA with amygdala-PFC connectivity. These findings suggest specificity in the types of early environmental experiences associated with accelerated biological aging and highlight the importance of evaluating how accelerated aging contributes to health disparities and whether this process can be mitigated through early intervention.

Public Significance Statement

This meta-analysis and systematic review suggests that biological aging following early life adversity, including earlier pubertal timing, advanced cellular aging, and accelerated thinning of the cortex, may be specific to children and adolescents who experienced violent or traumatic experiences early in childhood. No such effect was found for children who experienced deprivation or poverty in the absence of violence or trauma. These findings highlight a potential role of accelerated biological aging in health disparities associated with early life trauma, and a potential target for early interventions.

Keywords: threat, deprivation, pubertal timing, cellular aging, cortical thickness

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Exposure to early life adversity (ELA)—including exposure to child abuse, sexual assault, neglect, and chronic poverty—is associated with elevated risk for numerous mental and physical health problems, including depression, anxiety disorders, substance abuse, suicide, and cardiovascular disease (Felitti et al., 1998; Green et al., 2010; Heim & Binder, 2012; Kessler et al., 2010; McLaughlin et al., 2010; McLaughlin, Green, et al., 2012; Norman et al., 2012; Scott et al., 2011). The associations of ELA with mental and physical health problems are observable beginning in childhood and adolescence (Boynton-Jarrett, Ryan, Berkman, & Wright, 2008; Halpern et al., 2013; McLaughlin, Basu, et al., 2016; McLaughlin, Green, et al., 2012) and persist into adulthood (Dong et al., 2004; Felitti et al., 1998; Green et al., 2010; Kessler et al., 2010). Recent evidence from longitudinal and population-based studies indicates that exposure to ELA is also associated with elevated risk for premature mortality (Brown et al., 2009; Chen, Turiano, Mroczek, & Miller, 2016).

Accelerated Development/Biological Aging

One potential mechanism linking exposure to ELA with this wide range of physical and mental health problems is accelerated biological aging. Specifically, exposure to adversity early in life may alter the pace of development, resulting in faster aging. Most conceptual models on the link between ELA and accelerated development are based in life history theory (J. Belsky, Steinberg, & Draper, 1991; Ellis, Figueredo, Brumbach, & Schlomer, 2009; Ellis & Garber, 2000) and postulate that experiences in early life can program an individual's developmental trajectory in order to respond most effectively to the environmental demands they are likely to encounter later in life. The pattern and timing of life history events—such as age of sexual maturation, gestational period, number of offspring, birth spacing, length of parental investment, longevity, and others—is determined by the relative prioritization of time and energy invested in growth, reproduction, and survival (Del Giudice, Gangestad, & Kaplan, 2016; Hill & Kaplan, 1999). For instance, in a safe, predictable and enriched environment, a slow and protracted development may be optimal, as it allows for maximal parental investment prior to offspring independence. However, in a harsh or unpredictable environment, a faster pace of development in which individuals reach adult-like capabilities at an earlier age may be favored in order to maximize reproduction prior to potential mortality. Life history theories of human development argue that early environments characterized by harshness (e.g., trauma, violence exposure) may accelerate the onset of puberty in order to maximize the opportunity for reproduction prior to mortality (J. Belsky, 2012; Ellis et al., 2009; Rickard, Frankenhuis, & Nettle, 2014). However, in unpredictable environments, where there is large variation in harshness, it may be optimal to delay reproductive milestones, depending upon various features of the environment including population density and resource availability. For instance, according to some models, increased unpredictability in juvenile mortality tends to delay development, whereas increased unpredictability in adult mortality tends to accelerate development (J. Belsky, 2012; Ellis et al., 2009).

More recently, life history theories regarding the pace of development following ELA have been extended to focus on additional measures of biological aging. First, predictive adaptive response models (Nettle, Frankenhuis, & Rickard, 2013; Rickard et al., 2014) focus on cellular and molecular development and how it relates to an individual's morbidity and mortality across the life span. These models propose that ELA negatively influences physical health, through altered cellular development as a result of reduced energy to build or repair cellular tissue. This advanced cellular aging forecast may reduce longevity and contribute to acceleration in reproductive maturity (Nettle et al., 2013; Rickard et al., 2014). Second, the stress acceleration hypothesis (Callaghan & Tottenham, 2016) suggests that ELA accelerates the development of neural networks underlying emotional processing, specifically, the amygdala-prefrontal cortex (PFC) circuit thought to underlie emotion regulation capabilities. This accelerated development in the context of unreliable or absent caregiving may occur in order to allow for independent emotion regulation at an earlier age (Callaghan & Tottenham, 2016). Each of these theories rest on the assumption that ELA impacts the pace of development across multiple domains and metrics of biological aging (pubertal timing, cellular aging, and neural development).

ELA and Biological Aging

Biological aging following ELA has been measured with a variety of different metrics. By far the most commonly used metric is the timing and pace of pubertal development, including age of menarche in females (Boynton-Jarrett & Harville, 2012; Deardorff, Abrams, Ekwaru, & Rehkopf, 2014; Graber, Brooks-Gunn, & Warren, 1995) and pubertal stage controlling for chronological age (Colich et al., 2020; Mendle, Leve, Van Ryzin, Natsuaki, & Ge, 2011; Negriff, Blankson, & Trickett, 2015; Noll et al., 2017; Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2019). A second line of work has examined measures of cellular aging, including leukocyte telomere length (Coimbra, Carvalho, Moretti, Mello, & Belangero, 2017; Drury et al., 2014; Price, Kao, Burgers, Carpenter, & Tyrka, 2013) and DNA methylation (DNAm) age (Gassen, Chrousos, Binder, & Zannas, 2017; Wolf et al., 2018). A separate literature has examined markers of neural maturation such as amygdala-PFC connectivity (Callaghan & Tottenham, 2016; Gee, Gabard-Durnam, et al., 2013) and cortical thickness (McLaughlin, Sheridan, Winter, et al., 2014).

Evidence for accelerated biological aging following ELA has been found across all of these metrics. For example, numerous studies have found that ELA is associated with earlier pubertal timing (Graber et al., 1995; Hartman, Li, Nettle, & Belsky, 2017; Mendle et al., 2011; Negriff, Blankson, et al., 2015). Similarly, a small but increasing number of studies have reported accelerated cellular aging following ELA, including shorter telomere length (Drury et al., 2014, 2012; Mitchell et al., 2014; Shalev et al., 2013), and advanced DNAm age relative to chronological age (Jovanovic et al., 2017; Sumner et al., 2019). Finally, much of the evidence for accelerated neural development following ELA comes from studies examining amygdala-PFC functional connectivity (Colich et al., 2017; Gee, Gabard-Durnam, et al., 2013; Keding & Herringa, 2016) and cortical thinning across development (McLaughlin, Sheridan, Winter, et al., 2014). However, other studies have found no associations between ELA and pubertal timing (Negriff, Saxbe, & Trickett, 2015; Negriff & Trickett, 2012) or cortical thinning (McLaughlin, Sheridan, et al., 2016;

Rosen, Sheridan, Sambrook, Meltzoff, & McLaughlin, 2018). Some studies have even found that ELA is associated with slower or delayed pubertal timing (Johnson et al., 2018; Negriff, Blankson, et al., 2015; Sumner et al., 2019) and a more immature pattern of amygdala-PFC connectivity (Cisler, James, et al., 2013; Marusak, Martin, Etkin, & Thomason, 2015; Silvers et al., 2016). The strength and direction of the association between ELA and markers of biological aging varies widely across studies, and to date no systematic review or meta-analysis on this topic has been conducted.

We argue, and test through meta-analysis and systematic review, that the wide variability in the association of ELA with accelerated development might be explained—at least in part—by differences in how distinct types of ELA influence the pace of development. Existing studies have focused on a wide range of adversity experiences, ranging from physical abuse and violence exposure to physical and emotional neglect and institutional rearing, and provide some clues about the types of ELA that might be particularly likely to produce a pattern of accelerated development. For example, physical and sexual abuse have been consistently associated with accelerated pubertal development in females (Mendle, Ryan, & McKone, 2016; Natsuaki, Leve, & Mendle, 2011; Noll et al., 2017; Trickett, Noll, & Putnam, 2011; Trickett & Putnam, 1993). In contrast, studies of war and famine suggest that severe material deprivation can delay pubertal development (Prebeg & Bralic, 2000; van Noord & Kaaks, 1991). Although less work has examined the effects of neglect and psychosocial deprivation on biological aging, existing studies typically find no association of neglect or early institutional rearing with pubertal timing (Johnson et al., 2018; Mendle et al., 2011; Reid et al., 2017; Ryan, Mendle, & Markowitz, 2015). In contrast, early institutionalization is associated with an accelerated pattern of cellular aging (Drury et al., 2012) and maturation of the amygdala-PFC circuit (Gee, Gabard-Durnam, et al., 2013), suggesting that accelerated biological aging might not occur in a uniform manner across various neurobiological systems. It is important to note that sample size varies widely across these lines of research. For instance, studies of pubertal timing tend to be significantly larger in sample size than studies of fMRI connectivity or cortical thickness, which could influence the variability of the results.

Discrepancies in existing findings may be due to the treatment of ELA as a monolithic construct with equifinality across all metrics of biological aging. To date, no attempt has been made to consider how associations of ELA with accelerated biological aging might vary according to the nature of the adversity experienced. Systematic investigation into variability in the association of ELA with biological aging across adversity types may help to reconcile inconsistent findings and advance theoretical models of how early experiences alter the pace of development at reproductive, cellular, and neural levels of analysis. This meta-analysis aims to do so by: (a) examining how *different dimensions* of ELA influence biological aging, distinguishing between experiences characterized by threat versus deprivation; and (b) evaluating whether the associations of these different types of adverse early experiences with biological aging are global or specific to particular domains of aging—including pubertal timing, cellular aging, and brain development.

Conceptual Model of Early-Life Adversity and Accelerated Development

Many prior studies examining the effects of ELA on accelerated biological aging have focused on a limited range of ELA experiences, typically focusing on relative extreme exposures like sexual abuse or institutional rearing. Other studies have utilized a cumulative-risk approach, which tallies the number of distinct forms of ELA experienced to create a risk score without regard to the type, chronicity, or severity of the experience and use this risk score as a predictor of outcomes, with the assumption that all forms of ELA have equal and additive effects on developmental outcomes (Evans, Li, & Whipple, 2013). Very few studies attempt to address the high co-occurrence of varying forms of ELA (Green et al., 2010; McLaughlin, Green, et al., 2012) or examine the differential influences of particular adversity types on biological aging, with some notable exceptions (Colich et al., 2020; Mendle et al., 2011; Mendle, Ryan, et al., 2016; Negriff, Saxbe, et al., 2015; Sumner et al., 2019).

The dimensional model of adversity and psychopathology (DMAP) argues that the wide range of experiences currently classified as ELA can be organized into core underlying dimensions that have unique influences on cognitive, emotional, and neural development (McLaughlin, Sheridan, & Lambert, 2014; McLaughlin & Sheridan, 2016; Sheridan & McLaughlin, 2014). This model attempts to distill complex adverse experiences into core underlying dimensions that cut across multiple forms of ELA that share common features. Two such dimensions are *threat*, which encompasses experiences involving harm or threat of harm to the child, and *deprivation*, which involves an absence of expected inputs from the environment during development, such as cognitive and social stimulation (e.g., complex language directed at the child) as well as emotional nurturance (e.g., emotional neglect). In addition, the DMAP model argues that these dimensions of adversity have influences on emotional, cognitive, and neural development that are at least partially distinct. Increasing evidence has demonstrated the unique developmental consequences of threat and deprivation on developmental outcomes (Busso, McLaughlin, & Sheridan, 2017; Dennison et al., 2019; Everaerd et al., 2016; Lambert, King, Monahan, & McLaughlin, 2017; Rosen et al., 2018; Sheridan, Peverill, Finn, & McLaughlin, 2017). Determining whether all forms of ELA are associated with accelerated development across multiple metrics of biological aging or whether only particular dimensions of ELA are associated with this pattern is critical for identifying the mechanisms linking ELA to health outcomes and to better inform early interventions.

The threat dimension of ELA is conceptually similar, though not identical, to the life history theory dimension of environmental harshness, and involves experiences of trauma and violence exposure. We expect that experiences characterized by threat will be associated with accelerated biological aging, potentially in order to maximize the opportunity for reproduction prior to mortality (J. Belsky, Schlomer, & Ellis, 2012; Ellis et al., 2009). However, it is unclear how experiences of deprivation align with life history theory; whereas nutritional deprivation and food insecurity are thought to delay pubertal timing to ensure maximal bioenergetic resources should reproduction occur (Rogol, Clark, & Roemmich, 2000), specific predictions about physical and emotional neglect are lacking in life history models. Preliminary evidence suggests

that accelerated development following ELA may vary across different dimensions of adversity. For instance, we have found that experiences characterized by threat, but not deprivation, were associated with accelerated pubertal stage relative to chronological age and accelerated epigenetic aging in a community-based sample of children and adolescents (Sumner et al., 2019). In contrast, experiences characterized by deprivation were associated with *delayed* pubertal timing, after controlling for co-occurring threat experiences. We recently replicated this work in a nationally representative sample of adolescent females, using age of menarche as our metric of accelerated aging (Colich et al., 2020); here, we observed earlier age of menarche among adolescents exposed to trauma and violence, but no association between deprivation and age of menarche. Determining whether accelerated biological aging is associated with exposure to ELA generally or with particular dimensions of ELA may help to elucidate the specific psychological and biological mechanisms underlying these associations. Here we extend the DMAP theoretical model to encompass multiple biological aging outcomes by integrating it with life history theory, a well-established conceptual model of how the early environment shapes reproductive strategies. We make novel predictions based on the integration of these two conceptual models that we then test using meta-analyses and systematic review.

Metrics of Biological Aging

Accelerated biological aging has been conceptualized in many ways, across multiple domains of biological development. Historically, these domains have been examined in isolation, independent of other domains of biological aging. Few studies have empirically explored the effects of ELA on multiple domains of accelerated development (D. W. Belsky et al., 2017; Sumner et al., 2019) and recent work suggests that accelerated telomere erosion and accelerated pubertal development represent similar biological processes as a consequence of ELA (Shalev & Belsky, 2016).

Pubertal timing. The most consistently examined marker of accelerated development in relation to ELA is pubertal timing, typically operationalized as the age of onset of pubertal development, or the age of achieving a reproductive milestone such as menarche. Puberty begins as early as ages 8–14 in females and 9–15 in males with the activation of the hypothalamic-pituitary-gonadal (HPG) axis. This ultimately initiates the start of gonadarche, in which the gonads mature and produce gonadal hormones or sex steroids. This in turn, leads to breast development and eventually menarche in girls, and in increased testicle size and the onset of spermarche in males. Typical measures of pubertal development use secondary sex characteristics as a metric of pubertal stage (Carskadon & Acebo, 1993; Marshall & Tanner, 1970). For the purposes of this meta-analysis, we have included studies that explore how ELA is associated with three commonly used metrics of pubertal timing—pubertal stage relative to chronological age, age at the achievement of the onset of secondary sex characteristics, and age of menarche. Although menarche occurs relatively late in the pubertal process, participants are relatively reliable in their reporting of this milestone, particularly in adolescence (Dorn, Sontag-Padilla, Pabst, Tissot, & Susman, 2013).

Cellular aging. The internal predictive adaptive response model of accelerated aging following adversity postulates that the early environment influences an individual's somatic state, which in turn influences reproductive timing and other life history events (Nettle et al., 2013; Rickard et al., 2014). One pathway linking ELA to somatic states is cellular aging. Some argue that if the body detects a shortened cellular life span, mechanisms may exist to accelerate the development of the reproductive system in order to maximize the chances of reproduction prior to mortality (Nettle et al., 2013; Rickard et al., 2014). Cellular aging in the context of ELA has been measured in two different ways—telomere length and metrics of epigenetic aging using DNAm patterns.

Telomeres are nucleopeptide complexes that sit at the end of chromosomes and protect the chromosome from degradation (Chan & Blackburn, 2004). Telomeres shorten due to both cell replication and exposure to oxidative stress and inflammation. In normal aging, telomeres shorten in all cell types, which allows for the use of telomere length as a biological marker of cellular age (Frenck, Blackburn, & Shannon, 1998). Chronic stress has been associated with shortened telomere length in adults (Epel et al., 2004), and several studies have demonstrated associations between ELA and telomere length in children (Coimbra et al., 2017; Essex et al., 2013; Price et al., 2013). Shortened telomere length has been implicated in the pathogenesis of both physical and mental health problems in adulthood (Gotlib et al., 2015; Hoen et al., 2013; Needham, Mezuk, et al., 2015; Tyrka et al., 2016), suggesting a potential mechanism linking ELA and maladaptive health outcomes in adolescence and adulthood.

A second recently established metric of cellular aging is an epigenetic clock that considers genome-wide DNAm patterns (both increased and decreased methylation of select CpG sites) to quantify biological age independent from chronological age (DNAm age; Hannum et al., 2013; Horvath, 2013). This metric correlates strongly with chronological age in both adolescents and adults (Horvath & Raj, 2018; Suarez et al., 2018) and shows strong positive associations with age of death (B. H. Chen et al., 2016; Marioni, Shah, McRae, Chen, et al., 2015), suggesting it is a valid metric of cellular aging. Deviations between DNAm age and chronological age have been used as a metric of accelerated development (Davis et al., 2017; Jovanovic et al., 2017; Sumner et al., 2019) and are associated with exposure to ELA (Jovanovic et al., 2017; Sumner et al., 2019). Advanced DNAm age has been associated with increased risk of cardiovascular disease, cancer, and obesity (Horvath et al., 2014; Marioni, Shah, McRae, Ritchie, et al., 2015; Perna et al., 2016), again potentially highlighting a mechanism linking ELA and physical health problems.

For the purpose of this meta-analysis, we have included studies that explore associations between ELA and cellular aging, as measured by both telomere length and DNAm age.

Brain development. Numerous studies have investigated the neural consequences of ELA. Here, we focus specifically on neural markers of maturation. As such, we focus on two metrics for which patterns of development have been well characterized: cortical thickness and functional connectivity between the amygdala and prefrontal cortex (PFC). We focus on cortical thickness as a metric of structural development because the pattern of development is well characterized, replicated across many studies, and shows a clear linear association with age, such that cortical thickness steadily decreases from middle childhood to early adulthood (Ducharme et al., 2016; LeWinn, Sheridan, Keyes, Hamilton, & McLaughlin, 2017; Vijayakumar et al., 2016; Wierenga, Langen, Oranje, & Durston, 2014). Second, we focus

on functional connectivity between the amygdala and PFC as a metric of maturation because it serves as a key component in the stress acceleration hypothesis, which posits that the amygdala-PFC circuit supporting emotional processing and regulation matures more rapidly among children exposed to ELA (Callaghan & Tottenham, 2016).

Cortical thickness declines steadily from childhood to early adulthood (Ducharme et al., 2016; LeWinn et al., 2017; Wierenga et al., 2014), as a result of developmentally appropriate pruning of synapses and increases in myelination of connections between neurons (Natu et al., 2019, 2018; Sowell et al., 2004). This linear pattern of development enables assessment of whether development is accelerated or delayed among children with ELA relative to their peers. Cortical structure can be measured in a variety of ways including surface area, thickness, and volume (for review, see Vijayakumar et al., 2016). However, cortical thickness is the only metric that has a linear developmental trajectory, declining steadily from early childhood through early adulthood (Ducharme et al., 2016; LeWinn et al., 2017; Walhovd, Fjell, Giedd, Dale, & Brown, 2017; Wierenga et al., 2014). In contrast, cortical surface area and volume exhibit nonlinear associations with age and the inflection points of these trajectories vary across samples and remain a source of debate (Ducharme et al., 2016; Giedd et al., 1999; Lenroot et al., 2007; LeWinn et al., 2017; Mills et al., 2016; Vijayakumar et al., 2016). These nonlinear patterns of development make assessing deviations from the expected pattern more difficult. Therefore, we focus only on studies that use cortical thickness—including both whole cortex and specific regions—as an outcome.

The stress acceleration hypothesis focuses on the impact of ELA on the developmental trajectory of neural circuits supporting emotion processing and regulation, particularly on connectivity between the amygdala and medial PFC (mPFC; Callaghan & Tottenham, 2016). Animal tracing studies demonstrate that feedforward connections between amygdala and PFC exist early in life, but feedback connections emerge later in development (Barbas & García-Cabezas, 2016). It has been proposed that in humans, changes in functional connectivity between the mPFC and amygdala may reflect the maturation of these feedback connections (Gee, Humphreys, et al., 2013). In some studies, the pattern of functional connectivity between the amygdala and the mPFC shifts from positive to negative across development in the context of emotional processing tasks (Gee, Humphreys, et al., 2013; Silvers et al., 2016; Wu et al., 2016).

For the purpose of this systematic review, we have included studies that explore how ELA impacts both cortical thickness and amygdala-mPFC functional connectivity.

Consistency/discrepancies across metrics of biological aging. Little research has explored how disparate metrics of biological aging relate to each other, especially in adolescence. As mentioned above, only one study has empirically explored the effects of ELA on multiple domains of accelerated development in adolescence (Sumner et al., 2019), and suggests that threat-related adversity has a similar effect on both pubertal timing and mDNA age (with these two metrics strongly correlated [$r = .52$]). Further evidence for homogeneity across metrics suggests that telomere length may be related to cortical thickness patterns in adults (Puhlmann et al., 2019). However, there is also evidence to suggest that metrics of biological aging are independent of each other. For instance, in a large sample of middle-aged adults from the longitudinal Dunedin Study, associations among multiple metrics of biological aging were largely absent, including telomere length and mDNA age ($r = -0.03$; D. W. Belsky et al., 2018). One possibility is that metrics of biological aging diverge in their trajectories across the life-course, producing weaker associations among adults than children and adolescents, although—to our knowledge—this has yet to be examined empirically. Finally, there are many other metrics of biological aging that we do not examine, including "brain age," markers of inflammation, and cardiovascular function (D. W. Belsky, Caspi, et al., 2015; Cole, Marioni, Harris, & Deary, 2019). Currently, it is unclear how these metrics of biological aging are related or independent of one another.

The Current Study

We aimed to test a novel hypothesis that experiences characterized by threat, but not deprivation, are associated with accelerated biological aging. This prediction is based in the DMAP framework (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014), but also extends that conceptual framework to encompass a wide range of developmental processes that serve as metrics of biological aging and that were not considered in the original model. Applying this theoretical approach may help to reconcile discrepant findings in the literature by evaluating how different dimensions of ELA influence biological aging. In addition, we aimed to integrate disparate literatures by examining whether different dimension of adversity have general or specific effects on multiple domains of biological aging—including pubertal timing, cellular aging, and brain development. We expected that threat and deprivation would have different influences on biological aging, with threat associated with accelerated biological aging across all metrics and deprivation associated with delayed pubertal development. We did not have specific hypotheses about how deprivation would influence cellular aging or brain development, given conflicting findings in the literature of both acceleration and delayed maturation following early deprivation. We also separately examined the associations of socioeconomic status (SES) with biological aging, as SES is a commonly used global measure of early experience that is associated with increased risk of exposure to both threat and deprivation (e.g., Green et al., 2010; McLaughlin, Green, et al., 2012). We had no a priori hypotheses about SES, given that SES is linked to greater risk for both threat and deprivation experiences. A final guiding question was whether the associations of ELA characterized by threat and deprivation with biological aging would be consistent across all metrics, given inconsistencies in the literature as to how these metrics relate to one another (Belsky et al., 2018). Whereas pubertal development reflects a more global measure of aging, cellular aging is a metric of biological aging most relevant to physical health, and cortical thickness and development in the amygdala-PFC circuit may reflect learning or adaptation to a stressful early environment, but not aging in a global way. Finally, given the potential for genetic confounding in the link between ELA and accelerated development, we perform moderator analysis to evaluate whether effect sizes across studies that attempt to control for such confounding relative to those that do not.

Method

Information Sources and Search Strategy

This meta-analysis and systematic review was conducted in line with the PRISMA guidelines for meta-analyses (Moher, Liberati, Tetzlaff, & Altman, 2009; Figure 1). To identify studies with relevant data, literature searches were conducted using Internet databases (PubMed, SCOPUS, PsycINFO, Web of Science and Google Scholar) through May 2019. To ensure a thorough search, search terms encompassed various forms of ELA (e.g., violence, trauma, neglect, maltreatment, institutional rearing, deprivation, SES, poverty, early adversity, early life stress) as well as our dependent measures of interest (e.g., puberty, cell aging, methylation, menarche, telomere length, methylation, neural) and our targeted study population (e.g., infant, child, adolescent, pediatric; see online supplemental materials for all search terms). All included studies were published in English and from peer-reviewed journals. To further identify eligible studies, we reviewed references of identified articles for additional studies using forward and backward searching.

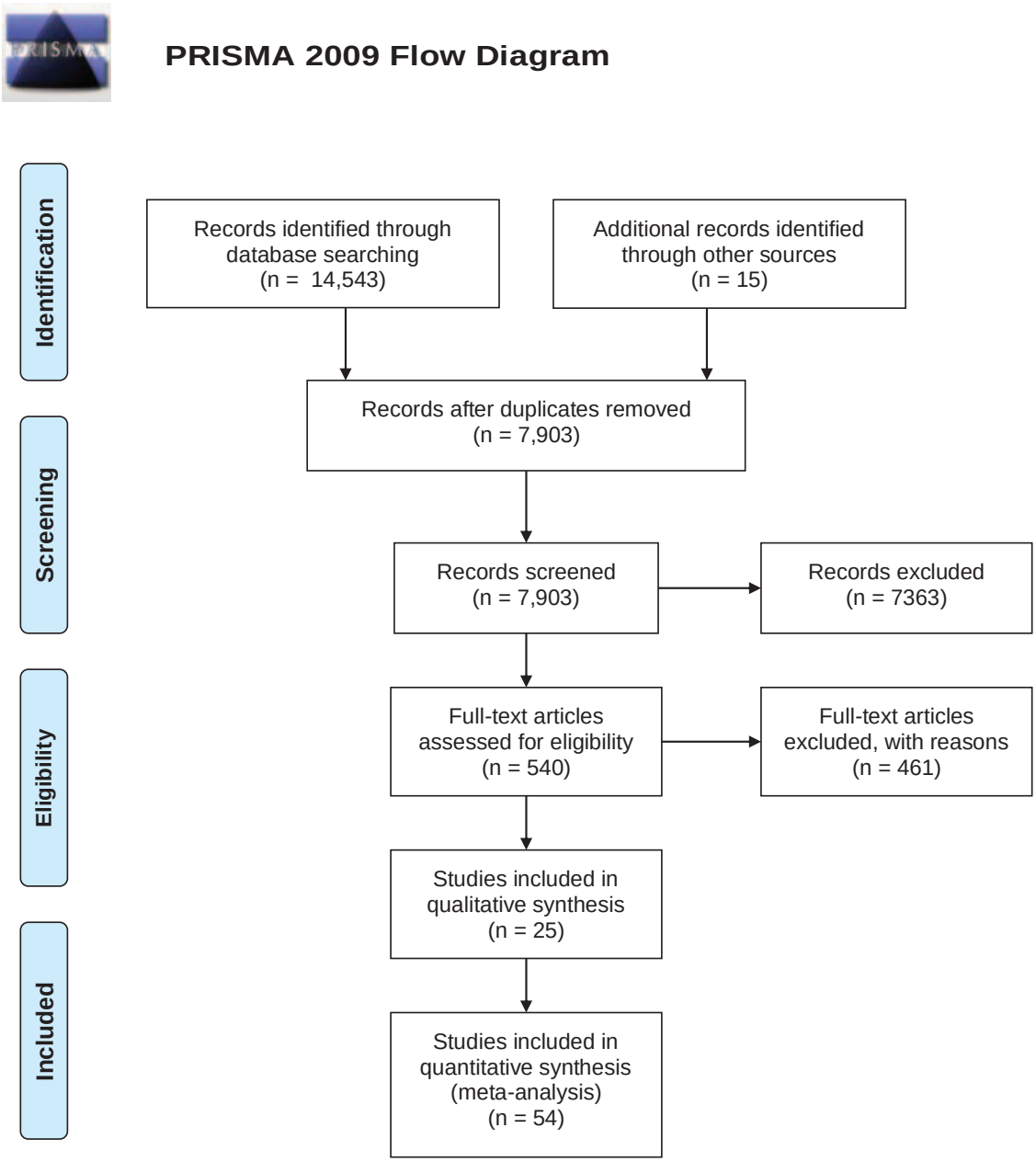
In order to be included in the meta-analysis, studies had to meet the following criteria. First, studies had to examine an association between ELA and one of our dependent measures (pubertal timing, cellular aging, or brain development) and report sufficient statistics to calculate an effect size. Second, exposure to ELA had to occur during childhood or adolescence (participants 18 and younger), rather than using retrospective reports of ELA in adults. This choice was made given the well documented recall biases associated with retrospective reporting of childhood experiences in adulthood (Baldwin, Reuben, Newbury, & Danese, 2019; Green et al., 2010; Hardt & Rutter, 2004; Widom, Raphael, & DuMont, 2004; Yarrow, Campbell, & Burton, 1970). Indeed, a recent meta-analysis comparing retrospective and prospective methods for measuring ELA exposure demonstrates very little overlap in the groups identified by each of these methods, suggesting that prospective and retrospective assessments identify fundamentally different groups of people (Baldwin et al., 2019). However, reports of age of menarche and metrics of cellular aging do not suffer this problem to the same degree (Cooper et al., 2006; Gilger, Geary, & Eisele, 1991). As such, we include studies where adversity was measured prospectively, but the metric of pubertal timing was retrospective or the measure of cellular aging was collected in adulthood. We did not include metrics of amygdala-PFC connectivity or cortical thickness measured in adulthood, given these metrics of development are specific to patterns that occur in childhood and adolescence, and it is not clear that more negative amygdala-PFC connectivity or thinner cortical thickness in adulthood reflects accelerated biological aging.

Inclusion criteria for ELA. We draw on a recent definition of ELA as experiences that were either chronic or severe in nature that require psychological or neurobiological adaptation by an average child and that represent a deviation from the expectable environment (McLaughlin, 2016). As detailed above, we used a wide range of search terms for ELA encompassing maltreatment experiences (e.g., physical, sexual, and emotional abuse; physical and emotional neglect), exposure to traumatic events (e.g., observing domestic violence, being the victim of interpersonal violence), institutional rearing, material deprivation (e.g., food insecurity), and childhood SES. We did not consider biological father absence as a form of ELA given that: (a) it is not clearly a form of ELA based on prevailing definitions (McLaughlin, 2016); and (b) a meta-analysis on father absence and pubertal timing was recently conducted (Webster, Graber, Gesselman, Crosier, & Schember, 2014). We did not include other early experiences or more global stressful life events that did not clearly meet our definition of ELA (e.g., parental psychopathology, peer victimization).

Inclusion criteria for studies of pubertal timing. To retain as many studies as possible, we included studies that used self-report, parent-report, and physician-rated Tanner/PDS stage (controlling for age) or age of menarche. Physician-rated Tanner stage and interview-based assessments of age of menarche in adolescence have been shown to be acceptably reliable (Coleman & Coleman, 2002; Dorn & Biro, 2011; Dorn et al., 2013; Petersen, Crockett, Richards, & Boxer, 1988; Shirtcliff, Dahl, & Pollak, 2009). Similarly, self-report of age of menarche, including retrospective reports, show relatively high reliability (Dorn et al., 2013; Lundblad & Jacobsen, 2017). We examined whether the specific measure of pubertal timing or including maternal age at menarche as a covariate significantly moderated the ELA-puberty associations.

Inclusion criteria for studies of cellular aging. Although there have been prior reviews and meta-analyses exploring the effects of ELA on telomere length (Coimbra et al., 2017; Price et al., 2013) or DNAm age (Gershon & High, 2015; Lewis & Olive, 2014; Silberman, Acosta, & Zorrilla Zubilete, 2016; Vinkers et al., 2015; Wolf et al., 2018), none has focused on differences across distinct adversity types or restricted the focus to studies measuring ELA in childhood or adolescence. Telomere length and DNAm age can be assessed through both blood and saliva samples, using multiple analysis techniques. Due to the limited number of studies on this topic, we have included all tissue types and analysis techniques in our analyses. Tissue type and analysis technique have been shown to influence reliability estimates of telomere length (Aviv et al., 2011; Elbers et al., 2014; Kim, Sandler, Carswell, Weinberg, & Taylor, 2011; Martin-Ruiz et al., 2015). However, mDNA age appears to be more consistent across tissue types (Horvath & Raj, 2018). Regardless, we examined whether metric of cellular aging (telomere length and DNAm age) or tissue type were moderators of the ELA-cellular aging association.

Inclusion criteria for studies of brain development. We included only studies that assessed cortical thickness—including both whole cortex and specific regions—as an outcome and not other measures of cortical structure (e.g., volume and surface area) where age-related patterns are nonlinear and thus more difficult to interpret with regard to acceleration of development. If ELA-exposed youth exhibit thinner cortex than nonexposed youths of the same age, this was interpreted as accelerated maturation; if ELA-exposed youths exhibit thicker cortex than nonexposed youths of the same age, this was interpreted as delayed development. Similarly, we focused only on studies exploring task-related amygdala-mPFC functional connectivity, where a developmental shift from positive to negative in task-related amygdala-mPFC connectivity has been documented (Callaghan & Tottenham, 2016; Gee, Gabard-Durnam, et al., 2013). We will evaluate studies of ELA with this normative developmental pattern in mind; if children who have experienced adversity demonstrate greater negative connectivity for their age than children who have not, this would



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1. 2009 PRISMA flow diagram of literature search and screening process. See the online article for the color version of this figure.

reflect accelerated development and if children who have experienced adversity exhibit more positive or less negative connectivity than comparison children, this would reflect delayed development. Measures of cortical thickness have shown to be highly reliable, particularly when processed using the same analysis pipelines (Dickerson et al., 2008; Han et al., 2006; Iscan et al., 2015). In contrast to clear developmental changes observed in cortical thickness estimates, studies investigating developmental patterns of connectivity at rest have been more mixed, with some studies demonstrating an increase in connectivity with age (e.g., Gabard-Durnam et al., 2014) and others demonstrating a decrease (Jalbrzikowski et al., 2017). Because a consensus has not been reached on the normative developmental pattern of amygdala-mPFC connectivity during rest, we focus only on articles that explore the associations of ELA with amygdala-mPFC connectivity using task-related functional connectivity. Task-related activation has been shown to be highly reliable both within-subjects and across test sites (Gee et al., 2015), however the exact reliability of functional connectivity within these regions remains unknown.

We conducted a systematic review for metrics of brain development rather than a meta-analysis for the following reasons. First, whole-brain fMRI meta-analyses focus on the spatial nature of associations across the brain as opposed to the strength of effect sizes within a designated region. Given our focus on a specific measure of functional connectivity (amygdala-mPFC), spatial maps do not sufficiently address our research question regarding this metric of neural development. Second, the use of heterogenous ROIs in studies of cortical thickness and amygdala-mPFC connectivity (e.g., different regions of mPFC), make it difficult to quantitatively compare results across studies. Third, meaningful differences in task design and task demands make it difficult to directly compare results of amygdala-mPFC connectivity using meta-analysis.

Because we were unable to meta-analyze the neuroimaging studies, we implemented the following criteria to assess the quality of each study included in the systematic review. This includes four criteria for PFC-amygdala connectivity studies and three criteria for cortical thickness studies. If the study took adequate steps to address the criterion in question, it received 1 point. If adequate steps were not taken, it received 0 points. The criteria for both sets of studies included: (a) adequate sample size ($N > 20$ per group or $N = 40$ overall if using continuous independent variables); (b) appropriate cluster correction for whole-brain analyses and correction for multiple comparisons for ROI-based analyses; and (c) appropriate methods for correcting for motion artifacts, including checks for between-groups differences in motion. A final criterion applied only to studies of PFC-amygdala connectivity examined whether an appropriate control condition was used in the fMRI contrast (i.e., task-related activation was compared with an active control condition, not fixation).

Measuring and Coding Adversity

In order to directly compare results from the present study with the majority of the existing literature, we first conducted an analysis in which we include studies defining ELA broadly, regardless of adversity type. We then examined whether associations of ELA with biological aging metrics exhibited significant heterogeneity, and evaluated whether adversity type (i.e., threat, deprivation, SES) was a moderator of these associations (see Moderator Analysis for details). Consistent with previous work from our group (Colich et al., 2020; Dennison et al., 2019; McLaughlin, Sheridan, Lambert, 2014; Sheridan & McLaughlin, 2014), we conceptualized threat-related adversities to include experiences of physical abuse, domestic violence, sexual assault, witnessing or being the victim of violence in the community, and emotional abuse. Deprivation-related adversities included physical neglect, low cognitive stimulation, food insecurity, and early institutionalization/international adoption. We also examined the effects of SES, including family income and parental education. Although low SES is associated with reductions in cognitive stimulation among children (Bradley, Convyn, Burchinal, McAdoo, & Garcia Coll, 2001; Duncan & Magnuson, 2012; Gilkerson et al., 2017), SES is a proxy for deprivation rather than a direct measure. This is especially true when studies examine the effects of SES without controlling for co-occurring experiences of threat or violence. To ensure that we had not diluted our deprivation composite by including SES as an indicator, we chose to examine studies using SES as a metric of ELA separately.

The literature search yielded a total of 7,903 studies. Studies were first excluded based on their title or abstract ($k = 7363$) with exclusion decisions made by one of the authors (N.L.C.) and confirmed by another. Exclusion criteria included any publication that was not an analysis of primary data (i.e., a review, book chapter, etc.). We also excluded any studies conducted outside of the United States, Western Europe, or Australia, given well-documented effects of ethnicity, nutritional status, and SES on timing of development (Parent et al., 2003) and difficulties assessing SES consistently across different countries. A subset of studies were examined more thoroughly for eligibility ($k = 540$). After a careful review of the methods, studies were excluded if they didn't include a relevant independent or dependent variable (i.e., single gene methylation patterns rather than a measure of epigenetic aging or resting state amygdala-PFC connectivity rather than task-based connectivity; $k = 137$), if they were a review article or book chapter ($k = 140$), if they were conducted outside of the U.S./Europe/Australia ($k = 82$), if the study was conducted in infants ($k = 9$) or nonhuman animals ($k = 6$), if adversity was measured retrospectively in adults ($k = 39$), if we were unable to access the article ($n = 24$), if the data were from a conference abstract ($k = 8$), published in a foreign language only ($k = 3$), if the study was not sufficiently powered (i.e., less than or equal to five participants per group; $k = 2$), or the study was later retracted ($k = 1$). Given our focus on understanding deviations in developmental timing following ELA, studies were also excluded if the exposed and control group differed significantly in age ($k = 1$; Humphreys et al., 2016). Finally, studies were excluded if they did not include data that we were able to convert into an effect size after multiple attempts to contact the study authors for original data ($k = 9$). Overall, the current study included a total of 79 studies: 43 studies contributing to our meta-analysis exploring the effects of ELA on pubertal timing ($n = 114{,}450$), 11 studies contributing to our meta-analysis exploring the effects of ELA on cellular aging ($n = 1{,}560$), and 25 studies contributing to our systematic review exploring the effects of ELA on brain development ($n = 3{,}253$; with one study [Sumner et al., 2019] contributing to both pubertal timing and cellular aging analyses).

Management of Nonindependent Samples

In many cases, we extracted multiple effect sizes from the same sample. For example, some studies included multiple measures of pubertal timing (e.g., pubertal stage and age of menarche) or multiple measures of ELA (e.g., sexual abuse and physical abuse). Similarly, associations between ELA and developmental timing from a single study were sometimes examined across multiple publications using the same sample. To deal with this nonindependence, we conducted multilevel mixed effects analyses with restricted maximum likelihood estimation, including study nested within sample as a random effect, such that multiple effect size estimates are nested within a higher-level grouping variable (e.g., study or sample). In the case of longitudinal data, we always included data from Wave 1, as this wave tends to have the lowest attrition rate and in turn, the largest sample size (Borenstein, Hedges, Higgins, & Rothstein, 2009). If a separate article included data from a later wave, we included that data and did not report data from Wave 1 a second time (as these associations were included in the analysis from the Wave 1 article; e.g., (Mendle, Leve, Van Ryzin, & Natsuaki, 2014; Mendle et al., 2011).

Data Extraction

Three trained raters (N.L.C., M.L.R. & E.S.W.) coded individual studies. We screened each study and coded variables for study year, authors, participant composition/sample, mean age of participants, number of males and female participants, ethnicity, pubertal timing measure and informant, ELA measure and informant, cellular aging tissue type, and analysis technique, as well as whether analyses controlled for other types of adversity, parent psychopathology, child psychopathology, father absence, mother's age at menarche, and body mass index (BMI). All disagreements in coding were resolved via discussion among the three raters until consensus was achieved.

Data Analysis

To ensure consistency in the directionality of the effect sizes, in all cases, metrics of developmental timing were coded to indicate that numerically lower values (negative values) indicated accelerated development, to be consistent with age at menarche or age at pubertal attainment (the most commonly used metrics). Similarly, adversities were coded so that a numerically higher value indicates greater adversity. To be consistent with other variables, SES was coded to indicate that numerically higher SES values indicate lower SES.

For each study we calculated an effect size *d* and corresponding sampling variance (Cohen's *d*; Cohen, 1988) for each relevant analysis (all effect size and sampling variance listed in Table S1). A positive *d* indicates that exposure to ELA is associated with delayed development (later age at a developmental milestone), where as a negative *d* indicates that greater adversity is associated with accelerated development (earlier age at a developmental milestone). We derived *d*s from multiple reported statistics including: unadjusted or adjusted correlations between two variables, odds ratios, mean differences and standard deviations, *t* statistics, *F* statistics and associated *N*s and *p* values, as well as unstandardized and standardized regression coefficients. All effect sizes were computed in R (Version 3.4.1) using the escalc function in the "metafor" package (Viechtbauer, 2010) and converted to Cohen's *d* using established formulas (Borenstein et al., 2009). Authors were contacted when published articles met criteria for inclusion but did not include the necessary data to calculate an effect size amenable to our analyses, which occurred in 13 cases (of which four provided necessary data and were included in our analyses).

All meta-analyses were conducted using three-level mixed-effects models and the rma.mv function in the "metafor" package (Viechtbauer, 2010) in R (Version 3.4.1) including both study and sample as random effect (study nested within sample in order to deal with potentially nonindependent effect sizes coming from the same article or the same sample of participants; Assink & Wibbelink, 2016; Konstantopoulos, 2011). Publication bias was assessed using Begg's Rank correlation test (Begg & Mazumdar, 1994) and Egger's regression test of funnel plot asymmetry (Egger, Davey Smith, Schneider, & Minder, 1997). Additionally, we conducted p-curve analyses using the pcurve function in the "dmetar" package (Harrer, Cuijpers, Furukawa, & Ebert, 2019) to examine whether selective reporting of significant findings (clustering around $p = .05$ indicative of "p-hacking") contributed to our meta-analytic results (Simonsohn, Nelson, & Simmons, 2014). P-curve analysis is based on the assumption that a "true" effect is present only if significant *p* values resulting from studies included in the meta-analysis skew to the right (i.e., include more low vs. high statistically significant *p* values). All funnel plot and p-curve figures can be found in the online supplemental materials. These approaches may be less appropriate for mixed-effects meta-analysis which include nonindependent data points (Assink & Wibbelink, 2016). However, we provide the results of these tests to be consistent with prior meta-analyses. Heterogeneity was assessed using the Brestlow-day test (Cochran, 1954) and the method proposed by Higgins and colleagues (termed I-squared; Higgins & Thompson, 2002).

We conducted separate sets of meta-analyses to explore the associations of ELA with two metrics of biological aging: pubertal timing and cellular aging. Within each set of analyses, we began by exploring the association of all adversity types (regardless of dimension) with our two domains of biological aging, then examined whether adversity type was a moderator of these associations. We then ran separate sensitivity analyses to examine associations separately by threat, deprivation, and SES to assess associations of each adversity type with biological aging outcomes. As described above, data on neural development was not reported in a manner across studies that permitted meta-analysis; instead, these results were systematically reviewed.

Moderator Analyses

Given our primary objective of understanding how adversity type influences associations between adversity and biological aging, we always first explored adversity dimension (threat, deprivation, SES, general adversity) as a moderator of the association between adversity and biological aging. In addition, in cases where effect sizes showed significant heterogeneity, we tested whether demographic or methodological factors moderated the associations between ELA and biological aging. These factors were based on prior literature, and included sample race/ethnicity (% White), sex composition of the sample (% male) and whether the study con-

trolled for BMI (0/1) or other forms of adversity (0/1). Additionally, for pubertal timing analyses, we examined metric of pubertal timing (age of menarche OR measure of secondary sex characteristics) and whether the association differed for studies that included maternal age at menarche relative to those that did not. For telomere length and DNAm age we also examined the use of blood versus saliva and cellular aging metric (telomere length vs. DNAm age) as potential moderators in our analyses. If there was no information given by the article regarding a specific moderator then they were marked as missing and not included in the moderator analysis. We tested each moderator separately using the moderator flag in the rma.mv function.

Results

Pubertal Timing

The 43 studies included in this meta-analysis produced 94 effect sizes and a total of 114,450 participants. Sample sizes ranged from 25 to 20,345 (median = 587). Of the 94 effect sizes, 21 focused on ELA characterized as threat, 21 focused on deprivation, 40 on SES, and 12 used a cumulative approach of summing across multiple forms of adversity. Table 1 presents descriptive demographic information for each study.

All adversities. We first examined the effect of all forms of adversity on pubertal timing across all 43 studies included in the meta-analysis. Greater exposure to ELA was associated with earlier pubertal timing ($d = -0.10$, 95% CI [−0.18, −0.01]) and significantly differed from zero ($z = -2.14$, $p = .03$; Figure 2). Significant heterogeneity was observed across studies, $Q(93) = 653.92$, $p < .0001$; $I^2 = 95.40$. The result of Begg's publication bias test (Kendall's $\tau = -0.10$, $p = .18$) and Egger's linear regression test ($z = -1.65$, $p = .10$) were not significant, suggesting no publication bias in our sample of studies (see sFigure1 for a funnel plot of all adversities and pubertal timing). The results of the p-curve analysis, in which 36 effect sizes were included and 30 had p values lower than .025, suggest that there is a "true" effect size driving these findings, and the results are not due to publication bias or p-hacking (sFigure 2).

Using adversity type as a moderator, we tested our hypothesis that threat would have a significant negative effect on pubertal timing (suggesting accelerated development), whereas deprivation would a significant positive effect on pubertal timing (suggesting delayed development). The random-effects meta-analysis including four adversity types as a moderator (threat, deprivation, SES, and any studies using only a composite measure of adversity) revealed that adversity type significantly moderated the association between ELA and pubertal timing, $F(3, 90) = 51.77$, $p < .0001$. Given significant differences across adversity type, we explored the effect of adversity on pubertal timing separately for each category of adversity.

Given concerns about genetic confounding of the association between maternal age at menarche and ELA exposure, we conducted a moderator analysis to test whether effect sizes derived from studies that controlled for maternal age at menarche differed significantly from those that did not. Of the 94 effect sizes included in this analysis, 19 of them came from articles that considered mother's at menarche. The random-effects meta-analysis including two categories as a moderator (study controlled for mother's at menarche or did not control for mother's age at menarche) revealed that controlling for mother's age at menarche did not significantly moderate the association between ELA and pubertal timing, $F(1, 92) = 0.08$, $p = .78$.

Threat. In studies that specifically explored the association of threat exposure with pubertal timing (12 studies; 21 effect sizes, $N = 36{,}194$), greater exposure to threat was associated with earlier pubertal timing ($d = -0.26$, 95% CI [−0.40, −0.13]). The effect size was small and significantly differed from zero ($z = -3.81$, $p < .001$; Figure 3). Significant heterogeneity was observed across studies, $Q(20) = 229.73$, $p < .001$; $I^2 = 94.37$. The results of Begg's publication bias test (Kendall's $\tau = -0.27$, $p = .10$) and Egger's linear regression test ($z = -1.45$, $p = .15$) were not significant, suggesting no publication bias in our sample of studies (see sFigure3 for a funnel plot of all threat-related adversities and pubertal timing). The results of the p-curve analysis, in which 21 effect sizes were included and 12 had p values lower than .025, suggest that there is a "true" effect driving these findings, and the results are not due to publication bias or p-hacking (sFigure 4).

Given significant heterogeneity in our studies examining the association of threat-related adversities with pubertal timing, we conducted a series of moderator analyses. None of the five moderators (metric of pubertal timing, sex, race/ethnicity, BMI, controls for other ELA types) were significantly associated with variations in effect size.

Deprivation. In studies that specifically focused on the association of deprivation exposure with pubertal timing (12 studies; 21 effect sizes, $N = 34{,}193$), deprivation was not associated with pubertal timing ($d = 0.05$, 95% CI [−0.07, 0.17]) and did not significantly differ from zero ($z = 0.81$, $p = .42$; Figure 3). Significant heterogeneity was observed across studies, $Q(20) = 51.17$, $p < .001$; $I^2 = 89.34$. The results of Begg's publication bias test (Kendall's $\tau = 0.23$, $p = .14$) and Egger's linear regression test ($z = 1.86$, $p = .06$) were not significant, suggesting no publication bias in our sample of studies. (see sFigure3 for a funnel plot of all deprivation-related adversities and pubertal timing). The results of the p-curve analysis, in which 21 effect sizes were included and four had p values lower than .025, suggest that the results are not due to publication bias or p-hacking (sFigure4).

Given significant heterogeneity in our studies examining the association of deprivation-related adversities with pubertal timing, we conducted moderator analyses. For the association between deprivation and pubertal timing, sex was significantly associated with variation in effect sizes (estimate = 0.01, $SE = 0.00$, $z = 3.50$, $p < .001$), suggesting that the more males included in the sample, the more positive the association between deprivation exposure and pubertal timing (i.e., the more delayed the pattern of maturation). Given that multiple forms of deprivation were included in this category, including emotional deprivation (e.g., emotional neglect) and markers of deprivation across emotional, cognitive, and social domains (e.g., institutional rearing), we also conducted a sensitivity analysis exploring whether the effect size varied across different indicators of deprivation. The random-effects meta-analysis, including two categories as a moderator (neglect, institutionalization), revealed that controlling for deprivation type did not significantly moderate the association between deprivation-related ELA and pubertal timing, $F(1, 19) = 0.53$, $p = .47$.

Table 1
Characteristics of Individual Studies Included in the Pubertal Timing Meta-Analysis

Study	Sample	Sample size (*N*)	Age range	Sex distribution	Early life adversity	Adversity details	Pubertal timing metric	Covariates
Acacio-Claro, Koivusilta, Doku, & Rimpelä, 2019	Adolescent Health and Lifestyle Surveys (AHLS)	37,876	14–43	54% Female	SES	Parental education	Age at menarche/first ejaculation	None
Amir, Jordan, & Bribiescas, 2016	Nationally Representative Sample (U.S.); Add Health Survey Participants	3,606	12–20	Female only	Threat/SES	Subjective ratings of the availability of resources (family income) and environmental safety	Age at menarche	None
Arim, Shapka, Dahinten, & Willms, 2007	Nationally Representative Sample (Canada); National Longitudinal Survey of Children and Youth	7,977	10–17	50% Female	SES	Family SES (composite of household income, parental education and occupation levels, weighted by the factor loadings obtained through principal components factor analysis with varimax rotation)	PDS	Sex
Blell, Pollard, & Pearce, 2008	Newcastle Thousand Families Study	276	0–51	Female only	SES	Father's occupation	Age at menarche	None
Boynton-Jarrett & Harville, 2012	Nationally Representative Sample (UK); National Child Development Study	4,524	11–16	Female only	Threat/Deprivation	Exposure to violence/ mental health issues; Lack of supportive caregiving	Menarche < 11 years	None
Braithwaite et al., 2009	Nationally Representative Sample (U.S.); National Growth and Health Study	2,077	9–19	Female only	SES	SES (parent education level and household income)	Age at menarche < 12 years	None
Colich et al., 2020	Nationally Representative Sample (U.S.); National Comorbidity Study - Adolescent Sample	4,937	13–18	Female only	Threat/deprivation	Threat exposure composite, deprivation exposure composite	Age at menarche	None
Culpin et al., 2014	Nationally Representative Sample (UK); Avon Longitudinal Study of Parents and Children	3,776	8–18	Female only	SES	Presence of financial problems at age 6 and age 8 and mother's education status	Age at menarche	None
Deardorff, Abrams, Ekwaru, & Rehkopf, 2014	Nationally Representative Sample (U.S.); National Longitudinal Study of Youth	4,851	9–16	Female only	SES	SES before age 7 (Family income; Family wealth [income − total debt]; mother's education level; mother's employment status)	Age at Menarche	None

(*table continues*)

Table 1 (*continued*)

Study	Sample	Sample size (*N*)	Age range	Sex distribution	Early life adversity	Adversity details	Pubertal timing metric	Covariates
Deardorff et al., 2011	Cohort Study of Young Girls' Nutrition, Environment, and Transitions	444	6–10	Female only	SES	Family income (<75,000)	Tanner stage	None
Deardorff et al., 2012	Cohort Study of Young Girls' Nutrition, Environment, and Transitions	213	6–12	Female only	SES	Family income (<50,000)	Tanner stage	None
Ellis & Essex, 2007	Wisconsin Study of Families and Work	180	0–11	Female only	SES	SES	PDS and Tanner	None
Furu, 1976	Community sample from Sweden	917	10–17	Female only	SES	Father's or mother's occupation	Age at menarche	General Health; BMI
Graber, Brooks-Gunn, & Warren, 1995	Premenarcheal subset from a larger longitudinal sample	75	10–14	Female only	General	Number of stressful life events	Age at menarche and Tanner stage	None
Gur et al., 2019	Philadelphia Neurodevelopmental Cohort (PNC)	9,498	8–21	52% Female	Threat	Traumatic events composite	Tanner stage	None
Hartman, Li, Nettle, & Belsky, 2017	Nationally representative sample; NICHD Study of Early Child Care and Youth Development (SECCYD)	659	1–15	Female only	General	Composite of maternal sensitivity, maternal harshness, unpredictability, income harshness	Age at menarche	General Health; BMI
Hayes & Tan, 2016	Cohort of adopted Chinese girls	16,202	11–13	Female only	Deprivation	International Adoption (from China to North America)	Age at menarche	None
James-Todd, Tehranifar, Rich-Edwards, Titievsky, & Terry, 2010	Collaborative Perinatal Project	237	0–47	Female only	SES	Composite measure of father's education, income, occupation at age 7	Age at menarche	None
James, Ellis, Schlomer, & Garber, 2012	Longitudinal cohort	238	11–18	54% Female	SES	Hollingshead	Age at menarche	Non
Johnson et al., 2018	Bucharest Early Intervention Project (BEIP)	107	0–12	49% Female	Deprivation	Institutionalization	Age at menarche and Tanner stage	None
Kelly, Zilanawala, Sacker, Hiatt, & Viner, 2017	Longitudinal cohort from UK Millennium Cohort Study	5,839	0–11	Female only	SES	SES (income quartiles)	Menarche status at age 11	None
Lynne-Landsman, Graber, & Andrews, 2010	Longitudinal cohort from Oregon Youth Substance Use Project; 538 females; 537 males	1,075	Grades 1–12	52% Female	SES	Household resources, conflict and stability	PDS	None
Mendle, Leve, Van Ryzin, & Natsuaki, 2014	Longitudinal intervention cohort of girls in foster care	100	10–12	Female only	Threat/Deprivation	Sexual abuse, neglect, physical abuse, foster care placement	PDS	None

(*table continues*)

Table 1 (*continued*)

Study	Sample	Sample size (*N*)	Age range	Sex distribution	Early life adversity	Adversity details	Pubertal timing metric	Covariates
Mendle, Leve, Van Ryzin, Natsuaki, & Ge, 2011	Longitudinal intervention cohort of girls in foster care	100	10–12	Female only	Threat/Deprivation	Sexual abuse, neglect, physical abuse, foster care placement	Age at menarche and PDS	All forms of adversity, child's age, child's race
Mendle, Moore, Briley, & Harden, 2016	Nationally Representative Sample (U.S.); Add Health Survey Participants	1,260	11–21	Female only	SES	SES (parental education)	Age at menarche	None
Mendle, Ryan, et al., 2016	Nationally Representative Sample (U.S.); Add Health Survey Participants	6,273	11–34	Female only	Threat/Deprivation/SES	Sexual abuse, physical abuse, physical neglect, undetermined maltreatment, SES (income to needs ratio)	Age at menarche and secondary sex characteristics (breast and curve development)	None
Milicer, 1968	Community sample in Wroclaw, Poland	5,859	9–17	Female only	SES	SES (parental education, occupation and income)	Age at menarche	age, BMI, race
Monteilh et al., 2011	Nationally Representative Sample (UK); Avon Longitudinal Study of Parents and Children (ALSPAC)	2,249	0–14	Male only	SES	Mother's education	Tanner stage (age at pubic hair stage > 1)	None
Negriff & Trickett, 2012	Longitudinal cohort in U.S.	454	9–13	47% Female	General	Active case within Department of Child and Family Services	Tanner stage and PDS	None
Negriff, Blankson, & Trickett, 2015	Longitudinal cohort in U.S.	454	9–13	47% Female	Threat	Sexual Abuse, Other Maltreatment	PDS	ethnicity, obesity, biological father absence
Negriff, Saxbe, & Trickett, 2015	Longitudinal cohort in U.S.	454	9–13	47% Female	General	Active case within Department of Child and Family Services	PDS	None
Noll et al., 2017	Longitudinal cohort in U.S.	173	11–20	Female only	Threat	Sexual Abuse	Tanner stage	None
Reagan, Salsberry, Fang, Gardner, & Pajer, 2012	Nationally representative sample (U.S.); National Longitudinal Study of Youth	2,337	12–17	Female only	SES	% time in poverty between ages 0–5	Age at menarche	All forms of adversity, child's age, child's race
Reid et al., 2017	Cohort of internationally adopted youth	165	7–14	Female only	Deprivation	Institutionalization	% menstruating	BMI, people in household, father's occupation
Ryan, Mendle, & Markowitz, 2015	Nationally representative sample (U.S.); Add Health Survey Participants	6,273	11–34	Female only	Threat/Deprivation/SES	Sexual Abuse, physical abuse, physical neglect, SES (income to needs ratio)	Age at menarche	None
Salces, Rebato, Susanne, San Martin, & Rosique, 2001	Community sample from Basque Country, Spain	196	9–17	Female only	SES	SES (father's occupation)	Age at menarche	None

(*table continues*)

Table 1 (*continued*)

Study	Sample	Sample size (*N*)	Age range	Sex distribution	Early life adversity	Adversity details	Pubertal timing metric	Covariates
Sonuga-Barke, Schlotz, & Rutter, 2010	Cohort of adopted Romanian youth	197	6–15	~ 50% Female	Deprivation	Institutionalization	Tanner stage	Parental early puberty history, perinatal factors, childhood and current adiposity, physical activity, sleep duration, presence of stepfather, stressful life events
Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2019	Community sample of maltreated children and adolescents from Seattle, WA	247	8–16	48% Female	Threat/deprivation/SES	Threat exposure composite, deprivation exposure composite, SES (below or above poverty line)	Tanner stage	Sex, race/ethnicity, family poverty status, other adversity exposure composite
Sun, Mensah, Azzopardi, Patton, & Wake, 2017	Nationally representative sample (Australia); The Longitudinal Study of Australian Children	3,764	0–11	48% Female	SES	SES (family income, education and occupation)	PDS	None
Sung et al., 2016	Nationally representative sample (U.S.); NICHD Study of Early Child Care and Youth Development (SECCYD)	492	0–15	Female only	SES	SES (income to needs ratio) in the first 5 years of life	Age at menarche	BMI, race, age, other adversity
Teilmann et al., 2009	Cohort of Internationally adopted individuals in Denmark	1,376	4–13	Female only	Deprivation	International Adoption (from Asia, South America, Eastern Europe and Africa to Denmark)	Tanner stage	None
Turner, Runtz, & Galambos, 1999	Canadian cohort of girls recruited from outpatient clinical agencies and public schools	44	12–19	Female only	Threat	Sexual abuse	Age at menarche	None
Windham, Zhang, Longnecker, & Klebanoff, 2008	New York site of Collaborative Perinatal Project	1440	7–22	Female only	SES	Income and crowding/ number of persons per room in the household at age 7/8	Age at menarche	None

Note. BMI = body mass index; PDS = Pubertal Development Scale; SES = socioeconomic status.

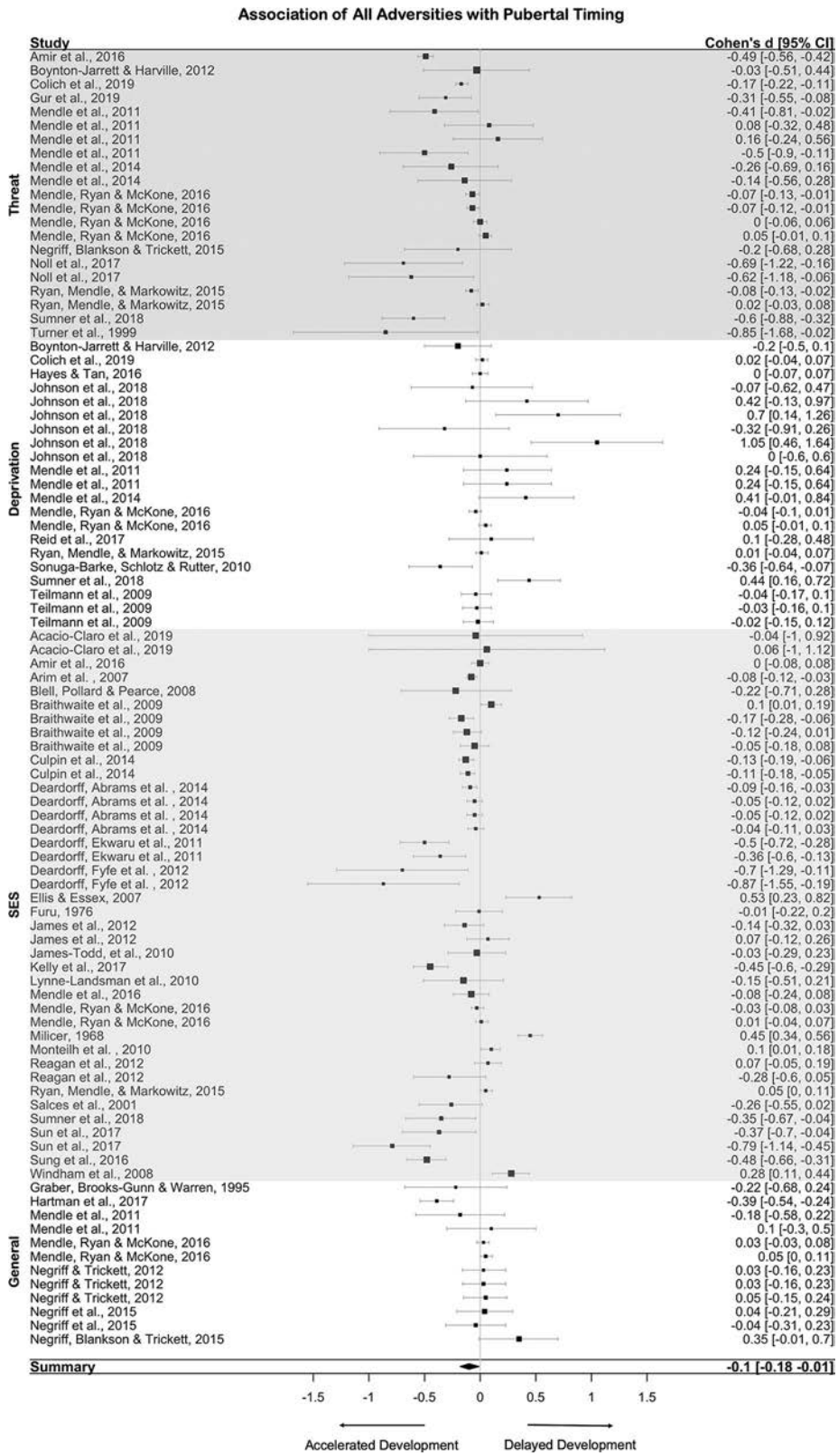


Figure 2. Association of all adversities and pubertal timing. The point sizes are an inverse function of the precision of the estimates.

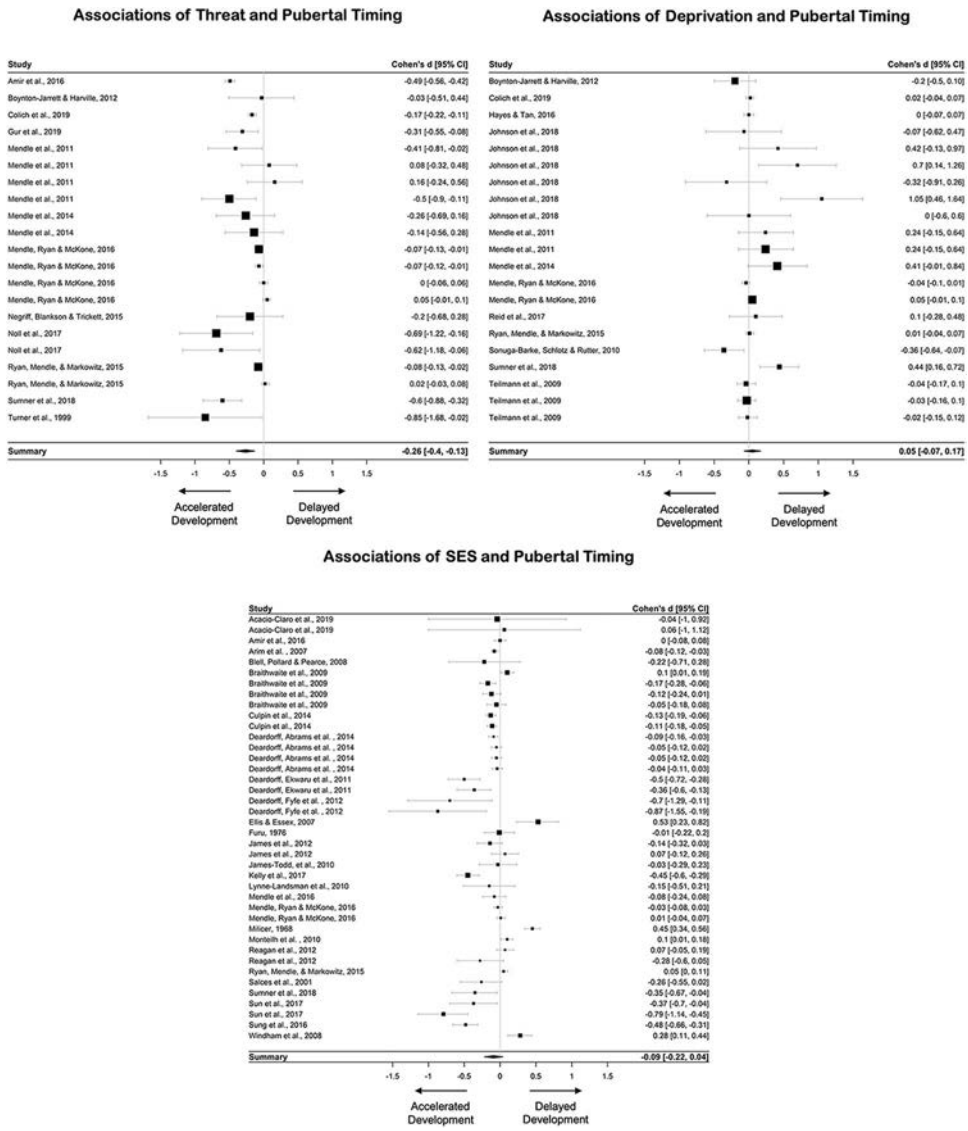


Figure 3. Association of all adversities and cellular aging. The point sizes are an inverse function of the precision of the estimates. SES = socioeconomic status.

SES. For studies that explored the association of SES with pubertal timing (26 studies; 40 effect sizes, $N = 87{,}654$), the random-effects meta-analysis found that SES was associated with earlier pubertal timing ($d = -0.09$, 95% CI [−0.22, 0.04]), but the effect size was not significantly different than zero ($z = -1.40$, $p = .16$; Figure 3). Significant heterogeneity was observed across studies, $Q(39) = 285.68$, $p < .001$; $I^2 = 96.38$. The result of Begg's publication bias test (Kendall's $\tau = -0.15$, $p = .18$) and Egger's linear regression test ($z = -1.44$, $p = .15$) were not significant, suggesting no publication bias in our sample of studies (see sFigure3 for a funnel plot of all SES-related adversities and pubertal timing). The results of the p-curve analysis, in which 40 effect sizes were included and 19 had p values lower than .025, suggest that the results are not due to publication bias or p-hacking (sFigure4).

Given significant heterogeneity in our studies examining the association of SES with pubertal timing, we conducted a series of moderator analyses. For the association between SES and pubertal timing, race/ethnicity was significantly associated with variation in effect sizes (estimate = −0.002, $SE = 0.001$, $z = -3.39$, $p < .001$), suggesting that the higher percentage of White individuals in the sample, the more negative the association between SES-related adversity and pubertal timing (i.e., the more accelerated the pattern of maturation).

Cellular Aging

A total of 11 studies (nine examining telomere length, two examining DNA methylation age) produced 17 effect sizes across a total of 1,560 participants. Sample sizes for included studies

ranged from 38 to 293 (median = 100). Of the 17 effect sizes, four focused on the effect of threat on cellular aging, two focused on deprivation, seven on SES, and four used a cumulative approach of summing across multiple forms of adversity. Table 2 presents descriptive demographic information for each study.

All adversities. We first examined the effect of all forms of adversity on cellular aging across all 11 studies included in the meta-analysis. The random-effects meta-analysis found that greater exposure to ELA was associated with accelerated cellular aging ($d = -0.21$, 95% CI [−0.39, −0.04]) and significantly differed from zero ($z = -2.43$, $p = .01$; Figure 4). There was significant heterogeneity observed across studies, $Q(16) = 44.27$, $p < .001$; $I^2 = 61.47$. The result of Begg's publication bias test (Kendall's $\tau = -0.34$, $p = .06$) was not significant, but Egger's linear regression test ($z = -2.06$, $p < .05$) was significant, suggesting a slight asymmetry of the funnel plot and potential publication bias in our sample of studies (sFigure5). The results of the p-curve analysis, in which seven effect sizes were included and four had *p* values lower than .025, were inconclusive. The results of this analysis do not indicate a "true effect," free of publication bias, but also do not verify that evidential value or a "true effect" is absent or inadequate (sFigure6). These results are most likely due to the small number of effect sizes included in the p-curve analysis, and the high heterogeneity across all effect sizes. These results should be viewed as preliminary, until more studies on this subject are published.

Using adversity type as a moderator, we tested our hypothesis that threat would have a significant negative effect on cellular aging (suggesting accelerated development) and evaluated whether these effects were similar for other adversity types. Adversity type moderated the association between ELA and cellular aging, $F(3, 13) = 7.69$, $p = .05$. As such, we explored the associations of ELA with cellular aging separately for each adversity type.

Given that multiple forms of cellular aging were included in this analysis, including telomere length and DNAm age, we also conducted a sensitivity analysis exploring the impact of adversity on telomere length alone, and a using cellular aging metric (telomere length and mDNA age) as a moderator of the association between ELA and cellular aging. In telomere studies only, greater exposure to ELA was associated with shorter telomere length ($d = -0.21$, 95% CI [−0.41, −0.01]) and significantly differed from zero ($z = -2.03$, $p = .04$). Significant heterogeneity was observed across studies, $Q(12) = 33.16$, $p < .001$; $I^2 = 61.99$. The result of Begg's publication bias test (Kendall's $\tau = -0.35$, $p = .09$) was not significant; however, Egger's linear regression test was marginally significant ($z = 01.98$, $p = .05$), suggesting potential publication bias in our sample of studies. The results of the p-curve analysis, in which five effect sizes were included and two had *p* values lower than .025, were inconclusive. The results of this analysis do not indicate a "true effect," free of publication bias, but also do not verify that evidential value or a "true effect" is absent or inadequate. These results are most likely due to the small number of effect sizes included in the p-curve analysis, and the high heterogeneity across all effect sizes. Cell type (buccal, saliva, blood) did not significantly moderate this association, $F(2, 10) = 4.20$, $p = .12$. Similarly, cellular aging metric (telomere length and mDNA age) did not moderate the association between ELA and cellular aging, $F(1, 15) = 0.04$, $p = .85$.

Threat. In studies that explored the association of threat exposure with cellular aging (four studies; four effect sizes, $N = 664$), greater exposure to threat was associated with accelerated cellular aging ($d = -0.43$, 95% CI [−0.61, −0.25]). The effect size was moderate in magnitude and differed from zero ($z = -4.65$, $p < .0001$; Figure 5). Significant heterogeneity was not observed across studies, $Q(3) = 0.39$, $p = .94$; $I^2 = 0.00000001$. The results of Begg's publication bias test (Kendall's $\tau = -0.33$, $p = .75$) and Egger's linear regression test ($z = -0.43$, $p = .67$) were not significant, suggesting no publication bias in our sample of studies (see sFigure 7 for a funnel plot of threat-related adversities and cellular aging). The results of the p-curve analysis, in which three effect sizes were included and three had *p* values lower than .025, were inconclusive (sFigure 8). The results of this analysis do not indicate a "true effect," free of publication bias, but also do not verify that evidential value or a "true effect" is absent or inadequate. As with the other analyses examining cellular aging, this is most likely due to the small number of effect sizes included in the p-curve analysis, and the high heterogeneity across the effect sizes.

Deprivation. In studies that explored the association of deprivation exposure with cellular aging (two studies; two effect sizes, $N = 347$), the random-effects meta-analysis found that deprivation was not associated with cellular aging ($d = -0.01$, 95% CI [−0.24, 0.23]), with an effect size that did not significantly differ from zero ($z = -0.07$, $p = .94$; Figure 5). Significant heterogeneity was not observed across studies, $Q(1) = 0.31$, $p = .58$; $I^2 = 0.00000002$. The results of Begg's publication bias test (Kendall's $\tau = -1.000$, $p = 1.000$) and Egger's linear regression test ($z = -0.56$, $p = .56$) were not significant, suggesting no publication bias in our sample of studies. However, given this analysis only contained two effect sizes, this is not a reliable estimate of publication bias. P-curve analyses were not conducted due to the small number of significant *p* values $< .05$ ($n \leq 2$), which suggests no evidence of p-hacking or publication bias given the absence of significant published effects. We did not explore moderators given the lack of heterogeneity in effect sizes.

SES. In studies of SES and cellular aging (six studies; seven effect sizes, $N = 1{,}005$), SES was not associated with cellular aging ($d = -0.03$, 95% CI [−0.20, 0.14]), with an effect size that did not significantly differ from zero ($z = -0.35$, $p = .73$; Figure 5). Significant heterogeneity was not observed across studies, $Q(6) = 8.94$, $p = .18$; $I^2 = 25.48$. The result of Begg's publication bias test was not significant (Kendall's $\tau = -0.52$, $p = .14$), however Egger's linear regression test ($z = -2.45$, $p = .01$) was significant, suggesting a slight asymmetry of the funnel plot and potential publication bias in our sample of studies. P-curve analyses were not conducted due to the small number of significant *p* values $< .05$ ($n \leq 2$). We did not explore moderators given the lack of heterogeneity in effect sizes.

Brain Development

We systematically reviewed the associations between ELA and two metrics of brain development: cortical thickness and task-based amygdala-PFC functional connectivity. Across the two metrics there were 25 studies and a total of 3,253 unique participants (17 cortical thickness articles, $N = 2{,}825$; 7 amygdala-PFC connectivity articles, $N = 428$). As described above, we created

Table 2
Characteristics of Individual Studies Included in the Cellular Aging Meta-Analysis

Study	Sample	Sample size (*N*)	Age range	Sex distribution	Early life adversity	Adversity details	Cellular aging metric	Covariates
Asok, Bernard, Roth, Rosen, & Dozier, 2013	Longitudinal cohort examining efficacy of attachment-based intervention for infants in Child Welfare System	38	4–7	58% Female	General	Identified by Child Welfare System as being at-risk for maltreatment (conditions noted most often include child neglect, domestic violence, parental substance use, inadequate housing)	Telomere length (buccal swabs)	Household income, sex, minority status
Brody, Yu, & Shalev, 2017	Cohort from a family-based prevention study	293	17–22	63% Female	SES	Composite metric considering family poverty, caregiver unemployment, government assistance, single parenthood, caregiver education level, and self-reported inadequacy of family income	Telomere length (blood)	None
Drury, Mabile, Brett, et al., 2014	Community sample from New Orleans, LA	80	5–15	49% Female	Threat/general	Family instability (witnessing family violence, suicide, incarceration)	Telomere length (buccal swabs)	None
Drury, Theall, Gleason, et al., 2012	Bucharest Early Intervention Project (BEIP)	100	6 months - 10	41% Female	Deprivation	Early institutionalization (% of time spend in institution at 54 months)	Telomere length (buccal swabs)	Group, sex, ethnicity, age at telomere collection and low birth weight
Jovanovic et al., 2017	Longitudinal cohort of trauma exposed children and adolescents	101	6–13	54% Female	Threat	Violence Exposure	Horvath DNAm age (saliva)	None
Mitchell, Hobcraft, McLanahan, et al., 2014	2 cohorts including Fragile Families and Child Wellbeing Study and an independent cohort	40	9	Male only	General/SES	Harsh environment determined by equally weighted combination of (a) family economic conditions, (b) parenting practices, and (cc) family structure/stability – then incorporating maternal depression; income to needs ratio	Telomere length (saliva)	None

(*table continues*)

Table 2 (*continued*)

Study	Sample	Sample size (*N*)	Age range	Sex distribution	Early life adversity	Adversity details	Cellular aging metric	Covariates
Needham, Fernandez, Lin, Epel, & Blackburn, 2012	Admixture Mapping for Ethnic and Racial Insulin Complex Outcomes (AMERICO) cohort	70	7–13	53% Female	SES	SES (family income and parental education)	Telomere length (blood)	None
Ridout et al., 2019	Cohort of children and adolescents, half of whom had child welfare documentation of moderate-severe maltreatment	256	3–5	52% Female	General/SES	Number of types of maltreatment experienced, number of lifetime contextual stressors, and number of other traumatic life events; composite measure of socioeconomic adversity including parental education, parental unemployment, and single parenthood	Telomere length (saliva)	Age, ethnicity
Shalev et al., 2013	Environmental-Risk Longitudinal Twin Study	236	5–12	49% Female	Threat	Domestic violence, bullying victimization, physical maltreatment	Telomere length (buccal swabs)	None
Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2019	Community sample of maltreated children and adolescents from Seattle, WA	247	8–16	48% Female	Threat/deprivation/SES	Threat exposure composite, deprivation exposure composite, SES (below or above poverty line)	Horvath DNAm age (saliva)	Sex, race/ethnicity, family poverty status, other adversity exposure composite
Theall, Brett, Shirtcliff, Dunn, & Drury, 2013	Community sample from New Orleans, LA	99	4–14	53% Female	SES	Household socioeconomic position	Telomere length (saliva)	None

Note. SES = socioeconomic status.

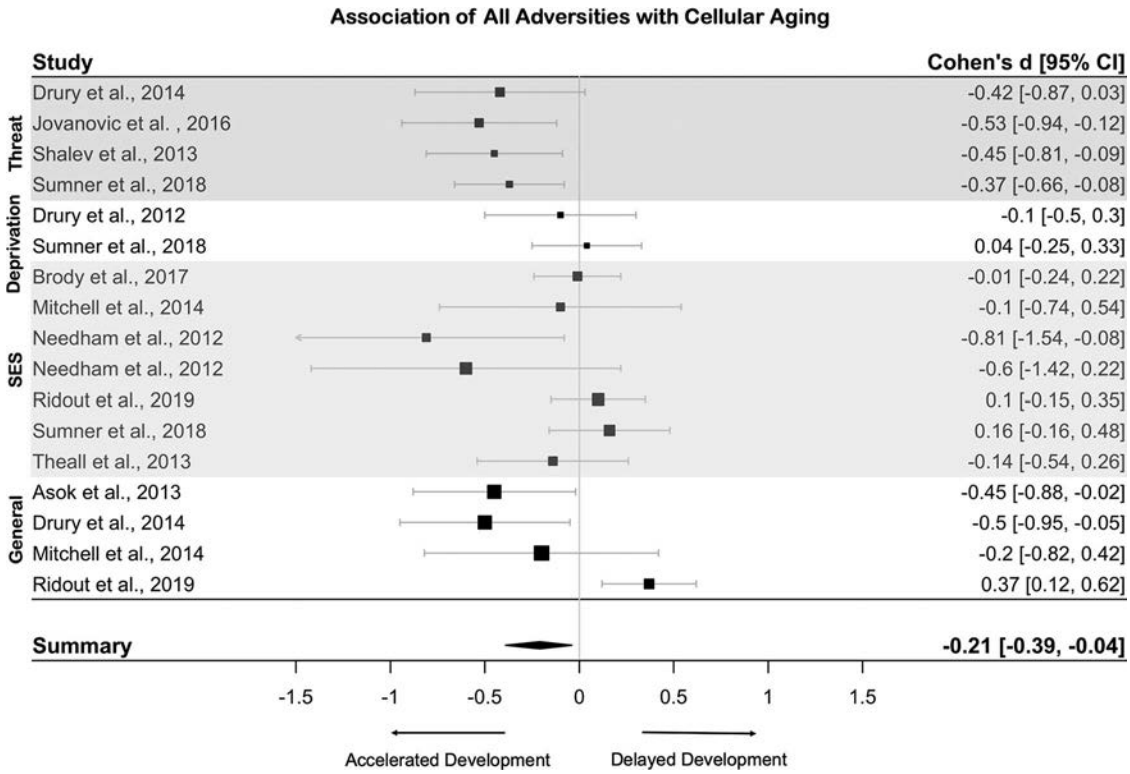


Figure 4. Association of adversity and pubertal timing by adversity type. The point sizes are an inverse function of the precision of the estimates.

quality ratings for these studies with a 3-point scale for cortical thickness articles and a 4-point scale for amygdala-PFC connectivity articles. All ratings can be found in Table 3 and Table 4.

Cortical thickness.

Threat. We found six articles that investigated the association between experiences of threat and cortical thickness in childhood and adolescence (N = 232; Busso, McLaughlin, Brueck, et al., 2017; Edmiston et al., 2011; Gold et al., 2016; Kelly et al., 2013; Lim et al., 2018; McLaughlin, Sheridan, et al., 2016). Of these six studies, five found that children exposed to threat had accelerated thinning of the cortex. Four of these studies found decreased cortical thickness among children exposed to threat in the ventro-

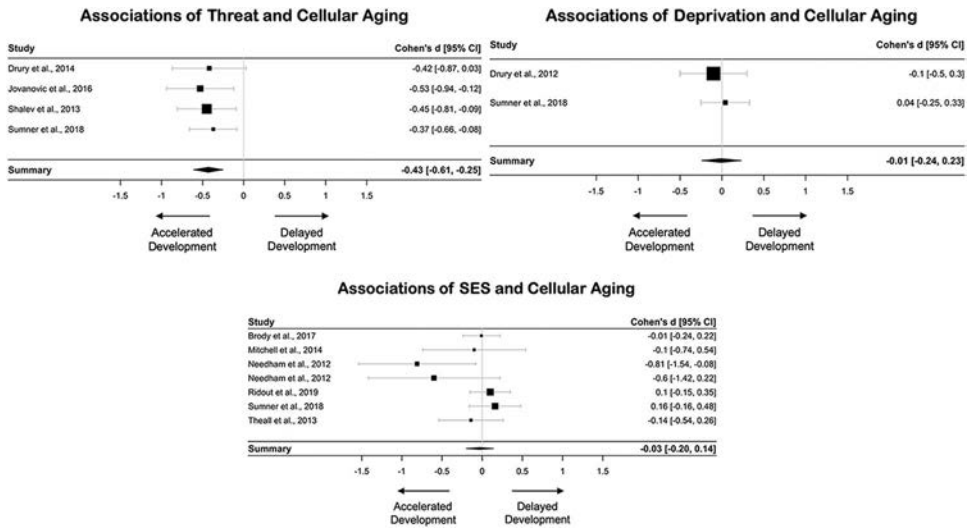


Figure 5. Association of adversity and cellular aging by adversity type. The point sizes are an inverse function of the precision of the estimates. SES = socioeconomic status.

Table 3
Characteristics of Individual Studies Included in the Cortical Thickness Systematic Review

Authors	Sample	Sample size (*N*)	Age range[a]	Sex distribution	Early-life adversity	Adversity details	ROI or whole brain?	Brain regions with significant associations with adversity	Covariates	Group matching characteristics	Study quality rating (out of 3)
Avants, Hackman, Betancourt, Lawson, Hurt, & Farah, 2015	Community sample	52	19.16 (1.32)	52% Female	Deprivation	Environmental stimulation measured by the HOME at ages 4 and 8	Whole brain	Thicker cortex among children with lower levels of cognitive stimulation at age 4 (but not 8) in L lateral inferior temporal—posterior, L lateral inferior temporal -anterior, bilateral fusiform, R lateral inferior temporal	Age at scan, maternal IQ, gender, foster care and prenatal cocaine	N/A	2
Busso, McLaughlin, Brueck, Peverill, Gold, & Sheridan, 2017	Community based sample of children in Boston, MA exposed to high rates of maltreatment	51	13–20	60% Female	Threat	Childhood Trauma Questionnaire and Childhood Experiences of Care and Abuse to assess emotional, sexual, and physical abuse	ROI (vmPFC, lateral OFC,anterior and posterior cingulate cortices, ventrolateral PFC (including inferior frontal gyrus [IFG]), dorsolateral PFC (including middle and superior frontal gyri),insular cortex, parahippocampal gyrus, temporal pole, and lateral temporal cortex (spanning inferior, middle, and superior temporal gyri)	Thinner cortex among abused in vmPFC, right inferior frontal gyrus, left and right parahippocampal gyri, right inferior temporal gyrus, and right middle temporal gyrus compared with nonexposed controls	Age, gender, parental education	Race, IQ, handedness	2
Edmiston, Wang, Mazure, et al., 2011	Community sample without *DSM* Axis I diagnoses	42	12–17	50% Female	Threat/Deprivation	Childhood Trauma Questionnaire to assess physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse	Whole brain	Thinner left DLPFC, left RPFC, right orbitofrontal cortex, insula and temporal association cortex with greater physical abuse; thinner RPFC, parietal association cortex, cerebellum, bilateral DLPFC, dorsal ACC, SFG, OFC, sgPFC, parietal association cortex, right temporal association cortex, and left occipital association cortex, with greater neglect	Age	N/A	1

(*table continues*)

Table 3 (*continued*)

Authors	Sample	Sample size (*N*)	Age range[a]	Sex distribution	Early-life adversity	Adversity details	ROI or whole brain?	Brain regions with significant associations with adversity	Covariates	Group matching characteristics	Study quality rating (out of 3)
Gold et al., 2016	Community based sample of children in Boston, MA exposed to high rates of maltreatment	58	13–20	60% Female	Threat	Childhood Trauma Questionnaire and Childhood Experiences of Care and Abuse to assess emotional, sexual, and physical abuse	ROIs in medial and lateral prefrontal cortex, and medial and lateral temporal cortex	Thinner cortex among abused sample in bilateral ventromedial prefrontal cortex, right orbitofrontal cortex, left temporal pole, right inferior frontal gyrus, left and right parahippocampal gyri, left and right inferior temporal gyrus, right superior temporal gyrus, and right middle temporal gyrus	Race, age, sex, and parental education		3
McLaughlin et al., 2016	Community based sample of children in Seattle, WA exposed to high rates of maltreatment	60	18-Jun	48% Female	Threat	Childhood Trauma Questionnaire and Childhood Experiences of Care and Abuse to assess emotional, sexual, and physical abuse	ROI in dorsal anterior cingulate and ventromedial prefrontal cortex	No significant associations with cortical thickness	Age, sex		3
Kelly et al., 2013	Community based sample recruited from London Social Services department	43	12.77(1.19) for controls, 12.27(1.41) for maltreated	56% Female	Threat	Social worker report using Kaufman's 4-point scale for physical abuse, emotional abuse, sexual abuse, and neglect	Whole brain	Decreased cortical thickness in mPFC in maltreated	Age and sex	Tanner stage, handedness, cognitive ability, ethnicity	3
Lawson, Duda, Avants, Wu, & Farah, 2013	Participants from NIH Pediatric MRI Data Repository	283	11.47 (3.50)	53% Female	SES	Family income, parental education summed from two parents; parental education variable was square-root transformed	ROIs in the prefrontal cortex	Lower parental education was associated with decreased cortical thickness in right anterior cingulate cortex and left superior frontal gyrus. No associations emerged with parental income.	Age, sex, total brain volume, race, body mass index	N/A	3

(*table continues*)

Table 3 (*continued*)

Authors	Sample	Sample size (*N*)	Age range[a]	Sex distribution	Early-life adversity	Adversity details	ROI or whole brain?	Brain regions with significant associations with adversity	Covariates	Group matching characteristics	Study quality rating (out of 3)
Leonard et al., 2019	Community sample from two other studies in the Greater Boston Area: one on executive function development and one on parenting intervention (only data from before the intervention included in this sample)	115	4–7	46% Female	SES	Highest level of maternal education	Whole-Brain	At the threshold presented throughout the article ($p < .005$) there is no main effect of maternal education on thickness, but at a more liberal threshold of .05, there is a significant positive association in right superior parietal lobule / intraparietal sulcus and lateral occipital complex	Age, gender, image quality	N/A	3
Lim et al., 2018	Community sample in South London recruited through social services and psychiatric clinics	68	13–20	50% Female	General	Childhood Trauma Questionnaire to measure childhood physical, sexual and emotional abuse, and physical and emotional neglect. Used a sum score across the whole CTQ.	Whole brain and ROI	Thinner left precentral, postcentral and paracentral gyri in abuse group compared with healthy controls and reduced left precentral compared with controls matched on psychiatric conditions. ROI analyses also revealed reduced cortical thickness in left insula and right lateral orbitofrontal cortex in the abuse group compared to healthy controls.	IQ, age, mean cortical thickness	Age, gender, psychiatric disorders	2
Mackey et al., 2015	Community sample from Boston, Massachusetts area	58	Lower income: 14.47 (0.38), Higher income: 14.35 (0.47)	53% Female	SES	Free or reduced-price lunch status obtained from the Massachusetts Department of Elementary and Secondary Education	Whole brain	Thinner cortex in lower income group in bilateral temporal and occipital lobes and in right lateral prefrontal cortex	Sex, intracranial volume; associations also hold when controlling for race and ethnicity	None	3

(*table continues*)

Table 3 (*continued*)

Authors	Sample	Sample size (*N*)	Age range[a]	Sex distribution	Early-life adversity	Adversity details	ROI or whole brain?	Brain regions with significant associations with adversity	Covariates	Group matching characteristics	Study quality rating (out of 3)
McDermott et al., 2019	Community sample collected at NIMH	623	5–25	48% Female	SES	Hollingshead Two-Factor Index of Social Position using maternal report of maternal occupation and education	Whole brain	SES is positively associated with mean cortical thickness, but when looking at regional specificity, found that the association was only significant in the right supramarginal gyrus.	Sex, age, each individual's ID (to account for multiple longitudinal scans per individual) and family ID (to account for the presence of dizygotic twin pairs and siblings in the sample) as nested random effects. IQ as a sensitivity analysis	N/A	3
Jednoróg et al., 2012	Community sample from Paris, France	23	8–10	57% Female	SES	Hollingshead Two-Factor Index of Social Position using maternal report of maternal occupation and education	Whole brain	Positive associations between SES and thickness in L angular gyrus, L Heschl's gyrus, L post-ventral cingulate, and L anterior occipital sulcus. Negative associations between SES and thickness in L fronto-marginal gyrus/sulcus, L middle frontal sulcus, and L intraparietal sulcus.	None	N/A	1
Noble et al., 2015	Pediatric Imaging, Neurocognition, Genetics Study (PING)	1,148	3–20	48% Female	SES	Parent report of income and education	Whole brain	No significant associations between cortical thickness and SES or SES × Age interactions	Age, age-squared, scanner, sex, genetic ancestry	N/A	3
Piccolo et al., 2016	Pediatric Imaging, Neurocognition, Genetics Study (PING)	1,148	3–20	48% Female	SES	Parent report of income and education	Whole brain	Age(squared) × SES (both income and education) interaction in average cortical thickness, such that lower SES children demonstrate faster thinning across the whole cortex. No specific regions survive correction for multiple comparisons.	SES measure, age, age-squared, scanner, sex, genetic ancestry, and parental SES Measure × Age	N/A	3

(*table continues*)

Table 3 (*continued*)

Authors	Sample	Sample size (*N*)	Age range[a]	Sex distribution	Early-life adversity	Adversity details	ROI or whole brain?	Brain regions with significant associations with adversity	Covariates	Group matching characteristics	Study quality rating (out of 3)
Rosen, Sheridan, Sambrook, Meltzoff, & McLaughlin, 2018	Community based sample of children in Seattle, WA exposed to high rates of maltreatment	53	6–19	48% Female	Deprivation/SES	SES-family income divided by the federal poverty line for a family of that size; cognitive stimulation-parent report using Home Observation Measurement of the Environment (HOME)-short form	Whole brain and ROI	Lower levels of cognitive stimulation were associated with thinner cortex in left superior parietal lobule and left middle frontal gyrus. There were no associations with SES and no significant whole brain associations.	Age, sex, violence exposure	N/A	3
Hodel et al., 2015	110 postinstitutionalized children, from Minnesota International Adoption Project	172	12–14	61% Female	Deprivation	Previously institutionalized children adopted into the United States	Whole brain	Thinner cortex in right inferior frontal gyrus among previously institutionalized children compared with controls.	Age, sex		3
McLaughlin et al., 2014	Bucharest Early Intervention Project (BEIP)	80	8–10	50% Female	Deprivation	Part of a randomized control trial where half of the institutionalized children were placed in high quality foster care. There were no differences between the care as usual group and foster care group, so all analyses compared the Ever Institutionalized Group (EIG) to the Never Institutionalized Group (NIG).	Whole brain	Widespread reductions in cortical thickness across frontal, parietal and temporal lobes in children who were ever institutionalized.	Age, sex, total brain volume, and TR length (due to different acquisition parameters)		3

Note. SES = socioeconomic status; ROI = region of interest; OFC = orbital frontal cortex; PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; RPFC = right prefrontal cortex; ACC = anterior cingulate cortex; SFG = superior frontal gyrus; TR = repetition time.
[a] Age range (in. years) was the most commonly used descriptor of the full sample. When this was not available, means and standard deviations are given.

Table 4
Characteristics of Individual Studies Included in the Amygdala-mPFC Review

Authors	Sample	Sample size (*N*)	Age range	Sex distribution	Early-life adversity	Adversity details	Seed-to-seed or whole brain?	Task	Associations with adversity and amygdala-mPFC connectivity	Covariates	Group matching characteristics	Study quality rating (out of 4)
Cisler, Scott, Smitherman, Lenow, & Kilts, 2013	Community based sample in Arkansas	30	12–16	100% female	Threat	Assessed using the trauma assessment section of the National Survey of Adolescents (sexual assault, physical assault, severe abuse from caregiver)	Whole brain	Implicit emotion processing task	Greater connectivity between right amygdala and left middle frontal gyrus, and right amygdala and left perigenual anteriorcingulate	None	Age, ethnicity, anxiety and depression diagnoses	3
Colich et al., 2017	Community based sample in the San Francisco Bay area	137	9–13	57% female	Threat	Based on modified version of Traumatic Events Screening Inventory for Children	Seed-to-seed	Implicit emotion regulation task	ELA was associated with increased negative connectivity between the right ventrolateral prefrontal cortex and bilateral amygdala	Age	N/A	3
Gee et al., 2013	Post institutionalized children adopted into the United States and comparison children	89	6–18	56% female	Deprivation	Sample of previously institutionalized children adopted into the United States	Whole brain	Emotional face viewing task	Comparison group children showed positive amygdala-mPFC connectivity during viewing of fearful faces while adolescents showed comparison group adolescents showed negative connectivity. In contrasts, both PI children and adolescents. showed negative amygdala-mPFC connectivity.	Amygdala reactivity	Pubertal status	2
Keding & Herringa, 2016	Community based sample in Wisconsin; sampled specifically for PTSD	53	8–18	58% female	Threat	All trauma exposed participants also had PTSD. Trauma exposures were Sexual abuse, traumatic death of loved one, witnessing violence, accident, physical abuse	Whole brain	Implicit dynamic emotion face	PTSD sample showed reduced connectivity between amygdala and both dorsal anterior cingulate and ventrolateral PFC during angry trials and increases connectivity to happy faces. Control participants showed the opposite pattern of results.	Age, sex	Age, pubertal status, IQ, handedness	4

(*table continues*)

Table 4 (*continued*)

Authors	Sample	Sample size (*N*)	Age range	Sex distribution	Early-life adversity	Adversity details	Seed-to-seed or whole brain?	Task	Associations with adversity and amygdala-mPFC connectivity	Covariates	Group matching characteristics	Study quality rating (out of 4)
Marusak, Martin, Etkin, & Thomason, 2015	Community based sample in Detroit, MI	30	9–17	80% female	Threat	At least one traumatic life event endorsed on parent or child report of Children's Trauma Assessment Center Screen Checklist. These included sexual abuse, physical abuse, neglectful home environment, exposure to domestic violence, exposure to other violence, multiple separations from caregiver	Whole brain	Emotional Stroop	During emotional conflict regulation, trauma exposed group demonstrated positive amygdala - pregenual cingulate cortex connectivity while the control group demonstrated negative connectivity.	None	Age, sex, IQ	2
Peverill, Sheridan, Busso, & McLaughlin, 2019	Community based sample in Boston, MA exposed to high rates of maltreatment	57	13–20	61% female	Threat	Childhood Trauma Questionnaire and Childhood Experiences of Care and Abuse to assess emotional, sexual, and physical abuse	Whole brain	Emotion regulation task	During emotion processing, exposure to abuse was associated with more negative task-related functional connectivity of left amygdala and 2 vmPFC clusters (mOFC and sgACC) relative to control participants	None	Sex, race, IQ, handedness, SES	4
Silvers et al., 2016	Postinstitutionalized children adopted into the United States and comparison children	89	7–16	62% female	Deprivation	Sample of previously institutionalized children adopted into the United States	Whole brain	Aversive learning paradigm	During a fear conditioning task, PI youth demonstrate positive connectivity between the amygdala and vmPFC, dmPFC, and vlPFC, while the comparison group demonstrates negative connectivity	Average head motion	Age, IQ	3

Note. SES = socioeconomic status; OFC = orbital frontal cortex; PFC = prefrontal cortex; ACC = anterior cingulate cortex; ELA = early life adversity.

medial PFC (Busso, McLaughlin, Brueck, et al., 2017; Edmiston et al., 2011; Gold et al., 2016; Kelly et al., 2013). Four found additional associations that follow the same pattern of decreased thickness among threat-exposed youths in regions including the lateral PFC (Busso, McLaughlin, Brueck, et al., 2017; Edmiston et al., 2011; Gold et al., 2016; Lim et al., 2018). Three found evidence for reduced thickness in the orbitofrontal cortex (Edmiston et al., 2011; Gold et al., 2016; Lim et al., 2018) and three found evidence for reduced thickness in medial and lateral temporal cortex (Busso, McLaughlin, Brueck, et al., 2017; Edmiston et al., 2011; Gold et al., 2016). In contrast, one study that spanned a larger age range found no association between experiences of threat and cortical thickness in regions of interest in the dorsal anterior cingulate or ventromedial PFC (McLaughlin, Sheridan, et al., 2016). As a whole, these studies provide support for the hypothesis that experiences of threat are associated with accelerated development, especially in the ventromedial PFC.

Deprivation. A total of four studies ($N = 353$) met inclusion criteria for our review of the association between experiences of deprivation and cortical thickness. This included two studies investigating cortical structure among previously institutionalized children (Hodel et al., 2015; McLaughlin, Sheridan, Winter, et al., 2014) and two investigating the association between cognitive stimulation/deprivation in the home environment and cortical structure (Avants et al., 2015; Rosen et al., 2018). Both studies of institutionalized children demonstrate support for the hypothesis that experiences of deprivation are associated with accelerated cortical thinning. In one study institutionalization was associated with widespread reductions in cortical thickness, including in nodes of the frontoparietal and dorsal attention networks (superior parietal lobule, frontal pole, superior frontal gyrus), default mode network (inferior parietal cortex, precuneus, midcingulate), lateral temporal cortex, parahippocampal cortex, and insula at age 8–10 years (McLaughlin, Sheridan, Winter, et al., 2014). In contrast, Hodel et al. (2015) examined only prefrontal cortex regions of interest and found reduced cortical thickness only in the inferior frontal gyrus among previously institutionalized children compared with controls at age 12–14 years.

The other two studies investigated cortical thickness and its association with cognitive stimulation/deprivation in the home environment. In a cross-sectional study spanning children and adolescents, cognitive stimulation (i.e., lower deprivation) was positively associated with cortical thickness in two nodes in the left, but not right frontoparietal network (superior parietal lobule and middle frontal gyrus; Rosen et al., 2018). These results are consistent with the idea that deprivation (i.e., low cognitive stimulation) is associated with accelerated development. In contrast, in a longitudinal study, results revealed that cognitive stimulation at age 4, but not at age 8, was negatively associated with cortical thickness at age 19, such that lower deprivation was associated with thicker cortex in the ventral temporal cortex and inferior frontal gyrus. These results suggest that cognitive deprivation is associated with delayed development in these regions.

SES. Eight studies met the criteria for inclusion examining SES and cortical thickness ($N = 2{,}303$; Jednoróg et al., 2012; Lawson, Duda, Avants, Wu, & Farah, 2013; Leonard et al., 2019; Mackey et al., 2015; McDermott et al., 2019; Noble et al., 2015; Piccolo, Merz, He, Sowell, & Noble, 2016; Rosen et al., 2018). Of those, five found that low SES was associated with thinner cortex across large swaths of cortex encompassing the frontoparietal network (lateral prefrontal cortex, superior parietal cortex), default mode network (lateral temporal cortex, precuneus), and the visual system (lateral occipital and ventral temporal cortex), supporting the idea that low SES is associated with accelerated cortical development. Piccolo, Merz, He, Sowell, and Noble (2016) found that SES moderates the association between age squared and cortical thickness such that low SES individuals show a sharper decline in cortical thickness early in development, which may reflect accelerated development compared with higher SES individuals. Additionally, Lawson and colleagues (2013) demonstrate that low parent education is associated with reduced cortical thickness in the right cingulate gyrus and right superior frontal gyrus, and Mackey and colleagues (2015) demonstrate that low SES individuals demonstrate thinner cortex across much of the brain including the frontoparietal network (right middle frontal gyrus, left superior parietal lobule, right frontal pole), default mode network (left precuneus, bilateral lateral temporal cortex, right frontal pole), and visual system (bilateral occipital and ventral temporal cortex). McDermott et al. (2019) demonstrate that SES is positively associated with mean cortical thickness, but when looking at regional specificity, found that the association was only significant in the right supramarginal gyrus. Two studies spanning large age ranges (Noble et al., 2015; Rosen et al., 2018) found no association between SES and cortical thickness. Importantly, Noble et al. (2015) and Piccolo et al. (2016) used the same sample and while there were no main effects of SES on cortical thickness and no Age $\times$ SES interactions (Noble et al., 2015), Piccolo et al. (2016) demonstrate an Age Squared $\times$ SES interaction such that children from low-income households demonstrate accelerated thinning compared with high-income counterparts. One other study in young children (Leonard et al., 2019) found that SES was positively associated with cortical thickness in the occipital cortex and posterior intraparietal sulcus, but only at a very liberal threshold.

Amygdala-PFC connectivity.

Threat. Our search yielded five articles that evaluated the association between amygdala-PFC connectivity and threat-related experiences. Of these five studies ($N = 250$), three support the hypothesis that experiences of threat are associated with accelerated maturation of this network such that threat-exposed children exhibit more negative connectivity between amygdala and PFC during an implicit dynamic emotion face task, an explicit affect labeling task, and viewing of negative versus neutral images, than children of the same age (Colich et al., 2017; Keding & Herringa, 2016; Peverill, Sheridan, Busso, & McLaughlin, 2019). The two other studies demonstrate the opposite pattern of results such that children who have experienced threat demonstrate more positive task-related amygdala-PFC connectivity compared to controls while viewing emotional faces and while performing an emotional conflict task (Cisler, Scott Steele, Smitherman, Lenow, & Kilts, 2013; Marusak et al., 2015). These mixed findings do not provide conclusive evidence that experiences of threat are associated with either accelerated or delayed development of the circuits.

Deprivation. Our search yielded two articles ($N = 89$) that evaluated the association between experiences of deprivation and task-related connectivity between mPFC and amygdala. Of these two studies, one demonstrated evidence for accelerated development of these circuits such that children who have experienced

deprivation exhibit more negative connectivity earlier in development than comparison children in a passive viewing task of facial emotion (Gee, Gabard-Durnam, et al., 2013). The other study found the opposite pattern of results such that children who had experienced deprivation demonstrated more positive amygdala-mPFC connectivity than comparison children in a fear conditioning paradigm (Silvers et al., 2016).

Discussion

Through the use of meta-analysis and systematic review, we provide evidence for an association between ELA and accelerated biological aging, as measured by pubertal timing, cellular aging, and cortical thinning in childhood and adolescence. We found no evidence for a consistent association of ELA and accelerated development of amygdala-mPFC connectivity. First, although we observed an overall association of ELA with pubertal timing, moderator analysis revealed that ELA characterized by threat, but not deprivation or SES, was associated with accelerated pubertal development with a small effect size, suggesting specificity in the link between ELA and pubertal timing to threat-related adversity. Second, ELA was also associated with accelerated cellular aging as measured by both leukocyte telomere length and DNA methylation age. Again, moderator analyses revealed accelerated aging among children exposed to threat of moderate effect size, but no association with deprivation or SES. However, given the limited number of studies published on early adversity and cellular aging, these analyses, though promising in their consistency with the other metrics of biological aging, should be interpreted as preliminary. Finally, the results of our systematic review of the effects of ELA on brain development revealed a consistent association between ELA and accelerated cortical thinning across multiple types of ELA, although the specific brain regions involved varied by adversity type. Associations of threat with cortical thinning were most consistent in ventromedial PFC, whereas associations of deprivation with cortical thinning were most consistent in the frontoparietal and default mode networks and the ventral visual stream. In contrast, there was no consistent association of ELA with amygdala-mPFC connectivity. These results support the broad predictions of the DMAP model in demonstrating divergent patterns of association of different dimensions of ELA with pubertal timing, cellular aging, and cortical thickness and extend this model to encompass biological aging as an additional developmental domain beyond those proposed in the original theory where the effects of different forms of adversity are at least partially distinct.

ELA and Pubertal Timing

ELA was associated with accelerated pubertal timing overall, but significant heterogeneity existed in this effect as a function of adversity type. The strength of the association of ELA with pubertal timing was significantly moderated by adversity type, such that the association between ELA and accelerated pubertal timing was specific to experiences characterized by threat, and showed no association with deprivation or SES. These results are consistent with predictions from life history models that exposure to environmental harshness (i.e., threat) in childhood accelerates sexual maturation, in order to increase chances of reproduction prior to mortality (J. Belsky et al., 2012; Ellis et al., 2009). They are also consistent with recent findings from our lab demonstrating that threat-related adversities are associated with accelerated pubertal development even after adjustment for exposure to co-occurring deprivation (Colich et al., 2020; Sumner et al., 2019). Some have argued that ELA impacts pubertal timing through influences on the hypothalamic-pituitary-adrenal (HPA) axis (Negriff, Saxbe, et al., 2015; Saxbe, Negriff, Susman, & Trickett, 2015). Given associations between threat-related adversity and altered diurnal patterns of cortisol and cortisol reactivity in childhood (Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2011; Jaffee et al., 2015; King et al., 2017; Tyrka et al., 2009), it is plausible that trauma-related alterations of the HPA-axis may interact with the HPG-axis to accelerate the onset of pubertal development (J. Belsky, Ruttle, Boyce, Armstrong, & Essex, 2015; Negriff, Saxbe, et al., 2015; Saxbe, Negriff, Susman, & Trickett, 2015).

It is also important to consider the role of gene-environment correlations in the association between threat-related ELA and pubertal timing (Cousminer, Widén, & Palmert, 2016; Harden, 2014; Rowe, 2002). For instance, mothers who experience earlier onset of puberty may reproduce at an earlier age, and have children who are both more likely to experience trauma and an earlier onset of puberty (de Vries, Kauschansky, Shohat, & Phillip, 2004; Towne et al., 2005). This topic has been written on extensively (Barbaro, Boutwell, Barnes, & Shackelford, 2017; Gaydosh, Belsky, Domingue, Boardman, & Harris, 2018; Mendle et al., 2006; Tither & Ellis, 2008), however most studies exploring the association between ELA and age at menarche do not control for potential genetic confounding, as the influence of genetics versus the shared and nonshared environment on development can be difficult to disentangle (see Gaydosh, Belsky, Domingue, Boardman, & Harris, 2018; Mendle et al., 2006 for research designs that have attempted to disentangle these factors). However, many more studies have used maternal age at menarche as a covariate in analyses exploring associations between ELA and age at menarche, including nine of the 43 studies included in the pubertal timing meta-analysis. We found no variation in effect size in the studies that controlled for maternal age of menarche from those that did not, which provides some support for the notion that these effects are environmentally mediated to at least some degree. Future research using genetically informed designs is needed to disentangle the genetic versus environmental pathways through which ELA influences pubertal timing in order to better understand the mechanisms linking threat-related ELA and accelerated pubertal development.

We did not find support for our hypothesis that ELA characterized by deprivation would show an association with delayed pubertal timing. Instead, we found no association between deprivation and pubertal timing. Life history theory posits that deprivation of bioenergetics resources could result in delayed maturation and later pubertal development (J. Belsky et al., 2012; Ellis et al., 2009). In this analysis, we included emotional and physical neglect (Boynton-Jarrett & Harville, 2012; Colich et al., 2020; Mendle et al., 2014, 2011; Mendle, Ryan, et al., 2016; Ryan et al., 2015; Sumner et al., 2019), and early institutionalization (Hayes & Tan, 2016; Johnson et al., 2018; Reid et al., 2017; Sonuga-Barke, Schlotz, & Rutter, 2010; Teilmann et al., 2009) as forms of deprivation. It is likely that deprivation in our modern context, represented by the forms of psychosocial deprivation included in

our analyses, is qualitatively different from deprivation in our evolutionary past, and as conceptualized in life history theory. Whereas there is strong evidence for associations of food insecurity and severe deprivation associated with war and famine with delayed pubertal timing (Prebeg & Bralic, 2000; van Noord & Kaaks, 1991), there is less support for association of early institutionalization (where most children experience severe emotional deprivation but not necessarily food insecurity) with pubertal timing (Johnson et al., 2018; Reid et al., 2017). Our novel finding that deprivation is unrelated to the pace of biological aging has clear theoretical implications for life history theory, which to date has made no clear predictions about how psychosocial forms of deprivation should impact the pace of aging and relevant reproductive milestones.

In this meta-analysis, we decided to isolate the effects of deprivation (including neglect and early life institutionalization) from the effects of SES. Low SES, defined as poverty and low parental education, has previously been used as an indicator of deprivation in studies that adjust for co-occurring threat exposure (e.g., Lambert et al., 2017; Sheridan et al., 2017), based on extensive evidence demonstrating that children from families with low parental education and/or income experience reductions in cognitive and social stimulation than children from higher-SES families (Bradley et al., 2001; Duncan & Magnuson, 2012). However, within the DMAP model, poverty is conceptualized as a risk factor for both threat and deprivation, rather than a direct marker of deprivation (McLaughlin, Sheridan, Lambert, et al., 2014; Sheridan & McLaughlin, 2014). Indeed, there is a strong association between SES and exposure to violence (Foster, Brooks-Gunn, & Martin, 2007) in addition to deprivation. Here, the association of SES with accelerated pubertal timing was not significant, potentially reflecting the fact that SES is a risk marker for exposure to other forms of adversity (e.g., trauma) that are associated with accelerated pubertal development rather than having a direct association with pubertal timing. Despite little overlap in inclusion/exclusion criteria and resulting studies included in the analyses, results of a recent meta-analysis examining associations between SES and pubertal timing in males similarly observed no association between SES and pubertal timing (Xu, Norton, & Rahman, 2018). Overall, these findings highlight the importance of considering the nature of the exposure when exploring the developmental consequences of ELA. Future research should carefully distinguish between the effects of threat- and deprivation-related adversities on pubertal timing.

There was no evidence for the moderating effect of metric of pubertal timing (age of menarche vs. secondary sex characteristics) on associations of ELA with pubertal timing, or whether studies controlled for BMI or exposure to other adversity types. However, sex did moderate the association between deprivation-related adversities and pubertal timing such that the more males included in the sample, the more positive the association between deprivation exposure and pubertal timing, suggesting more delayed pubertal maturation. These results suggest that deprivation may have a differential effect on males and females. Sex differences in the impact of adversity on pubertal timing are not surprising, given significant sexual dimorphisms in the development of biological systems beginning in early development and continuing throughout sexual maturation and adulthood (Cousminer et al., 2016). Animal models of nutritional challenge (including undernutrition and obesity) have differential effects on pubertal timing in male and female rats (Sánchez-Garrido et al., 2013), suggesting that sex-specific metabolic effects of deprivation may have a significant impact on pubertal timing. Future research in humans studying the impact of food insecurity specifically, should explore this question directly. These results, along with the fact that pubertal timing differs significantly in males and females (Dorn & Biro, 2011), suggest that future analyses exploring the impact of deprivation on pubertal timing should be conducted separately in males and females.

Race/ethnicity also significantly moderated the association between SES and pubertal timing, such that the higher percentage of white individuals in the sample, the more negative the association between SES-related adversity and pubertal timing (i.e., the more accelerated the pattern of development). Documented differences in pubertal timing depending upon race/ethnicity suggest that Mexican American and non-Hispanic Black girls develop secondary sex characteristics earlier and experience earlier age at menarche than non-Hispanic White girls (Biro et al., 2010). Similarly, there are well-documented differences in SES across race/ethnicity among adolescents in the U.S. (McLaughlin, Costello, et al., 2012). These results highlight the need to carefully consider race and ethnicity in studies examining ELA and pubertal timing and evaluate whether these factors moderate observed associations.

ELA and Cellular Aging

ELA was associated with accelerated cellular aging, as measured by both leukocyte telomere length and DNAm age, such that greater exposure to adversity was associated with decreased telomere length and more advanced DNAm age relative to chronological age. These results replicate earlier meta-analyses conducted in adult populations of adversity with DNAm age (Wolf et al., 2018) and telomere length (Hanssen, Schutte, Malouff, & Epel, 2017). These results are also broadly consistent with an earlier meta-analysis exploring the effects of stress exposure (broadly defined) on telomere length (Coimbra et al., 2017). The consistency in findings is striking given significant differences in the approach of these meta-analyses. Whereas Wolf et al. (2018) and Hanssen, Schutte, Malouff, and Epel (2017) examined the association between ELA and accelerated biological aging in adults, Coimbra et al. (2017) examined a broad range of stressors in childhood and adolescence, including stress reactivity as indexed by cortisol reactivity and parental psychopathology. We did not include cortisol reactivity or parental psychopathology as adversities in the current meta-analysis, yet results are largely consistent with Coimbra et al. (2017). However, it important to note the small number of studies included and the potential publication bias present in this meta-analysis. Thus, these results should be interpreted as preliminary, and further meta-analyses should be conducted once more studies on this topic are conducted.

Despite the small number of studies, we conducted a stratified analysis and found that exposure to threat was associated with accelerated cellular aging of moderate magnitude, whereas neither deprivation nor SES was associated with cellular aging. These results support our hypotheses based on the DMAP model that threat-related adversities would be specifically associated with accelerated cellular aging. Again, these differential associations should be interpreted with caution, however, as the number of

studies examining deprivation and SES with cellular aging was small. Similarly, Egger's linear regression test was significant and results of the p-curve analysis suggest potential publication bias in this sample of studies, which is unsurprising given the small number of studies included in these analyses. Nonetheless, these findings provide preliminary evidence that threat-related adversities are associated with accelerated cellular aging. Greater work is needed to clarify the magnitude and direction of associations of deprivation and childhood SES with cellular aging.

These cellular aging results are consistent with "internal prediction" models of predictive adaptive response (Nettle et al., 2013; Rickard et al., 2014), which propose that ELA negatively influences physical health through altered cellular development as a result of reduced energy to build or repair cellular tissue. This theory expands earlier models focused on allostatic load, or the accumulation of environmental insults on biological systems (Danese & McEwen, 2012; McEwen, 1998; McEwen & Stellar, 1993), and developmental origins of health and disease models (Barker, 2007) focused on how early experience programs biological development to adapt to later environmental conditions. These theories all suggest that accelerated cellular aging occurs as a result of environmental experiences in development. Accelerated cellular aging following ELA may occur in response to alterations in mitochondrial function, oxidative stress, and inflammation (Shalev, 2012). Although we observed consistent effects of ELA across two metrics of cellular aging (telomere length and DNAm age), some work indicates that exposure to ELA may not have consistent associations across other metrics of biological aging (D. W. Belsky et al., 2018). Future research should explore the effect of distinct forms of ELA on additional metrics of allostatic load that may represent accelerated biological aging, including cardiometabolic risk, inflammation, and respiratory health.

Similar to pubertal timing, it is important to consider the role of gene-environment correlations when examining associations among ELA and cellular aging. It is plausible that a higher mutation load (i.e., number of genetic point mutations), associated with many physical and mental health problems, may underlie both exposure to adversity and accelerated cellular aging. For instance, parents who have higher mutation loads that may put them at risk for greater physical and mental health problems may then have children who are both more likely to experience trauma and also show accelerated cellular aging. Thus, the link between ELA and cellular aging could potentially be accounted for by genetic factors that could contribute to both adverse early environments and accelerated cellular aging. Future research should explore this important alternative explanation.

ELA and Brain Development

Cortical thickness. Consistent with the hypothesis that ELA leads to accelerated development, the majority of studies investigating the association between ELA and cortical thickness found that children exposed to adversity of any kind have thinner cortex than their nonexposed counterparts across threat, deprivation, and SES. However, it is critical to note that the specific brain regions that exhibited this pattern of thinning varied consistently by adversity type. This specificity may reflect precocious maturation of particular regions of the brain depending on the particular type of adversity experienced, reflecting adaptive experience-related tuning of neural systems to the environment in which they are developing. There was remarkable consistency across studies of threat-related experiences and cortical thickness—two of which were high-quality, one that was moderate quality, and one that was poor quality—with the majority observing thinner cortex in the ventromedial PFC among children exposed to trauma (Busso, McLaughlin, Brueck, et al., 2017; Gold et al., 2016; Kelly et al., 2013). The vmPFC is implicated in multiple forms of emotion processing, including recall of extinction learning, appraisal of episodic memories, and appraisal of simulated future events (Dixon, Thiruchselvam, Todd, & Christoff, 2017; Milad & Quirk, 2012; Phelps & LeDoux, 2005). The vmPFC has strong interconnections with the amygdala and modulates amygdala activation based on appraisals and prior learning (Phelps & LeDoux, 2005). Accelerated thinning of this region among children exposed to trauma could reflect earlier or more frequent recruitment of this region to modulate amygdala responses, which are well-established to be elevated in response to threat cues among children exposed to violence (Hein et al., 2017; McCrory, De Brito, & Viding, 2011; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015), ultimately producing more rapid specialization of this region, potentially through more rapid synaptic pruning or increased myelination in this region.

Association between experiences of deprivation and cortical structure were more mixed. While one high-quality study of previously institutionalized children demonstrated widespread reductions in cortical thickness across regions of the frontoparietal, default mode, and visual networks (McLaughlin, Sheridan, Winter, et al., 2014), another high-quality study that focused only on prefrontal cortex regions of interest found reduced cortical thickness only in the inferior frontal gyrus (Hodel et al., 2015). Studies investigating low cognitive stimulation have also been mixed in the two high-quality studies included here. One study found that low cognitive stimulation was associated with thinner cortex in the frontoparietal network across childhood and adolescence (Rosen et al., 2018), and another found that lower cognitive stimulation was associated with thicker cortex in the lateral prefrontal cortex and ventral visual stream in late adolescents (Avants et al., 2015). Differences in the age of the samples and timing of assessment of cognitive stimulation may have contributed to these inconsistent findings.

The studies investigating SES-related differences in cortical thickness also had mixed results. Two studies—one high-quality and the other low-quality—found widespread positive associations with SES and thickness in the frontoparietal and default mode networks and the visual system (Jednoróg et al., 2012; Mackey et al., 2015). One study of moderate-quality focused only on the PFC also found similar reductions in thickness (Lawson et al., 2013). Another high-quality study found overall SES related differences in mean cortical thickness, and a regional specificity analysis showed that higher SES was associated with greater cortical thickness specifically in the supramarginal gyrus, a region in the default mode network (McDermott et al., 2019). Broadly, these regions are involved in a wide range of cognitive processing including working memory, cognitive control, autobiographical memory, theory of mind, and visual processing (M. W. Cole & Schneider, 2007; Corbetta, Kincade, & Shulman, 2002; DiCarlo, Zoccolan, & Rust, 2012; Spreng & Grady, 2010). Given that SES-related differences in many of these domains are well-established (Noble, McCandliss, & Farah, 2007), these findings could represent a

neural mechanism explaining these SES-related differences in cognitive function. In contrast, two high-quality studies spanning a large age range did not find SES-related differences in thickness (Noble et al., 2015; Rosen et al., 2018). This could be because SES associations with cortical thickness vary across childhood and adolescence. Indeed, using the same sample as Noble et al., 2015, Piccolo et al. (2016) found an SES by age interaction for average cortical thickness such that lower SES was associated with a more rapid age-related decrease in cortical thinning early in development while higher SES was associated with a less steep linear decline in thickness from childhood to adolescence. These findings are consistent with the hypothesis that low SES is associated with accelerated maturation of the cortex.

Linear decreases in cortical thickness from infancy to adulthood are well-established (LeWinn et al., 2017; Vijayakumar et al., 2016; Wierenga et al., 2014), although the mechanisms by which this pattern emerges remain in question. One interpretation is that synaptic connections that are underutilized or inefficient are pruned, allowing the brain to adapt to the environment in which it develops (Huttenlocher, 1979; Petanjek et al., 2011; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986). If pruning is the primary mechanism driving cortical thinning, it is possible that ELA-related differences in cortical thickness are due to accelerated pruning. In the case of deprivation-related experiences, this may be due to a lack of experience with socially or cognitively stimulating environments (McLaughlin, Sheridan, & Nelson, 2017). Alternatively, greater pruning could reflect precocious specialization and maturation of circuits utilized more frequently by children exposed to ELA; in the absence of behavioral data associated with specific patterns of cortical thinning, caution is warranted in interpreting these patterns as either adaptive or maladaptive (Ellwood-Lowe, Sacchet, & Gotlib, 2016). Other work suggests that age-related decreases in cortical thinning may actually be due to increases in myelination across development (Natu et al., 2019, 2018; Sowell et al., 2004). Increased myelination, which is most pronounced in deeper cortical layers may increase the intensity of voxels at the gray-white matter border, therefore making the cortex appear thinner across age. If myelination is the primary mechanism by which cortical thinning happens, it is possible that increased cortical thickness in response to ELA may be due to faster development of structural connectivity between regions. Of course, these mechanisms are not mutually exclusive and future longitudinal work measuring multiple forms of ELA utilizing both T1-weighted imaging and diffusion tensor imaging is needed to disentangle the precise mechanisms by which ELA leads to thinner cortex in youths.

Estimates of heritability of cortical thickness ranges across specific regions of the cortex but have been shown to be consistently highly heritable (Blokland, De Zubicaray, McMahon, & Wright, 2012; Schmitt et al., 2008; Van Soelen et al., 2012; Winkler et al., 2010). However, despite high levels of heritability, environmental factors have also been shown to contribute to cortical thickness patterns across development in twin studies that control for genetic contributions to neural outcomes (Bootsman et al., 2015; Joshi et al., 2011; Yang et al., 2012). It is therefore clear that both the environment and genetic factors influence adversity-related differences in cortical structure. Only two studies reviewed here control for any genetic influence (Noble et al., 2015; Piccolo et al., 2016), but those studies control for genetic ancestry (a proxy for race) and not any genetic factors known to directly influence cortical thickness. One other study directly addresses the issue of heritability of cortical thickness in the discussion (Avants et al., 2015). That study demonstrated an age-dependent association between cognitive stimulation and cortical thickness such that cognitive stimulation at age 4 but not 8 is associated with differences in cortical thickness in late adolescence. However, as noted by the authors, while it is possible that there is a genetic influence on cortical thickness of parents that then influences the environment, it is unclear how this would explain differential timing of the environmental influence. It is also important to note that cortical thickness is positively associated with IQ in developmental samples, which may have implications for interpreting heritability of SES and cortical thickness (Karama et al., 2009, 2011). However, it has been argued that IQ should not be used as a covariate in analyses of neurocognitive development (Dennis et al., 2009), but many previous studies have conceptualized IQ as an outcome that is associated with cortical structure and have investigated cortical structure as a mechanism explaining SES-related differences in IQ (Hair, Hanson, Wolfe, & Pollak, 2015; Noble et al., 2015). Future studies focused on childhood adversity will be needed to disentangle the environmental and genetic contributions to cortical thickness.

Amygdala-PFC connectivity. Existing work examining ELA and task-related amygdala-PFC connectivity has produced mixed findings. Across both threat and deprivation, approximately half of the studies—three of which were high-quality and one of which was moderate-quality—observed that ELA was associated with more negative functional connectivity, indicating accelerated development (Colich et al., 2017; Gee, Gabard-Durnam, et al., 2013; Keding & Herringa, 2016; Peverill et al., 2019), while several others—two of which were moderate-quality and one of which was poor-quality—showed the opposite pattern of results such that youths exposed to ELA demonstrate more positive amygdala-PFC connectivity than nonexposed youths, indicating delayed development (Cisler, James, et al., 2013; Marusak et al., 2015; Silvers et al., 2016). Therefore, existing work has yet to provide clear evidence for an association between ELA and accelerated development of these systems. However, overall more studies showed evidence for an association between adversity and greater negative amygdala-PFC connectivity than for greater positive connectivity and these studies were overall of higher quality. Moreover, there is no clear evidence that specific types of adversity have differential influences on the development of this circuit.

One possibility is that amygdala-PFC functional connectivity is not a reliable marker of neural development (Zhang, Padmanabhan, Gross, & Menon, 2019). Unlike cortical thickness which has been studied widely across large representative samples (for review see Vijayakumar et al., 2016), research documenting amygdala-PFC connectivity as a marker of maturation is more modest (Gee, Humphreys, et al., 2013; Kujawa et al., 2016; Silvers et al., 2016; Wu et al., 2016), and to our knowledge, all of the studies that have demonstrated a developmental shift in this circuit have been cross-sectional. Recently, a large-scale cross-sectional study of 749 children, adolescents, and adults failed to replicate age-related developmental patterns in amygdala-PFC connectivity during emotion face processing (Zhang et al., 2019). As such, it is unclear whether amygdala-mPFC connectivity is a reliable marker of neural maturation. Alternatively, while all these tasks focused

on some sort of emotional processing, it is likely that heterogeneity in the specific tasks contributed to differences in the pattern of results across studies. Future longitudinal work with a range of emotional processing tasks will be needed to establish the developmental trajectory of amygdala-mPFC connectivity to determine whether it is a robust metric of development.

Associations Between ELA and Multiple Domains of Biological Aging

Given the range in operationalizing accelerated development and potential mechanisms linking ELA and accelerated biological development, it is surprising that few have attempted to reconcile across these different metrics of maturation. Only a handful of studies to our knowledge have incorporated multiple metrics of accelerated development in adolescence. J. Belsky and Shalev (2016) put forth a "two-hit" model suggesting that ELA accelerates development first through telomere erosion and second, through earlier reproduction, which can increase oxidative stress and accelerate telomere erosion. Although this model accounts for two forms of accelerated aging, it does not directly compare and contrast the effects of ELA on both metrics of accelerated development—cellular aging and pubertal timing. Sumner, Colich, Uddin, Armstrong, and McLaughlin (2019) examined how exposure to threat and deprivation-related ELA were associated with both DNAm age and pubertal timing. They found that exposure to threat, but not deprivation, was associated with both accelerated epigenetic aging and accelerated pubertal timing. There is also evidence to suggest that pubertal timing and cellular aging are highly correlated (Binder et al., 2018; Sumner et al., 2019), suggesting a potential shared mechanism contributing to the development of both domains. However, other work demonstrates variation in the rate of change across different metrics of biological aging in adults (D. W. Belsky, Caspi, et al., 2015), indicating that multiple mechanisms might underlie the ELA-accelerated development association, depending upon the metric of accelerated development and point in the life-course when aging is measured. Although increased allostatic load has been proposed as a mechanism linking ELA to accelerated pubertal timing (Danese & McEwen, 2012; McEwen, 1998), empirical evidence testing this possibility is currently lacking. Moreover, allostatic load is a multidimensional construct involving numerous biological systems, and it is unclear if accelerated weathering occurs across all systems to a similar degree (Geronimus, 1992; Geronimus, Hicken, Keene, & Bound, 2006). If allostatic load is a mechanism contributing to accelerated pubertal development, it could explain our disparate findings regarding threat and deprivation as exposure to early life trauma has been consistently associated with elevated allostatic load (Danese & McEwen, 2012; Scheuer et al., 2018; Widom, Horan, & Brzustowicz, 2015), whereas recent work indicates that even extreme exposure to deprivation association with institutional rearing is unrelated to allostatic load (Slopen et al., 2019). It is clear that greater work is needed to elucidate the mechanisms underlying accelerated development following exposure to ELA across domains, whether they are global or specific to particular dimensions of early experience, and how these mechanisms ultimately contribute to changes in reproductive function, cellular aging, and brain development. Similarly, longitudinal studies that can explore the time course of the associations of ELA with accelerated biological aging is necessary to further understand the mechanisms linking ELA and accelerated aging across multiple systems.

Implications of Accelerated Development

Accelerated aging across domains has been associated with a host of mental and physical health problems. For instance, accelerated pubertal timing is linked with a range of mental health problems including heightened levels of risk-taking behavior, delinquency, and substance abuse problems (Copeland et al., 2013; Harden & Mendle, 2012), as well as depression and anxiety disorders (Colich et al., 2020; Hamilton, Hamlat, Stange, Abramson, & Alloy, 2014; Mendle, Harden, Brooks-Gunn, & Graber, 2010; Mendle et al., 2014; Negriff & Susman, 2011; Platt, Colich, McLaughlin, Gary, & Keyes, 2017; Ullsperger & Nikolas, 2017). Accelerated pubertal timing is also associated with a range of physical health problems, including cardiovascular disease, polycystic ovarian syndrome in females, and testicular cancer in males (Day, Elks, Murray, Ong, & Perry, 2015; Golub et al., 2008; Lakshman et al., 2009; Velie, Nechuta, & Osuch, 2006). Accelerated cellular aging has also been associated with depression (Ridout, Ridout, Price, Sen, & Tyrka, 2016), anxiety (Malouff & Schutte, 2017), posttraumatic stress disorder (Li, Wang, Zhou, Huang, & Li, 2017), cardiovascular disease (Rehkopf et al., 2016), cancer (Zhu et al., 2016), and all-cause mortality (Needham, Rehkopf, et al., 2015). Finally, altered trajectories of cortical development have been linked to attention-deficit/hyperactivity disorder (McLaughlin, Sheridan, Winter, et al., 2014) and both internalizing and externalizing psychopathology (Busso, McLaughlin, Brueck, et al., 2017; Gold et al., 2016). Little research has directly examined whether accelerated development in these systems is a consequence of preexisting mental and physical disorders, or a mechanism explaining elevated risk for mental and physical health problems in youth who have experienced ELA (see J. Belsky et al., 2015; Colich et al., 2020; Mendle et al., 2014; Negriff, Saxbe, et al., 2015 for work that has explored this idea). For instance, some evidence suggests that accelerated pubertal timing explains a significant proportion of the association between threat-related ELA risk for mental health problems in adolescence (Colich et al., 2020), and that telomere shortening occurs prior to the onset of depression in an at-risk population (Gotlib et al., 2015). However, other evidence suggests that early psychosocial difficulties precede early pubertal onset (Mensah et al., 2013) and could potentially accelerate cellular aging as well (Lindqvist et al., 2015). A key issue for future research will be to determine whether early interventions targeting psychosocial mechanisms linking ELA with mental and physical health problems are capable of altering observed patterns of accelerated biological aging.

It is also important to acknowledge that although there are strong associations among accelerated development and negative mental and physical health outcomes, accelerated development is most likely an adaptation to current and presumably future environmental conditions (J. Belsky, 2019). In a highly dangerous or unpredictable environment, it may be adaptive in the short-term to reach adult-like capabilities at an earlier age, in order to either reach reproductive status earlier, or reach independence from the caregiving situation at an earlier age. This immediate goal may outweigh the longer-term consequences of mental and physical

health problems. If the environment is signaling imminent mortality, then this trade-off is one that is evolutionarily adaptive. It will be important that future work consider the adaptive significance of accelerated development in response to ELA.

Limitations and Future Directions

Several limitations of this work highlight key directions for future research. First, we examined a relatively small number of studies for some domains and within each dimension of adversity, particularly with regard to cellular aging and brain development. More research is needed to evaluate whether all forms of adversity influence cellular aging or whether these associations are stronger for experiences of threat. Similarly, due to the small number of studies published on these variables, we collapsed across measures of cellular aging, including telomere length and DNAm age. Although we ran sensitivity analyses to ensure that the effect was similar if only exploring studies examining telomere length and when using metric of cellular aging as a moderator, we could not conduct the same analyses for DNAm age due to the small number of studies published ($k = 3$). These markers reflect distinct biological processes with different molecular signatures, and we recognize that combining across these two metrics of cellular aging is most likely an oversimplification of the effects of ELA on cellular aging. These findings should be replicated when more studies have been published on the associations of ELA with both telomere length and DNAm age. We also collapsed across cellular aging metrics derived from saliva, buccal swabs, and blood. Although our moderator analysis revealed no moderation by cell type, it is likely that gene expression, DNA methylation patterns, and rates of telomere erosion differ across cell types. Once more studies have been published in this area, future work should conduct a meta-analysis for each cell type separately. Similarly, it is important to note that we did not include studies examining the effects of ELA on methylation patterns of single genes due to difficulties in understanding what typical developmental patterns of specific gene methylation would be. For a systematic review of the effects of ELA on gene-specific methylation patterns see Lang et al. (2019). Second, although we show associations among ELA, pubertal timing, cellular aging, and cortical thinning, we do not have the data to speak to the underlying mechanisms driving these associations. Although we speculate that accelerated biological development following ELA is most likely due to the effects of ELA on HPA-HPG axes interactions and allostatic load, future experimental work should investigate the underlying biological mechanisms supporting these associations.

Along these lines, we cannot rule out the effects of genetic heritability confounding our results. It is plausible that individuals who experience accelerated maturation may reproduce earlier, create a less stable family environment, and in turn put offspring at risk for higher exposure to ELA. Future studies examining the association of ELA and biological aging should consider the role of genetics in their approach. It is also important to note that our meta-analysis examines average effects of adversity on biological aging. It is likely that some children are more susceptible than others to the effects of trauma on biological aging (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2011). This may explain some heterogeneity across effect sizes, and future work should examine factors that confer risk or resilience to biological aging following ELA. Additionally, given strong links among ELA, accelerated development and psychopathology, it is impossible to confidently conclude that psychopathology is not driving the effects of ELA on accelerated biological development. Future longitudinal work using at-risk samples should address the directionality of these associations to determine with confidence the direct effect of ELA on accelerated biological aging.

Finally, although we explored multiple metrics of biological aging in this meta-analysis and systematic review, recent work highlights interesting future directions for the field to explore. Specifically, developments in neuroimaging analyses have led to algorithms that use whole-brain structural neuroimaging data (both gray matter and white matter) to accurately estimate deviations between brain maturation and chronological age, known as brain age metrics (Franke & Gaser, 2019; Franke, Ziegler, Klöppel, & Gaser, 2010). This metric has been associated with the onset of mental disorders and age of mortality (Cole et al., 2019; Cole et al., 2018), and has been validated for use in children and adolescents (Franke, Luders, May, Wilke, & Gaser, 2012), supporting its utility as a biomarker of biological aging across development. A recent study suggested that both trauma exposure and growing up in a low-SES neighborhood was associated with more advanced brain age relative to chronological age (Gur et al., 2019). Future studies should explore how this relatively novel metric of biological aging relates to established metrics of biological aging (including pubertal timing and metrics of cellular aging), and how exposure to different dimensions of ELA relates to deviations in brain age metrics across development.

Conclusions

Through meta-analysis and systematic review, we find support for the idea that ELA is associated with accelerated biological aging, as measured by pubertal timing, cellular aging, and cortical thinning in childhood and adolescence. However, these associations varied systematically as a function of adversity type. Specifically ELA characterized by threat was associated with accelerated pubertal development and accelerated cellular aging as measured by both leukocyte telomere length and DNA methylation age, but exposure to deprivation and low-SES were not, suggesting specificity in the association of certain forms of ELA with pubertal timing and cellular aging. ELA was consistently associated with accelerated cortical thinning, with threat-related ELA associated with ventromedial PFC thinning and deprivation and SES more consistently associated with thinning in the frontoparietal, default mode, and visual networks. We found inconsistent associations of ELA with amygdala-mPFC functional connectivity. These findings suggest specific associations of dimensions of ELA with multiple domains of biological aging and highlight the importance of delineating the mechanisms through which specific types of early environmental experiences influence different aspects of biological aging in childhood and adolescence and determining how these pathways ultimately contribute to health disparities.

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