DOI: 10.1111/cdep.12488

ARTICLE

Child Development Perspectives

Early origins of health and disease risk: The case for investigating adverse exposures and biological aging in utero, across childhood, and into adolescence

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Funding information
National Institute of Nursing Research, Grant/Award Number: R01 NR019610

Abstract

In this article, we suggest that aging and development are two sides of the same coin, and that developing a comprehensive understanding of health and disease risk requires examining age-related processes occurring throughout the earliest years of life. Compared to other periods in life, it is during this early period of acute vulnerability, when children's biological and regulatory systems are developing, that biological aging occurs most rapidly. We review theory and empirical research suggesting that processes of development and aging are intricately linked, and that early adversity may program biological parameters for accelerated aging and disease risk early in life, even though clinical signs of age-related disease onset may not be evident until many years later. Following from this, we make the case for widespread incorporation of biological aging constructs into child development research.

KEYWORDS
biological aging, development, early adversity

INTRODUCTION

Advanced chronological age is one of the most salient factors for increased risk of multiple diseases, therefore research on age-related health and disease historically focused on adults (Kennedy et al., 2014). Yet, recognition of the considerable heterogeneity in disease onset and progression necessitated a more accurate measure of risk than an individual's chronological age (Baker & Sprott, 1988). Advances in this arena highlighted *biological age*, rather than *chronological age*, as a more optimal predictor of age-related disease risk. In this context, biological age is conceptualized as the progressive decline in function of the body's cells, tissues, and organ networks, whereas chronological age is the measure of time since birth. Biological age can be measured at various levels, most commonly at the level of systemic physiological functioning (e.g., frailty indices, homeostatic dysregulation) and the cellular level (e.g., telomere length [TL], epigenetic age clocks, and epigenetic pace of aging; Jylhävä et al., 2017). Long-lived individuals (e.g., centenarians, super-centenarians) and their children often exhibit younger biological than chronological age (i.e., slowed biological aging); in contrast, individuals with an older biological age than chronological age (i.e., accelerated biological aging) are often diagnosed with age-related diseases at an atypically earlier chronological age (Wang et al., 2018).

Exposure to early adversity (e.g., maternal psychosocial stress, poverty, unpredictability, maltreatment, and toxic environmental factors) increases susceptibility to harmful health outcomes later in life, including premature mortality. This may occur in part due to biological aging trajectories set early in life. Critical windows of developmental plasticity occur prenatally and across childhood, wherein exposures to environmental stressors

Abbreviations: DOHaD, developmental origins of health and disease; TL, telomere length.

during key phases of development have greater impact on the future health of an individual than exposures during adulthood (Wright, 2017). Research in the field of stress and health has produced evidence that biological aging trajectories may be one such factor that is constrained by early life conditions (George et al., 2021), with little change in the rank order of biological age across adulthood (Benetos et al., 2019).

In this article, we offer a theoretical overview of biological aging as an adaptive response to early adverse environments and review evidence that exposure to adversity in utero, childhood, and adolescence shapes biological aging trajectories. We also present rationale and considerations for integrating biological aging constructs into child development research as tools to quantify the impacts of early environments and the utility of interventions.

ACCELERATED BIOLOGICAL AGING AS AN ADAPTIVE RESPONSE TO ADVERSE EARLY ENVIRONMENTS

The power of early environments to shape lifelong health trajectories (i.e., *developmental programming*) gained widespread research attention after the discovery of the influence of mothers' prenatal nutritional state on their children's later risk of cardiovascular disease (Barker, 2007). Barker's hypothesis, called the developmental origins of health and disease (DOHaD), spurred research on the importance of early development for later health outcomes and initially focused on metabolically oriented processes and outcomes (e.g., heart disease, type II diabetes). More recently, DOHaD has been applied to explain the contribution of early life exposures to more diverse outcomes, such as biological aging (Vineis et al., 2016).

Evolutionary perspectives endorsing a model of *early life sensitivity* propose that during this early period of malleability, an individual's brain and body are modified to maximize survival and reproduction in their predicted future environment (Ellis & Del Giudice, 2019). Individuals exposed to chaotic, threatening early environments experience modifications to their growth and development in such a way that they become adults maximally capable of survival and reproduction in chaotic, threatening environments. In children, modifications in response to adverse early environments often include accelerated pubertal development, earlier sexual functioning, heightened neuroendocrine stress responsivity, increased innate immune activity, and accelerated biological aging (Belsky, 2019). It seems counterintuitive to consider accelerated aging as an adaptive strategy—evolutionary theory does not support a specific biological program designed to promote aging as an adaptive trait (Kowald & Kirkwood, 2016). Rather, accelerated aging can be seen as adaptive in the sense that achieving milestones of growth and sexual maturity on an accelerated timeline in an adverse environment may increase the likelihood of reproduction before a predicted untimely death (Ellis & Del Giudice, 2019). Ultimately, as developmental programs responsible for accelerating biological aging in response to adversity play out across life, they may increase the risk of early onset age-related diseases (i.e., the programmatic theory of aging; see Gems, 2022, for a review). In this way, development and aging may be seen as deeply interconnected processes.

DEVELOPMENT AND BIOLOGICAL AGING: TWO SIDES OF THE SAME COIN?

Despite the frequency with which the term *development* is used across scientific disciplines (often without discussion of its conceptual boundaries), we lack a consensus definition as it applies to the human lifespan. Spatial boundaries (i.e., where do we draw the line around the entity that is developing?) to the definition of development have been discussed elsewhere (Maienschein, 2011; Pradeu et al., 2011); in our work, we emphasize considering the temporal boundaries of development: Does development start and stop at a certain age or stage (Gladyshev, 2021; Pradeu et al., 2011), or does it continue throughout life (Gilbert, 2011)? Similarly, disagreements about the temporal boundaries of the aging process abound, precluding a consensus definition of the term *aging* (Golubev, 2021). Here, we argue that one consequence of a lack of consensus definitions for development and aging is the flourishing of discipline-specific terminology and a lack of cross-discipline anchor concepts (Minelli, 2020). The perception that these terms represent completely distinct processes (i.e., *development* referring to early growth and maturation, and *aging* referring to gradual deterioration of function toward later life) stands in the way of broad application of interdisciplinary frameworks to understand the influence of early life exposures on lifelong health and well-being.

Our perspective in this debate aligns closely with the developmental aging theory, wherein development and aging are viewed not as separate, distinct processes, but as interconnected stages of a singular continuum through an individual's life (Dilman, 1971; Feltes et al., 2014; Gems, 2022). The developmental aging theory posits that genetic programs, experiences, and influences early in life can set the trajectory, quality, and rate of aging throughout life. This perspective underscores the idea that developmental processes, which begin in utero and continue through infancy, childhood, and adolescence, determine the foundation upon which the process of

aging unfolds. In this context, the developmental aging theory encourages a more holistic view, challenging the conventional notion of distinct processes of development and aging.

At the cellular level, evidence exists for aging as a repercussion of early developmental programs (Walker, 2022). The timing and pace of developmental processes, as well as the stability and resilience of the physiological systems developed early in life (e.g., inflammatory immune responses, glucose metabolism, and epigenetic regulation), play key roles in constraining an individual's lifelong aging trajectory (Feltes et al., 2014; Lui et al., 2010). Biological aging occurs throughout life but is generally most rapid in the early stages, particularly during embryonic development and childhood (Cowell et al., 2021; Snir et al., 2019; Ye et al., 2023). These periods are characterized by a high rate of growth and development, which is captured by biological aging measures as an increased rate of aging and an older biological age.

Traditionally, aging in children has been measured according to developmental milestones and physical growth parameters, such as pubertal timing. Work in this arena has provided support for links among adverse early environments, early puberty, and accelerated aging (Belsky & Shalev, 2016); however, such physiological measures cannot distinguish more nuanced changes to aging trajectories, especially those occurring prior to the onset of puberty. Incorporating cellular measures of biological aging within developmental research can provide more detailed assessments of aging patterns beginning in infancy and reveal consequences of these aging patterns (e.g., health and disease risk). At the cellular level, biological age is often measured using DNA collected from blood, buccal tissue, or saliva, and quantified as the length of telomeres or as epigenetic age. Telomeres are protective caps on the ends of chromosomes that shorten with each cell division, eventually leading to cellular senescence (i.e., cessation of cell division) and cell death. TL appears to be set early in life through a combination of genetics, in utero factors, and early exposures, with very little change in rank order of TL between individuals across the decades after childhood (Benetos et al., 2019). Theory and empirical evidence indicate that children's telomeres are plastic during development, receptive to the influence of early life conditions, and particularly vulnerable to environmental insults (Entringer et al., 2012; Shalev, 2012). TL shortening occurs naturally throughout life (Ye et al., 2023), but TL erodes most rapidly in the first years of life as a result of intense somatic growth (Zeichner et al., 1999) and rapid expansion of progenitor cells in the hematopoietic hierarchy (Sidorov et al., 2009; Werner et al., 2015), reflecting a sensitive period of development wherein adverse environmental exposures may be especially detrimental. Studies have shown that early life stress can lead to shorter telomeres in children (Coimbra et al., 2017), predisposing them to earlier onset health problems.

While TL has garnered much attention as a potential biomarker for aging, it is not without limitations (Sanders & Newman, 2013). For instance, a single measure of TL provides a snapshot of an individual's cellular age at a single point in time, without necessarily indicating the rate of aging or the cumulative impact of environmental stressors suffered. Also, TL features considerable inter-individual variability, with some individuals naturally having shorter telomeres without any apparent health implications (Monaghan & Haussmann, 2006). Finally, certain methodological factors, such as methods of DNA extraction and quantification, tissue types, or the use of diverse assays to measure TL (e.g., qPCR, Southern blot), can influence measured TL, complicating its interpretation across studies as a straightforward marker of biological age (Nettle et al., 2021; Wolf & Shalev, 2023; Ye et al., 2023).

Given these complexities, relying *solely* on TL to draw conclusions about the effects of early life stress on aging might be simplistic or even misleading. Researchers in this field are increasingly advocating for a multidimensional approach, incorporating other indices of aging like epigenetic age clocks and measures of homeostatic dysregulation (Vaiserman & Krasnienkov, 2021). Epigenetic age clocks assess age-related changes in DNA methylation patterns, providing insights into cellular age and the potential impact of environmental exposures. Exposure to stress prenatally and across childhood can lead to epigenetic modifications that affect cellular and molecular processes involved in aging (e.g., DNA repair, inflammation, and cellular senescence; Horvath & Raj, 2018), possibly via their impact on brain circuitry involved in emotion regulation, construction and function of stress response systems, and the responsiveness of the immune system to challenge (Chen et al., 2021; Jiang et al., 2019; Skyberg et al., 2023).

To capture an individual's epigenetic age, researchers are using epigenetic age clocks, which estimate biological age based on the accumulation of age-associated epigenetic changes. Since the creation of the first of these clocks, several generations have been introduced (for a review, see Simpson & Chandra, 2021), including some built to predict the physiological decline and increased risk of mortality inherent to older chronological ages. In studies of racially and ethnically diverse children, the clocks have yielded preliminary evidence that children exposed to disadvantages, such as low socioeconomic status, may experience faster rates of biological aging than children without such disadvantage (Raffington & Belsky, 2022). Perinatal- and pediatric-specific clocks are also beginning to emerge (Bohlin et al., 2016; Fang et al., 2023; McEwen et al., 2020), though evidence suggests adult-trained epigenetic age clocks have utility with pediatric samples (Bozack et al., 2023; Etzel et al., 2022). As with the early setting of TL, evidence suggests that

the rate of epigenetic aging (i.e., the "ticking" of the epigenetic age clock) across life may be set by early life conditions (Vaiserman, 2018).

Mechanistically linking biological aging metrics, such as TL and epigenetic age, to development and aging is an open issue for the field. While TL has been linked with processes of development and aging via cellular senescence and regulation of the genome (for a review, see Etzel & Shalev, 2021; López-Otín et al., 2013), mechanistic links between specific methylation sites included in many epigenetic age clocks and development and aging are for the most part unknown.

Setting of TL and epigenetic age are mechanisms hypothesized to transmit early environmental stress into later disease risk via setting of aging trajectories (e.g., starting rank order of biological age and the rate at which biological aging will occur across life; see Figure 1). Measuring these factors in childhood offers a unique opportunity to provide critical information about the ways early experiences may set parameters for deteriorating health despite the fact that clinical signs of disease may not be evident until adulthood (Coimbra et al., 2017). Although gerontological research is beginning to acknowledge the need to measure aging early in life, prior to onset of disease, much of this work is still relegated to adulthood. Such work is critical and should begin already in childhood. Including biological aging measures in child development research, particularly in longitudinal studies, can provide important insights into mechanisms linking early life stress to accelerated aging and moderators of this association, as well as highlight effective interventions and preventive measures for future age-related diseases.

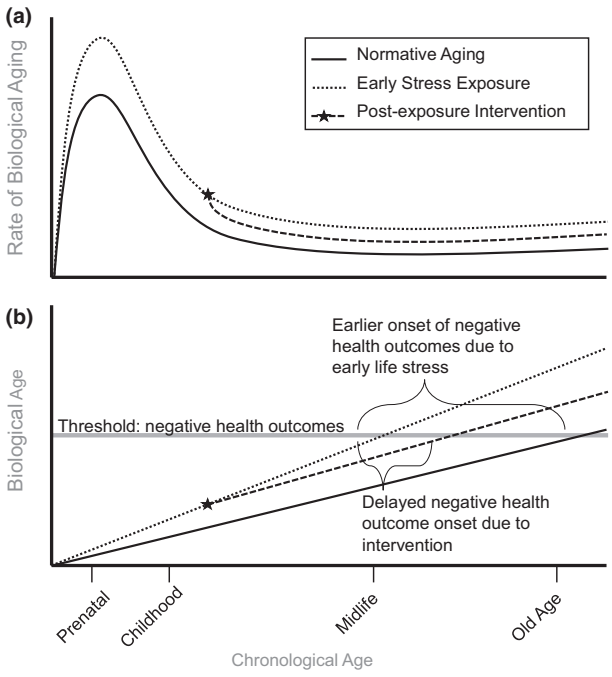

FIGURE 1 Biological aging trajectories. (a) Normative rate of biological aging across life, and (b) normative biological aging trajectory across life. Both the rate and the trajectory of biological aging are hypothesized to be altered due to early stress exposure and postexposure interventions.

ENVIRONMENTAL STRESS SHAPES BIOLOGICAL AGING TRAJECTORIES IN UTERO, CHILDHOOD, AND ADOLESCENCE

Exposure to stress in utero

Prenatally, features of the external environment are transmitted to the fetus through the maternal–fetal interface. Stressors, such as maternal health behaviors, adverse exposures, and socioeconomic factors, can be passed to the fetus via substances crossing the placenta (e.g., increased cortisol) or through changes in maternal physiology that affect the fetal environment (e.g., constricted blood flow, lower blood oxygen). Such stress exposures have been linked to accelerated biological aging in newborns of Black and White mothers, measured as shortened TL (Entringer et al., 2013). Maternal prenatal anxiety, depression, and exposure to intimate partner violence have also been associated with shortened TL in newborns (see Ridout et al., 2018, for a review), suggesting a programming effect of diverse intrauterine stress exposures on newborns' biological aging systems. Reinforcing the idea that the intrauterine environment plays a key role in biological aging trajectories, in a longitudinal prospective study measuring TL in a cohort of primarily White adults, perinatal stressors predicted shorter midlife TL despite controlling for many potential lifespan factors (e.g., lifetime stress, socioeconomic factors, and adult health behaviors; Shalev et al., 2014). Similarly, in a study of older White adults exposed in utero to the socioeconomic strain of the Great Depression, lower family wages were associated with accelerated epigenetic ages in later life (Schmitz & Duque, 2022). Longitudinal work with more diverse cohorts examining TL changes postnatally and throughout childhood is needed to clarify what role such associations play across development.

Exposure to stress in early childhood and adolescence

Exposure to environmental stress during childhood and through adolescence has also been shown to affect biological aging. Across childhood, exposure to maternal depression/anxiety and stress, low family socioeconomic status, and parental conflict have all been linked to accelerated aging in children (see Ridout et al., 2018, for a review). Longitudinal examinations of TL in children are sparse, particularly for the earliest years; however, in one study on the amount of time Romanian children spent in

institutional care, children with greater exposure to institutional care had significantly shorter TL at both baseline (1–2 years old) and follow-up (4–5 years old) than did those with less exposure (Drury et al., 2012). Similarly, in another study, 5- to 10-year-old White children exposed to violence had faster rates of telomere shortening than did peers who were not exposed to violence (Shalev et al., 2013).

Though limited, work has also examined accelerated epigenetic aging due to stress exposures in childhood. Exposure to threat, violence, and other types of adversity during childhood have all been associated with accelerated epigenetic aging (Colich et al., 2020; Palma-Gudiel et al., 2020). For instance, greater socioeconomic disadvantage seems to confer a faster pace of epigenetic aging among Latinx, White, and mixed-ethnicity 8- to 18-year-olds (Raffington et al., 2021).

LOOKING AHEAD

Research on the impact of adverse early environments on biological aging in children will benefit immensely from the use of prospective longitudinal designs and the application of frameworks, theories, and knowledge from the field of child development. Although research suggests that the impact of accelerated aging trajectories set in childhood can profoundly affect future health and disease risk, expected effect sizes during childhood are often small, necessitating careful consideration of several aspects of study design, including selection of theories (e.g., differential susceptibility, cumulative stress hypothesis, adaptive calibration model; see Ellis & Del Giudice, 2019, for a review of pertinent theories) and potential moderators.

Potential moderators of the relation between early life stressors and biological aging are diverse and may compound across early development. In work on accelerated biological aging early in life, researchers have identified several key factors that may increase risk of or confer protection against accelerated aging (e.g., see Table 1). But we lack a complete understanding of the impact of each moderator, as well as the mechanisms and intersectionality of multiple moderators. This research, which is in its infancy, is ripe with new and exciting opportunities for exploration.

TABLE 1 Factors that may moderate the impact of early adversity on accelerated aging.

Time frame	Moderators to consider
Prenatal	• Maternal exposure to trauma (Epel, 2020; Nwanaji-Enwerem et al., 2021) • Type and timing of exposure (Carroll et al., 2020) • Fetal sex-dependent effects (Bosquet Enlow et al., 2018) • Maternal racial/ethnic identity and experiences of discrimination (Drury et al., 2015)
Childhood	• Early parenting (Nelson et al., 2018) • Type and timing of exposure (Dunn et al., 2019; Marini et al., 2020) • Duration and intensity of exposure (Berens et al., 2017) • Number of exposures (Felitti et al., 1998; Mayer et al., 2019; Wallander et al., 2021) • Developmental stage during exposure (Marini et al., 2020) • Dimension of exposure (e.g., threat vs. deprivation; Colich et al., 2020; McLaughlin et al., 2021)
Adolescence	• Parenting (Brody et al., 2015) • Peer bullying (Zarate-Garza et al., 2017) • Experiences of discrimination (Argabright et al., 2022)

Note: These are moderators that have been researched at specific developmental stages, though future consideration of the impact of moderators should span all developmental time frames.

CONCLUSION

Building understanding of how aging trajectories are set early in life and when they are most malleable is a topic of interest to researchers spanning developmental and aging specialties. To facilitate a robust understanding of the mechanisms and consequences of early exposure to stress on lifelong health, existing and new measures of biological aging should be included in developmental research. The prenatal period through childhood reflects a time of heightened vulnerability to environmental inputs. This critical window coincides with the period when biological aging appears to occur most rapidly and when parameters restricting future aging trajectories are likely set. Understanding biological aging across the earliest stages of life can provide insights into the impact of social determinants of health, such as poverty and discrimination, on aging and disease processes. Measuring biological aging in children is feasible (see Fang et al., 2023; Horvath & Raj, 2018; Ryan, 2021; Wolf et al., 2023, for recommendations on incorporating biological aging measures into research) and may allow researchers to quantify the impact of early intervention programs aimed at reducing suboptimal health outcomes, particularly for vulnerable groups, such as those with early exposure to adversity and systematically disenfranchised or marginalized populations. Overall, the study of biological aging early in life has important implications for research and clinical practice, and offers valuable opportunities to improve health and promote healthy aging for individuals and populations across the lifespan.

FUNDING INFORMATION

This work was supported by a grant from the National Institutes of Health, National Institute of Nursing Research R01 NR019610 (P.G.P. and I.S.). The content is solely the responsibility of the authors and does not

necessarily represent the official views of the National Institutes of Health.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

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How to cite this article: Etzel, L., Garrett-Petters, P., & Shalev, I. (2023). Early origins of health and disease risk: The case for investigating adverse exposures and biological aging in utero, across childhood, and into adolescence. *Child Development Perspectives*, *00*, 1–8. https://doi.org/10.1111/cdep.12488