The Relationship Between Childhood Adversity and Aging:

Implications for Human Healthspans

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Summary

Adverse childhood experiences are a prominent issue that significantly shorten individuals' healthspans through biological alterations. On a cellular level, early life adversity and the subsequent stress can cause DNA methylation in genes that are essential for maintaining proper function in adulthood. They also lead to accelerated erosion of telomeres, causing earlier cellular senescence. From a clinical perspective, key indicators of morbidity, specifically chronic disease and frailty, are primary and secondary byproducts of childhood adversity. Childhood adversity may directly impact the biological systems that prevent the onset of morbidity while simultaneously contributing to the development of risk factors that result in morbidity. Considering the clear association between adverse childhood experiences and shorter healthspans, further research is needed to identify possible methods of building resilience to counteract the poor health outcomes.

INTRODUCTION

In an aging world, childhood adversity is a significant problem as it shortens healthspans by disrupting healthful cellular functioning and accelerating the onset of morbidity. The depth to which childhood adversity affects health and development across the lifespan was demonstrated by Felitti *et al.* in 1998. In addition to categorizing childhood adversity into seven distinct categories referred to as adverse childhood experiences (ACEs), their groundbreaking study identified two critical themes. First, childhood adversity was positively associated with outcomes in later life, including risk behaviors and poor health. Second, the greater the number of ACEs an individual had experienced, the greater their risk for negative consequences ("Adverse Childhood Experiences," n.d.). This study was the first of many to show that childhood adversity is not just a societal challenge, but a complex and multidisciplinary issue.

A simple search on the internet will reveal that the media latched on to the findings of the original ACE study. Websites advocating ACE quizzes or asking individuals "What's your number story?" are abounding. More importantly, however, the research done by Felitti *et al.* was the catalyst for a multiplicity of research surrounding the relationship between adversity in childhood and outcomes in adulthood. Since 1998, the scientific community has expanded the definition and categorization of adverse childhood experiences to include events ranging from racism to war-time separation and everything in between (Haapanen *et al.*, 2018; "Adverse Childhood Experiences," n.d.). The importance of inter-individual variation of experience and response has also been emphasized. Nevertheless, the connection between adversity in childhood and outcomes in later life still holds true.

The topic of early life adversity and later life outcomes is especially salient today for two reasons: 1) the world is aging; 2) a significant number of individuals have been exposed to adversity during their childhood. As an example, in 2020 16% of the United States population was over the age of 65 (Caplan, 2023). A 2018 report revealed that 45% of the United States population has experienced at least one ACE, with some samples having a percentage greater than 80 (ElHage, 2018; "Adverse Childhood Experiences," n.d.). The logical conclusion follows that longer lives allow for more individuals to be subject to the impact of childhood adversity for longer periods of time. Simply put, childhood adversity contributes to shorter healthspans, the period of life in which an individual is free from age-related disease and disability (Olshansky, 2018). Thus, childhood adversity fits quite naturally into the discussion of the compression of morbidity and longer healthspans. This paper strives to present literature that connects childhood adversity with the modern components of healthspan. Namely, it will examine cellular changes believed to be determinants of human healthspans (i.e., DNA methylation and telomere length) and clinical determinants of morbidity (i.e., disease and frailty). It will conclude with discussing possibilities for extending healthspans through the formation of resilience in the face of childhood adversity.

BACKGROUND

Defining childhood adversity

Initially, seven adverse childhood experiences were identified: psychological abuse, physical abuse, sexual abuse, witnessing violence towards mother, living with an individual abusing substances, living with an individual with a mental illness, living with an individual who had been incarcerated (Felitti *et al.*, 1998). Two and half decades of research have expanded upon the original definition. Figure 1 provides an example model of this expansion where the seven initial ACEs are joined by divorce of parents, physical neglect, and emotional neglect. Broadening the definition of childhood adversity has revealed that more individuals experience adverse events in childhood than first recognized, especially across diverse ethnic and socio-economic groups (Cronholm *et al.*, 2015). While this permits more effective intervention, providing a general definition becomes virtually impossible. The vastness of ACEs has resulted in literature that targets each one individually or in pairs. Few, however, experience ACEs in this isolated manner. Rather, the prevailing trend is for an individual to experience multiple ACEs simultaneously or across their childhood (Bellis *et al.*, 2019).

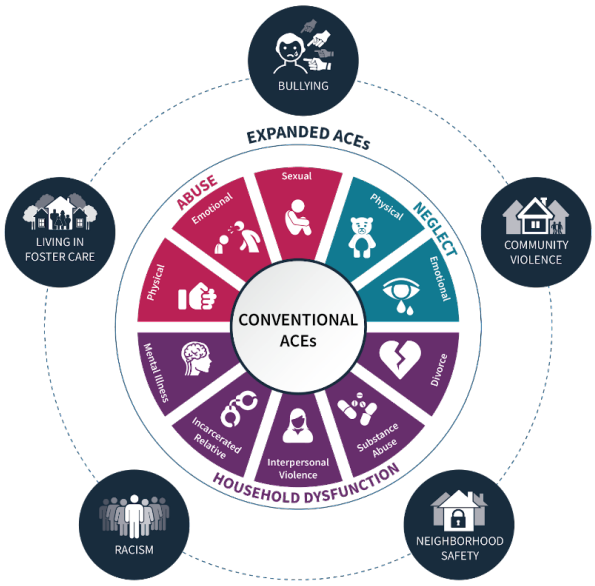

Figure 1. A model of ACE expansion. (Source: Cronholm *et al.*, 2015)

Despite these limitations, the underlying concept of all childhood adversity is the possibility of triggering a stress response in children, often repeatedly or for an extended period. The exhaustive use of this natural response alters the normative development of a child, leading to the outcomes observed in later life (Sacks and Murphey, 2018). For this reason, the term Early Life Stress (ELS) is also used in conjunction with adversity in childhood. Studies have focused on both ACEs and ELS independently and still yielded similar results. To clarify what childhood adversity means, this paper uses terms like

adverse experiences or events in childhood, adverse childhood experiences (ACEs), et cetera to refer to any event that may be a significant source of stress for a child (0 to 17 years of age). When referring to studies, the specific definitions will be addressed.

Life course perspectives

Life course approaches are used across disciplines to guide research on human health, development, and aging. More recent decades have extended this approach to include life course epidemiology, which suggests that "etiology extends across the lifespan" (Mian *et al.*, 2022). The implication is that what occurs in later adulthood is a byproduct of earlier life experience. Thus, under this framework, health in later life is intrinsically connected to influences from across the life course (dos Santos Gomes *et al.*, 2018). Life course epidemiology is specifically concerned with the long-term health outcomes resulting from experiences that occurred in early childhood and adolescence (Kuh *et al.*, 2003), making it a logical approach to use in studying the relationship between childhood adversity and healthspans.

The fundamentals of a life course epidemiology approach include the following: timing of experiences, cumulative exposure, changes to biological systems, detection of damaging trajectories and prevention of subsequent decline, individual differences, and resilience (Ben-sholmo *et al.*, 2016; dos santos Gomes *et al.*, 2018; Kuh *et al.*, 2003). While an in-depth knowledge of life course approach fundamentals is not necessary in the discussion of childhood adversity, a general understanding is critical. Timing of experiences refers to the lifespan from conception until death, but a special focus has been placed on the childhood and adolescent years (Kuh *et al.*, 2003). Cumulative exposure, also known as accumulative risk, refers to the complex ways that adverse experiences may build on each other and contribute to other risk factors (see Figure 2). Changes to biological systems implies the non-normative changes at both cellular and systemic levels. Detection, prevention, and resilience can be examined holistically as ways to counteract the correlation between childhood adversity and later health.

Figure 2. Model of accumulation of risk demonstrating the dose-graded relationship between ACEs and negative health outcomes and the probable development of risk factors that contribute to poor health in later life. (Source: "Adverse Childhood Experience Study (ACES)," n.d.)

Cellular Changes

Modern scientific advancements have produced multiple theories regarding the biology of finitude, that is why humans age. Applied to the healthspan, these ideas may also explain why the end of life is filled with a period of morbidity. The basic concept of aging theories is that cellular changes that occur throughout life, either by natural programming or damage from life experiences, leave an individual more susceptible to mortality and morbidity (Miller, 2023). In the case of ACEs, the evidence suggests that these experiences lead to DNA methylation and increase telomere attrition, degrading an individual's health.

DNA methylation

Every cell in the human body contains a complete copy of DNA, known as the genome. The closely related epigenome controls which genes within a cell are actively expressed, an essential process for the differentiation of cells within organisms (Moffitt and Klause-Grawe, 2013). The epigenome changes over the course of one's life through epigenetic processes that occur largely as a function of an individual's environment. This notable observation links epigenetics with aging and may provide an explanation for the many chronic diseases that occur in later life (Bjornsson *et al.*, 2008). The most common epigenetic mechanism is DNA methylation in which methyl groups bind to DNA base, directly preventing transcription of a gene. Methylation may also function by creating tightly wound chromatin structure, restricting the amount of DNA available for transcription.

Ethical regulations obviously prevent experimental human studies on the epigenetic outcomes of early life adversity. However, using rodent models, ELS has been associated with DNA methylation. In one study, researchers created an adverse environment through maternal maltreatment while rodents were in the juvenile stage. The results showed significant DNA methylation in the brain, specifically in the area responsible for producing brain-derived neurotrophic factor (BDNF), as shown in Figure 3 (Blaze *et a.l*, 2015). BDNF is essential for maintaining neural plasticity in life, therefore decreased levels correlate with cognitive decline (Blaze *et al.*, 2015; Suri *et al.*, 2013). This study demonstrates the long-lasting impact that ELS can have by way of epigenetics. The few a priori studies conducted with humans have shown some DNA methylation, but it is difficult to draw a direct line back to childhood adversity as has been done in rodent models due to the many other confounding factors (Moffit and Klaus-Grawe, 2013). Still, some researchers believe that methylation caused by ELS in humans may mimic the methylation of immune and inflammation genes observed in PTSD patients, while others suggest that methylation may be a secondary result of more primary consequences (Moffitt and Kraus-Grawe, 2013; Smith *et al.*, 2011; Uddin *et al.*, 2010). While knowledge associating DNA methylation and childhood adversity is still in the preliminary stages, the general ideology is that such experiences have the potential of epigenetic consequences that may inhibit a healthy aging process.

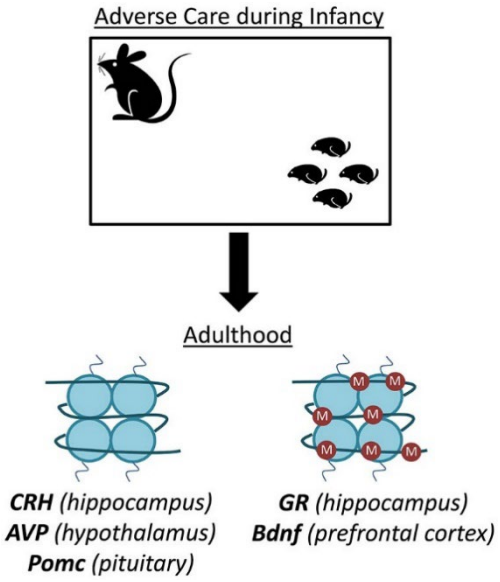

Figure 3. Adverse care during infancy causes DNA methylation in rats' brains. (Source: Blaze *et al.*, 2015)

Telomere length

The biological make-up of humans makes aging inevitable. Evidence for this is telomere erosion. Telomeres are caps at the end of each chromosome that shorten with each DNA replication, making mitosis a finite process. Telomere attrition rates determine when cells reach the Hayflick limit, the term used to describe how many times a cell may divide, and enter a state of senescence (Miller, 2023). This state brings many disease pathologies. Hence, shorter telomeres that erode more rapidly, especially those in immune cells, are associated with increases in age-related cancer, cardiovascular disease, and chronic disease in general (Botha *et al.*, 2012). As such, telomere shortening has been identified as a risk factor for shorter healthspans. Table 1 provides a concrete example of this relationship as it shows that many Alzheimer's patients have been observed to have shorter telomeres in their white blood cells and buccal cells (Thomas *et al.*, 2008).

Table 1. Average Absolute Telomere Length (Source: Thomas *et al.*, 2008)

	Cohort			
Cell Type	Control (Young)	Control (Old)	AD (Young)	AD (Old)
White Blood	144.70	110.30	72.04	79.36
Buccal	41.98	40.57	34.41	20.51

Infants, children, and adolescents who experience chronic stress by way of childhood adversity have been shown to experience telomere erosion at an increased rate. Thus, through biological processes, childhood adversity leads to shortened healthspans via telomere shortening (Epel, 2009). Even before disease pathologies are visible, this shortening can be observed. Multiple studies have correlated decreased telomere length with self-reported childhood adversity in adults (Kananen *et al.*, 2010; Kiecolt-Glaser *et al.*, 2011; O'Donovan *et al.*, 2011; Tyrka *et al.*, 2010). Others have observed telomere shortening occurring even earlier, as institutionalized children have shorter telomeres than their peers in middle childhood (Drury *et al.*, 2012). Perhaps the most notable, however, is the E-Risk study where children exposed to adversity had shorter telomeres at age five and again at age ten (Shalev *et al.*, 2013). This demonstrated that telomere shortening is a downward spiral and is difficult to reverse. Like DNA methylation, the data on telomere shortening is still young and not conclusive. Yet, generally, progressing research is displaying an association between poor health outcomes and shorter telomeres alongside an association between ACEs and shorter telomeres.

Effects on Morbidity

Unlike cellular changes, the data surrounding early life adversity and morbidity is vast and has definitive conclusions. Using life course epidemiology, ACEs have repeatedly been attributed to causing poor health outcomes across the lifespan due to internal biological changes. These outcomes include health risk behaviors, chronic disease, depression, disability, poor physical performance, frailty, and even mortality, all of which have been associated with exposure to violence in childhood (Airagnes *et al.*, 2016; Bethell *et al.*, 2014; dos Santos Gomes *et al.*, 2018; Guedes, 2016; Matsuyama *et al.*, 2016; Santaularia *et al.*, 2014). Among these outcomes, chronic disease and frailty are especially prevalent as morbidity may be defined "as that period from the onset of the first irreversible chronic disease or aging marker until death" (Fries, 1980).

Chronic disease

The positive correlation between chronic disease and early life adversity has repeatedly been replicated across differing variables. The data in Table 2 effectively demonstrate this as across all adversity types presented the odds ratios of physical conditions in relation to child abuse were higher among the physical condition cohort. These physical conditions were comprised of prominent age-related disease, encompassing arthritis and cancer (Afifi *et al.*, 2016).

Table 2. Odds ratios of physical conditions in relation to abuse in childhood (Source: Afifi et al., 2016)

	Cohort	
Type of Abuse	No Physical Condition	Physical Condition
Any Child Abuse	27.5%	36.0%
Physical Abuse	22.6%	29.0%
Sexual Abuse	7.0%	12.8%
Expose to Intimate Partner Violence	6.1%	9.4%

Cardiovascular disease and hypertension, the leading causes of disability globally (Joynt *et al.*, 2003), have also been associated with childhood adversity in the form of physical abuse and family violence (Parrish *et al.*, 2013). What is notable about the aforementioned relationships is that they maintained significance even when controlled for the confounding variable of socio-economic status and were discovered in two contrasting countries (Canada and Brazil), suggesting that the association between health and ACEs spans cultures and life circumstances. Possible explanations for this more direct association identify early life stress as a source of negative change in immune and inflammatory functions, metabolic health, and the microbiome. Changes in these biological systems can contribute to the onset of chronic disease, even in the absence of other risk factors (Berens *et al.*, 2017).

Still, it must be recognized that the association between ACEs and health is not always so clear; rather, there is a multiplicity of complex relations that change with the individuality of each person and each circumstance. Reactions to the stress caused by adversity can uniquely affect the psychological development of individuals, resulting in poor health choices. Engagement in risk factors such as smoking or sedentary lifestyles that lead to obesity have been associated with childhood adversity and contribute to developing a chronic disease (Bellis *et al.*, 2019). Chronic disease can therefore be observed as a primary and secondary reaction to early life adversity.

Frailty

If the trajectory of healthspan declination is viewed as morbidity, disability, and mortality (Fries, 1980), then frailty can be viewed at the progression from morbidity to disability. Identified by the World Health Organization as a symptom of unsuccessful aging, it most commonly occurs with the presence of comorbidity (Chan and Lin, 2015; Fried *et al.*, 2001). While multiple measures of frailty exist, the standard definition found

across multiple studies is when at least three of the following criteria are met: "unintentional weight loss (10 pounds in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity" (Fried *et al.*, 2001). An aging population has led to greater prevalence of frailty producing a greater focus on this age-related condition. Table 3 shows the general positive relationship between frailty and childhood adversity. Pulled from a diverse sample spanning multiple countries, frail adults reported experiencing adversity at a rate nearly double those in the non-frail group (17.8% relative to 9.7%) (dos Santos Gomes *et al.*, 2018).

Table 3. Frailty and Childhood Abuse (Source: dos Santos Gomes *et al.*, 2018)

	Cohort	
Childhood Physical Abuse	Non-frail: N (% of cohort)	Frail: N (% of cohort)
No	1668 (90.3%)	120 (82.2%)
Yes	179 (7.9%)	26 (17.8%)

Figure 4 adds to this discussion by showing more specific. It can be concluded that multiple types of adversity contribute to frailty and even a single ACE may result in greater frailty in later life. It is important to acknowledge, however, the dose-graded relationship between adversity and frailty as ACEs rarely occur in isolation. The results in Figure 5 maintained statistical, though slightly weaker, significance even in the presence of controls for smoking, education, socioeconomic status, and lifestyle (Mian *et al.*, 2022). This suggests that frailty, like chronic disease, may be a direct and indirect result of early life adversity.

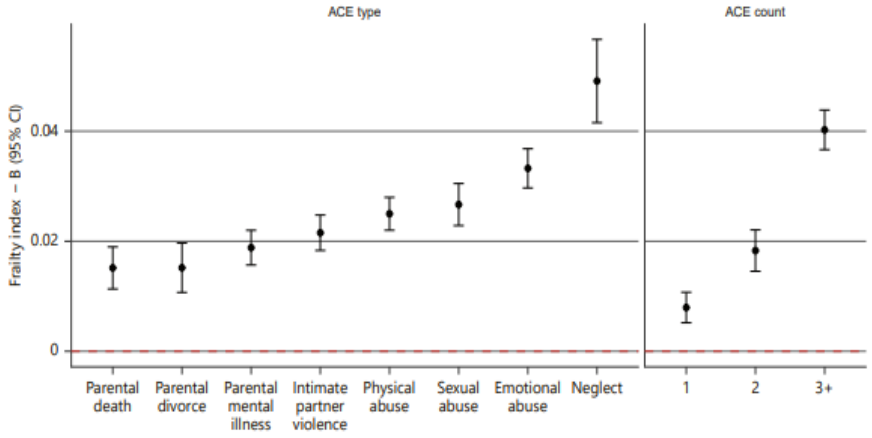

Figure 4. Adverse experiences in childhood are associated with greater frailty in older adults. (Source: Mian *et al.*, 2018)

A Positive Outlook

Resilience has been defined as "a dynamic process encompassing positive adaptation within the context of significant adversity" (Luthar *et al.*, 2000). This is critical in the discussion of childhood adversity as resilience could be an antidote to the ill-effects of adversity, thus reducing negative health outcomes and allowing for a longer healthspans. No definitive path for developing resilience in the face of ACEs has yet been identified. However, not all children subjected to maltreatment experience the negative consequences (Cicchetti and Toth, 2004), suggesting that resilience is attainable. Perhaps the most supported pathway to resilience involves accruing positive relationships during and following adversity exposure. In rodent models, the consequences of maternal neglect were counteracted when interventions of quality maternal care took place (Asok *et al.*, 2014). This idea is supported by the Helinski cohort, who were separated from their parents in childhood due to war. As expected, these individuals experienced poor health in late adulthood. However, the researchers hypothesized that these consequences could have been mediated if extended familial relationships, not available due to conflict, had curbed the impact of the stress felt (Haapanen *et al.*, 2018). Rodent models have also demonstrated the possibility of using exercise as a way to counteract the effects of childhood adversity (Botha *et al.*, 2012). The complete eradication of ACEs is both idealistic and unrealistic. However, preliminary research demonstrates the possibility of identifying ways in which individuals may develop resilience to mitigate the impact of childhood adversity.

Conclusions

As an aging world moves the scientific focus to health in later life, it is crucial that the impact of experiences in early life are not discounted. Evidence has clearly suggested that adversity in childhood has far-reaching implications, both in biological and clinical contexts. The prevalence of ACEs suggests that limiting their impact could have a positive influence on the healthspan of the general population. By maintaining a life course epidemiological perspective, further research may identify the exact mechanisms by which childhood adversity functions to deteriorate human health, opening the door to identify pathways of resilience. The "number story" of an individual may in fact determine their health in later life currently, but this need not remain so in the future.

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