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REVIEW

Epigenetic age acceleration and psychosocial stressors in early childhood

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ABSTRACT

The impact of psychosocial stress on mental and physical health is well-documented. Adverse experiences that occur early in life are particularly impactful on later life health. Epigenetic modifications, such as DNA methylation, have been proposed as a possible mechanism to mediate the impact of childhood events on adult health outcomes. The development of epigenetic clocks to estimate epigenetic age has revealed many examples of epigenetic age acceleration (and deceleration) in association with exposure to psychosocial stressors. Furthermore, altered epigenetic aging has been associated with downstream health outcomes. Here studies are discussed that have reported associations of epigenetic aging with early-life exposure to psychosocial stressors, such as childhood abuse and neglect, and with later-life health outcomes, including increased mortality, morbidity, and disease risk. Protective factors that may mitigate the effect of psychosocial stress on epigenetic aging, and possibly enable reversal of epigenetic aging, are also discussed.

PLAIN LANGUAGE SUMMARY

Too much stress can lead to poor health. Stressful events that occur in childhood are very important. Childhood stress can even affect health in adulthood. Scientists are trying to understand how stress affects health. One possibility is chemical changes to the genome, or DNA, that change how information from the genome is used. These chemical changes are called DNA methylation and may preserve information about a stressful event. These changes could affect health long after the stressful event. Childhood abuse and neglect are related to changes in DNA methylation. These changes are then related to poor health as an adult, such as sickness and even early death. Exercise and medication may prevent some of these changes in DNA methylation and lead to improved health.

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1. Introduction

Life can wear us out. Throughout our lives, we age chronologically, physically, biologically, even molecularly. More specifically, our chronological age increases, our bodies accumulate physical damage, our risk of adverse health outcomes increases, and molecular tags on our chromosomes deteriorate. The aging process can be further accelerated by stressful conditions, such as poverty, poor mental health, and other psychosocial stressors [1–3]. Geronimus proposed the "weathering hypothesis" to explain racial health inequalities caused by the cumulative effect of psychosocial stressors related to socioeconomic adversity and discrimination that literally wear a person out throughout their life [4,5]. Adverse events that occur in early life, including prenatal exposures, can affect a child's psychological, emotional, and physical development and even influence adult mental and physical health [6,7].

Although the impact of early childhood on later life health is well documented, the underlying mechanism is not well understood. Epigenetic modifications have emerged as a possible mechanism to biologically embed (i.e., to encode, preserve, and transmit) information from early life events throughout the life course [8,9]. Epigenetic modifications can also be used to estimate the biological age of an individual. Epigenetic clocks were first developed to measure epigenetic age based on a subset of sites that are associated with chronological age [10]. Differences between epigenetic and chronological age, termed epigenetic age acceleration (or deceleration), reflect increased (or decreased) biological aging relative to chronological age. The original epigenetic clocks estimated the biological age of cells, but more recent clocks have been developed to estimate mortality and the pace of aging and may capture the impact of environmental stressors that are not reflected in chronological age. Thus, epigenetic variation, as well as epigenetic age acceleration and deceleration, can be tested as mechanisms that capture and mediate the impact of early childhood events on later life health and wellbeing (Figure 1).

The Developmental Origins of Health and Disease (DOHaD) hypothesis posits that events occurring during sensitive windows of development, such as early childhood and in utero, are highly impactful on adult health [11,12]. The rationale is that sensitivity to the early environment can be adaptive and allow selection of an optimal phenotype for later life, assuming the early environment is representative of the later environment. However, if the early environment is unusually limiting or adverse or otherwise unrepresentative, the selected

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Article highlights

- Exposures to childhood maltreatment (e.g., sexual and physical abuse and neglect), as well as low SES and SES-related factors such as low levels of education, are associated with EAA.
- Prenatal and childhood exposures to maternal mental health disorders, such as anxiety and depression, are associated with both EAA and EAD. Personally experienced mental health disorders are more consistently associated with EAA only.
- In terms of health outcomes, EAA is strongly associated with morbidity and all-cause mortality and is less strongly associated with cognitive dysfunction and specific diseases, such as cancer, cardiovascular disease, and diabetes.
- Lifestyle factors (meditation, physical activity, exposure to green space, higher levels of education, and supportive family environments) and medication (SSRI treatment of depression) are associated with slower epigenetic aging and may be protective against EAA.
- Many epigenetic clocks have been developed that estimate age, disease risk, and mortality, and are specific for different tissues and stages of development. When using different epigenetic clocks, different associations emerge with psychosocial stressors and health outcomes, which is not surprising given that epigenetic clocks were trained on different datasets to model different outcomes.

phenotype may ultimately prove to be maladaptive and result in poor health or increased disease risk in adulthood. Ideally, a match between the early and late environments would support the fitness, or adaptiveness, of the selected phenotype and encourage optimal adult health.

1.1. DNA methylation and epigenetic clocks

DNA methylation (DNAm) is one of the most studied types of epigenetic variation and typically occurs as the attachment of a methyl group to a cytosine nucleotide followed by a guanosine, i.e., a CpG site. There are almost 30 million CpG sites in the human genome, of which 70–80% are methylated [13,14]. Approximately 70% of promoters contain a CpG island (a region with a high frequency of CpG sites) [15], demonstrating the widespread influence of CpG methylation on gene expression and resultant phenotypes. The most common method of assaying CpG methylation is the Infinium MethylationEPIC array, which interrogates 850K sites, and the newer EPIC v2.0 array that interrogates 930K sites, thus representing about 3% of CpG sites in the human genome. Methods that combine enrichment of methylated regions of the genome with DNA sequencing can achieve over 90% coverage of the methylome and are growing in popularity as costs become comparable to methylation arrays [16].

In order to leverage the power of distantly located but mechanistically related CpG sites, epigenetic clocks were developed that combine sites associated with a phenotype of interest, such as age or mortality. Over the past 10 years, a veritable smorgasbord of epigenetic clocks have been developed that estimate age, disease risk, and mortality [10,17,18], and are specific for different tissues (blood, skin, buccal) [19–21] and stages of development (gestational, childhood, adolescence, adulthood) [10,21–23] (Table 1). Specifically, the 1st generation Horvath [19] and Hannum [24] clocks provide an estimate of epigenetic age and other 1st generation clocks are tissue- or age-specific, such as the PedBE clock developed for pediatric buccal epithelial cells [21]. The 2nd generation clocks include GrimAge [18] that estimates mortality and PhenoAge [25] that incorporates clinical measures with DNAm to estimate phenotypic aging. The 3rd generation DunedinPACE [26] measures the pace of aging and 4th generation clocks use Mendelian randomization to identify sites that maybe causally linked to aging and age-related diseases [27].

Epigenetic age acceleration (EAA) and epigenetic age deceleration (EAD) have been associated with both adverse childhood events such as prenatal maternal anxiety and stress [28], maternal trauma including sexual trauma [29], low socioeconomic status (SES) [30] and low birthweight [31] as well as later life outcomes such as earlier onset of puberty [32], increased risk of chronic disease [33], low-grade inflammation or inflammaging [34], and increased mortality [35] (both steps in Figure 1. However, it's not clear if EAA/EAD, and DNAm

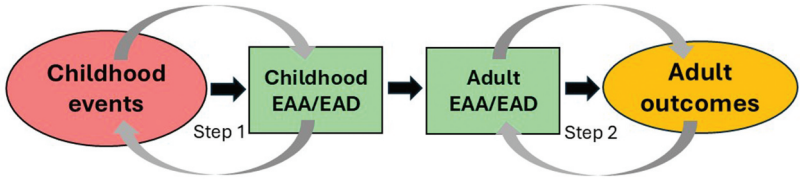

Figure 1. Model to test the role of epigenetic variation, and epigenetic age acceleration (EAA) or epigenetic age deceleration (EAD), as a mediating mechanism of the impact of childhood events on adult outcomes. Black arrows indicate a linear relationship between childhood events, childhood epigenetics, adult epigenetics, and adult health outcomes. Gray arrows indicate the possibility that variables may feedback on each other in a cyclical manner, e.g., childhood poverty may create epigenetic modifications that increase the risk factors for childhood poverty (step 1) and similarly epigenetic modifications may increase the risk of adult health outcomes that feedback and further influence epigenetic modifications (step 2). Childhood events are particularly impactful on the epigenome and adult outcomes, although psychosocial stressors occur throughout the life course and continue to influence the epigenome and health outcomes.

Table 1. Four generations of epigenetic clocks.

Generation	Type of clock	Details	Examples	References
1st	Epigenetic age	Specific for tissue and development stage	Horvath, Hannum, PedBE	[19,21,24]
2nd	Mortality (phenotypic aging)	Predict length of life and health, incorporates clinical measures	GrimAge, PhenoAge	[18,25]
3rd	Pace of aging	Rate of change in epigenetic age	DunedinPACE	[26]
4th	Causal	Uses Mendelian randomization to identify genetic sites causally linked to aging	CausAge, AdaptAge, DamAge	[27]

more generally, are causal mechanisms that mediate the impact of early exposure to psychosocial stressors on later life health, or are simply biomarkers of psychosocial stress exposure. Epigenetic clocks are based on CpG sites that are associated with age (or other phenotypes such as mortality), but are agnostic with respect to gene, so the effect of changes in DNAm at these sites on health outcomes is unclear. Specifically, these sites were identified by computational algorithms to associate with chronological age, but the sites might not be causally related to age or other associated phenotypes and it is not clear how they relate to biological pathways of aging. Furthermore, most clocks are specific to certain tissues or stages of development so caution should be exercised when interpreting EAA or EAD results across studies.

Ultimately, epigenetic clocks represent only one measure of aging and the functionality of the sites on which clocks are based is unclear. Aging is a complex phenotype and is, therefore, influenced by a broad range of variables. Yi noted that the majority of studies that report environment-associated epigenetic differences cannot rule out the role of genetic effects, further complicating the relationship between stressor, epigenetics, and health outcomes [36]. A recent study by Tung's group proposed that environment-associated epigenetic marks may be best viewed as a "mixed bag" that includes sites with no regulatory effect plus a smaller number of sites that play a key role in gene regulation, sites that affect gene regulation only under certain conditions, and passive biomarkers [37].

1.2. Evolution and adaptation

Patterns of DNAm and gene expression are established early in embryonic development and differ significantly between cell types, thus the same genome is differentially expressed to produce different cells and tissues. Across the methylome, global methylation levels decrease steadily throughout life although methylation at the majority of CpG sites remains relatively stable. In contrast, methylation at certain CpG sites may be more plastic and may have evolved as an adaptive mechanism that is responsive to environmental exposures, in accord with DOHaD tenets, in contrast to the long-term adaptation provided by the genome [9]. From an evolutionary perspective, the number of CpG sites and genes that may be epigenetically sensitive to the psychosocial environment must be small since the majority of genes must continue to function regardless of environmental changes [38]. For example, a study of prenatal exposure to maternal stress in mother-infant dyads in the Democratic Republic of Congo reported only 212 CpG sites out of 431,048 studied sites correlated with prenatal maternal stress exposure (false discovery rate = 5%) [39].

If some of the CpG sites associated with early exposures to psychosocial stress are associated in a causal manner, it is interesting to speculate on the adaptive or maladaptive nature of EAA and EAD in response to psychosocial stress. EAA is most often considered a maladaptive response in which accelerated aging leads to an earlier emergence of aging-related diseases. Similarly, EAD could be maladaptive if children's cognitive and physical development is delayed and children are late in reaching developmental milestones. Alternatively, EAD might represent an adaptive response to slow down the aging process in order to allow time to tackle an adverse environment. Alternatively, both EAA and EAD may function more as biomarkers that track the aging process, but do not play a causative role. EAA and EAD likely manifest differently in different tissues and at different times and may include a range of impacts on gene expression and phenotype as well as passive biomarkers [37].

2. Psychosocial stress and epigenetic age acceleration

This narrative review focuses on psychosocial stressors, with an emphasis on early childhood exposures, in relation to epigenetic aging. Although many articles have been published on this topic, most articles do not use typically use "psychosocial stress" either as a keyword or in the title or abstract. A Pubmed search for "epigenetic aging" and "psychosocial stress" in the Title/Abstract retrieved only eight articles and only one was focused on childhood (and is cited here [40]). Thus, a customized search for relevant articles was performed that queried almost 2000 articles on epigenetics and related topics, with the vast majority (98%) published in the past two decades. Approximately one hundred articles were chosen for preliminary review and 76 articles on epigenetics and/or psychosocial stress and/or early adversity were included in this article. Details on key studies that tested for associations with epigenetic aging and early childhood psychosocial stressors and/or health outcomes are summarized in Table 2.

Psychosocial stressors are adverse psychological and social events that challenge an individual's ability and resources to cope. Examples of psychosocial stressors include, but are not limited to, childhood abuse and neglect, poverty, poor education, lack of family support, war trauma, racial discrimination, and mental health disorders. Multiple studies have reported associations between EAA or EAD and a range of stressors, including maternal mental health, childhood adversity, and sexual abuse [41–44]. Studies that demonstrate and explicate these associations (as depicted in the first step of the model outlined in Figure 1) are detailed below.

2.1. Mental health challenges

Prenatal and childhood exposures to maternal mental health disorders, physical and sexual abuse, and neglect are predictive of later life poor mental and physical health; these stressors have been associated with EAA and EAD. For example, a study of two longitudinal cohorts from the Netherlands and Singapore demonstrated that prenatal maternal anxiety was associated with childhood EEA (using the PedBE clock and measured at 6 and 10 years old or 3, 9, and 48 months in the two studies), an effect seen primarily in males [42]. A study of the impact of maternal trauma on mothers and newborns in the Democratic Republic of Congo reported epigenetic age acceleration in both mothers (associated with sexual trauma) and newborns (associated with general and war trauma) using 1st and 2nd generation clocks [29]. *These results suggest that*

Table 2. Summary of cited studies that tested for associations between epigenetic aging and psychosocial stressors and/or health outcomes.

Exposure	Outcome	Clocks used	Samples	Reference
Prenatal maternal anxiety	None tested	PedBE	Children and infants from 2 cohorts, buccal	[42]
Maternal mental health	None tested	Horvath, PedBE	1 yr olds, buccal	[28]
Maternal trauma including war and sexual trauma	None tested	Horvath, PhenoAge, GrimAge, telomere	Mothers and newborns, blood	[29]
Familial risk for mental health disorders	None tested	Horvath, Hannum, PedBE, PhenoAge, telomere	Youth (6–17 yrs), blood and saliva	[43]
Range of psychosocial stressors	None tested	Horvath, Hannum, PedBE, Skin & blood	Children (6–13 yrs) of Latinx immigrants, saliva	[40]
Childhood maltreatment	PTSD	Horvath	Children and adolescents (8–15 yrs), buccal	[44]
Childhood sexual abuse	Cortisol trajectory	Horvath, Hannum, PhenoAge, GrimAge	Female Growth and Development study, age 6–16 yrs, blood	[45]
Childhood adversity, SES	None tested	Horvath	Women from 2 cohorts, blood	[41]
SES	None tested	PhenoAge, GrimAge, Dunedin, mortality risk	Adults, mean age 52 yrs, blood	[46]
SES	None tested	Horvath, Hannum	Adults from 3 European cohorts, blood	[47]
SES	Cognitive dysfunction, morbidity, mortality	2nd & 3rd generation clocks	Adults over 50 yrs	[54]
SES	Health outcomes	1st, 2nd, 3rd, 4th generation clocks	Health and Retirement Study, adults over 56 yrs, blood	[30]
Low birthweight	None tested	Horvath	Birth to 3 yrs, blood	[31]
Short gestational age (GA)	Developmental delay	Cord blood DNAm GA clocks	Upstate KIDS Study, birth to 3 yrs, dried blood spot	[50]
None tested	Mortality	Horvath, Hannum	4 cohorts, elderly adults over 70 yrs, blood	[35]
None tested	Temperament, psychological symptoms	Horvath	Newborns, cord blood	[55]
None tested	Breast cancer	Horvath, GrimAge	Black and White women, blood	[56]
None tested	Early onset of puberty, breast development	Horvath	Growth and Obesity Cohort Study, adolescent girls, blood	[32]
Protective factors against epigenetic aging				
Meditation		Horvath	Adults, blood	[57]
Physical activity	None tested	Horvath, Hannum, PhenoAge, GrimAge	Adults, mean age 56 yrs, blood	[58]
Childhood adversity, years schooling	None tested	Horvath, Hannum, PhenoAge	Adults, blood	[59]
Racial discrimination, supportive family environment	None tested	Hannum	2 cohorts of African American youth, 16–19 yrs, blood	[60]
Exposure to green space	None tested	GrimAge, PhenoAge, DunedinPACE	Adults from CARDIA Study, blood	[61]

the origins of EAA start in utero and support the idea that biological embedding of prenatal adversity through EAA may be an underlying mechanism for the fetal origins of mental health. Similarly, Fransquet et al. reported that EAD was associated with perinatal maternal anxiety and stress ($p = 0.003$ and 0.036, respectively), but not depression ($p = 0.111$), in 1-year-old infants, but only in a model including all covariates and only when estimated with the PedBE clock (not the Horvath clock) [28]. Another study of children and adolescents, aged 6–17 years old, at familial high risk for schizophrenia and bipolar disorder reported EAD in high-risk individuals relative to controls (using the Horvath, Hannum, and PedBE clocks) [43]. *These studies highlight the importance of specialized epigenetic clocks, such as the PedBE clock, which was trained on healthy individuals aged 0–20 years old. These results also illustrate the reality of conflicting results from different studies. EAA and EAD may be adaptive or maladaptive in different environments and may change with time or population or stressor.*

2.2. Sexual, emotional, physical abuse and neglect

Lawn et al. tested two cohorts of women for associations of childhood exposure to adverse events (e.g., sexual, emotional, or physical abuse or neglect, parental absence, and low socioeconomic position) with EAA in adulthood. They reported a strong association of sexual abuse with EAA, specifically an increase of 3.41 years associated with sexual abuse at the 47-year timepoint [41]. *The authors propose that EAA is a mechanism that links the impact of childhood sexual abuse with poor outcomes in adulthood*. Shenk et al. [44] studied adolescents who had experienced childhood maltreatment, which is one of the strongest predictors of PTSD and includes sexual abuse, physical abuse, and neglect, and they reported that EAA predicted PTSD status in a linear manner, i.e., increasing maltreatment was associated with increased EAA, ($p = 0.015$), with a moderate effect size (OR = 2.35). *The authors proposed that biological embedding of child maltreatment through EAA may help explain why only some victims of childhood maltreatment develop PTSD and could help target treatment to the most vulnerable individuals*. A 30-year prospective study of cortisol levels reported that women exposed to childhood sexual abuse demonstrated EAA and, furthermore, their cortisol concentrations peaked at a lower level and transitioned to the decline phase at an earlier age compared to participants with no history of abuse [45]. *These results suggest that biological embedding of childhood adversity through EAA persists through adulthood and may impact health outcomes through hormonal dysregulation and an altered aging trajectory.*

2.3. Socioeconomic status

SES is one of the most frequently investigated psychosocial stressors in epigenetic studies. Low SES is a psychosocial stressor that is associated with premature aging and early onset of

age-related disease. Low SES can occur throughout the life course and both early life and later life SES have been associated with EAA [46]. SES, along with SES-associated factors such as education, financial hardship, living conditions, and social mobility, are unlikely to be direct causative factors of EAA, but they are linked to more proximate factors such as smoking, drinking, and obesity.

In a recent study, Crimmins, Klopack and Kim tested epigenetic age, as estimated by the four generations of epigenetic clocks, for association with SES-associated variables and health outcomes [30]. The authors reported that education had the most consistent effect across statistical models and lower levels of education were associated with EAA, but only when estimated with 2nd and 3rd generation clocks. EAA was also associated with mortality and morbidity, but only when using 2nd and 3rd generation clocks. The 2nd and 3rd generation clocks were trained on health indicators and outcomes so it is not surprising that they show the strongest associations with morbidity and mortality. *These results suggest that low levels of education are associated with EAA, which in turn is associated with increased morbidity and mortality, completing the relationship illustrated in* Figure 1. Low childhood SES gave more mixed results. Low SES was associated with EAA in most models, but was associated with EAD in one model using a 4th generation clock. *SES is a complicated variable that can be difficult to measure accurately so consensus across all epigenetic clocks may be difficult to achieve given that epigenetic clocks were trained on different datasets to model a range of outcomes.*

Another study based on three cohorts from Italy, Australia, and Ireland reported that EAA was associated with low SES (an increase of 0.99 years) [47]. Furthermore, the authors reported that individuals who experienced changes in SES over their lifetime had intermediate EAA compared to the extreme SES categories. *This result supports the importance of early childhood events as setting a baseline epigenetic age and suggests that increases in epigenetic aging may be mitigated, and possibly reversed, by later life experiences.*

2.4. Birthweight and gestational age

An important indicator of adult health, including disease risk and mortality, is birthweight (BW); specifically, low BW has been associated with increased risk of coronary heart disease and other chronic diseases as well as all-cause mortality [48,49]. In a recent longitudinal study, EAA was reported during the first three years of life (measured at birth, 6 m, 1 yr, 2 yrs, 3 yrs) and was associated with low BW [31]. No EAA was observed at birth or any individual timepoint, but emerged over time, highlighting the importance of longitudinal studies. *These results suggest that accelerated epigenetic aging may shape the trajectory of biological aging in early childhood and may be a pathway that links low birthweight and poor adult health outcomes. Specifically, the later life health disadvantages associated with low BW may be biologically embedded in the first years of life and EAA may be a mechanism by which the impacts of low BW are preserved and manifested in later life.*

Gestational age is the common term to describe how far along a pregnancy is and it is measured from the woman's last menstrual cycle. Short gestational age (GA) is a risk factor for development delay in children. A recent study compared clinical GA with a new measure of DNAm-estimated GA and reported that higher values of both measures were protective against overall development delay [50]. In contrast, gestational age acceleration (higher DNAm GA than clinical GA) was not associated with development delays. *These results suggest that DNAm GA and clinical GA capture the same risk or protective factors for development delay, and that the DNAm GA clock could be a useful measure when GA is unknown.*

3. Epigenetic age acceleration and health outcomes

The epigenome accumulates damage over the life course and that damage has been associated with a range of health outcomes (the final step in the model outlined in Figure 1), including age-related disease and disability, as well as an altered aging trajectory [51]. EAA associated with prenatal and early childhood psychosocial stressors is thought to be particularly impactful on many later-life health outcomes. Furthermore, the psychosocial stress of systemic racism has been proposed to leave heritable marks in the epigenome that impact future generations and may play a role in maintaining racial health inequities [52]. Salas et al. call for a transdisciplinary approach to study racial and ethnic health inequities that incorporate epigenetic data as a means to capture the impact of psychosocial stressors that racial and ethnic minorities experience, such as racism, discrimination, and increased exposure to toxins [53].

A recent study provides a wealth of information on the interconnectedness of childhood stressors, EAA/EAD, and adult health outcomes. Faul et al. studied 43,000 individuals over age 50 and compared EAA estimated with 1st, 2nd, and 3rd generation epigenetic clocks and standard health risk factors, such as childhood SES and health behaviors, to determine if epigenetic age improved the prediction of later life health outcomes [54]. EAA was associated with most health predictors, such as low childhood SES (also a psychosocial stressor), obesity, smoking, and heavy drinking. In terms of health outcomes, EAA estimated by three clocks (PhenoAge, GrimAge and DunedinPACE) significantly predicted cognitive dysfunction and increased difficulties of daily living in old age. EAA estimated by all five tested clocks predicted morbidity and mortality. EAA and the other risk factors differed in their relative contributions to the studied health outcomes. EAA explained more variation in morbidity and mortality compared to cognitive dysfunction and daily life difficulties. SES factors (education and race) were the major contributors to cognitive dysfunction and demographic factors (age and sex) were the major contributors to mortality. *These results demonstrate that epigenetic age, demographics, SES, and health behaviours are all important predictors of later life health outcomes. The association of epigenetic age with both stressors and health risk factors demonstrates a potential mediating role for EAA in these associations.*

Manczak, Scott and Millwood reported evidence of an epigenetics x environment (ExE) effect where children born with EAA (estimated with umbilical cord blood) demonstrated an interaction between EAA and the parenting style to which

they were exposed. Specifically, children born with higher levels of EAA showed more unpredictable temperaments and more psychological symptoms if their mothers engaged in hostile parenting, but fewer difficulties if their mothers used less hostile parenting [55]. In contrast, children with lower levels of EAA did not show associations between their temperaments and parenting style. *The authors propose that high EAA may function as a differential susceptibility variant, similar to genetic differential susceptibility variants, that signals increased risk for psychopathology when a child is raised in an adverse environment, but decreased risk when raised in a less adverse environment* [55].

3.1. Breast cancer

Associations have been reported between EAA and altered aging trajectories. Binder et al. studied a group of adolescent girls to investigate the effect of EAA on earlier onset of pubertal development, which has been associated with increased cancer risk and mortality in females [32]. They reported that a 5 year increase in EAA was associated with a decrease in time to menarche (5 months sooner), increased pubertal tempo (6.6 months faster), and increased fibroglandular volume (5% higher), which measures breast density and is associated with breast cancer risk. *These results highlight the critical developmental window during adolescence when rapidly developing breast tissue is thought to be most susceptible to carcinogens and suggest that EAA is linked to faster pubertal development and may be an early life predictor of breast cancer*. A recent study of breast cancer in Black and White women reported EAA in patients relative to controls (2.48 years) and reported a 14% increase in breast cancer risk for a one-year increase in GrimAge acceleration [56]. Slightly lower odds ratios (ORs) for cancer were detected for Black women versus White women (OR = 1.08 vs 1.17) despite Black women having an earlier age of onset and higher mortality compared to White women. *These results show a clear association of EAA with increased cancer risk and suggest the association may vary by self-reported race.*

3.2. Mortality, morbidity, and inflammaging

EAA has been associated with increased mortality and increased risk for a range of diseases and inflammaging (low-grade inflammation associated with aging). An early landmark study of epigenetic age reported that EAA was associated with all-cause mortality across four longitudinal cohorts (5 years of EAA was associated with 21% higher mortality risk) [35]. A systematic review of 156 publications tested more than 1300 reports of associations between psychosocial factors, EAA estimated with different epigenetic clocks, and a range of health outcomes. The authors reported that EAA estimated with a range of clocks was significantly related to cardiovascular disease, cancer, and diabetes [33]. They also reported that results based on the Horvath, Hannum, PhenoAge, and GrimAge clocks were generally consistent in the direction of reported effects, but varied in the size of effect. Inflammaging is low-grade, long-term inflammation associated with aging that is not resolved after an infection as in a controlled inflammatory state. Thus, inflammaging is believed to play a key role in the aging process and emergence of age-related chronic diseases. Alimohammadi et al. explain how disruptions to biological processes are driven by inflammaging and changes in DNAm, leading to increased risk of chronic diseases [34].

The studies in this section help us better understand how increased epigenetic aging, health risk factors, and chronic low-grade inflammation are linked to altered aging trajectories and disrupted physiological functions, which are then linked to the emergence and progression of aging-related diseases.

4. Protective factors against epigenetic aging

Relatively few studies have investigated the effect of positive factors, or protective factors, on epigenetic aging. If accelerated epigenetic aging is maladaptive, it is intriguing to consider the possibility there are factors that could slow, or even reverse, epigenetic aging, and thus weaken the link between early life adversity and adult health outcomes. The protective effect of lifestyle or behavioral factors on epigenetic aging is particularly interesting because these factors are potentially more modifiable than other factors such as poverty or poor mental health. Chaix et al. tested the effect of meditation on epigenetic aging and reported that older, long-term meditators did not show the same increase in epigenetic aging that older, non-meditators showed relative to younger participants [57]. Increased physical activity and higher levels of schooling have also been associated with slower epigenetic aging [58,59]. Epigenetic aging scores could be used as a measure for the effectiveness of interventions developed to slow aging and possibly improve long-term health.

Resilience, or the ability to recover quickly and "bounce back" from difficulties, may also be protective against EAA. Clausing et al. studied a wide range of psychosocial stressors and resilience factors in Latinx children (6–13 years old) of immigrants before and after the 2016 presidential election [40]. They reported an association of lower epigenetic age (Hannum clock) with higher maternal subjective social status, which is a measure of resilience, but this association disappeared in the smaller, post-election sample. *Further study is warranted to determine how lifestyle and resilience factors may protect against, or even reverse, accelerated epigenetic aging.*

4.1. Protective factors in minority populations

Several studies have focused on minority groups to better understand the unique psychosocial stressors faced by minorities and identify factors that protect against EAA associated with race-related stressors, such as racial discrimination and neighborhood characteristics. Brody et al. tested the ability of supportive family environments during adolescence to protect against the effects of discrimination in two cohorts of African American youth [60]. They reported that youth in supportive family environments who were exposed to higher levels of racial discrimination did not exhibit EAA in contrast to youth in less supportive family environments exposed to higher levels of racial discrimination who did exhibit EAA. These results were confirmed in both study cohorts. Another study

investigated the negative association between urban greenness and epigenetic aging, i.e., slower epigenetic aging is associated with exposure to green space, by race and neighborhood SES [61]. In general, having green space within 5 km of one's residence was associated with a slower GrimAge of 0.47–0.93 years compared to having no green space. However, Black participants had less surrounding green space and showed a weaker association between green space and GrimAge compared to White participants (slower GrimAge of 0.80 years vs 3.03 years with respect to green space). *These results suggest there are modifiable, positive factors that can protect against accelerated epigenetic aging, and these factors may be particularly important in more disadvantaged populations.*

4.2. Medication as a protective factor in depression

Many studies have investigated the association between depression and epigenetic aging, but the results can appear contradictory. The majority of studies have reported that depression is associated with accelerated epigenetic aging, such as depressive symptoms in adolescence associated with adult EAA [62], prenatal maternal depression associated with maternal EAA but not newborn EAA [63], prenatal maternal depression associated with placental EAA [64], and a Mendelian randomization analysis that reported a causal relationship between depression and GrimAge EEA [65]. Other studies have found no EAA associated with depression in childhood or adolescence [66] or postnatal maternal depression associated with newborn EAD [67]. Some researchers have speculated that antidepressant use might mitigate depression-related changes in epigenetic age and may account for some of the inconsistent studies. Two studies included only untreated patients with major depressive disorder and documented EAA with multiple clocks [68,69]. McKenna et al. specifically studied the effect of SSRI antidepressants and reported that maternal SSRI treatment for depression was strongly associated with newborn EAD ($p = 0.001$) [70]. Furthermore, when SSRI use was included in the model, the previously noted association of EAD with maternal prenatal depression disappeared. *These results suggest that previously reported associations between EAD and depression may instead reflect SSRI use and suggests that SSRI use may mitigate the EAA associated with depression.*

4.3. Reversibility of epigenetic aging

There are intriguing data in animal models that suggest epigenetic age can be experimentally manipulated and reversed. A recent mouse study demonstrated that epigenetic age increased when young mice were exposed to the blood of older mice (specifically, a 3-month-old mouse was surgically joined to a 20-month-old mouse for three months). Epigenetic age decreased following separation, suggesting that stress-induced changes in epigenetic age are fluid and reversible [71]. Another mouse study demonstrated that ectopic expression of three genes in retinal ganglion cells resulted in the restoration of DNAm patterns, promoted axon regeneration after injury, and reversed vision loss in a mouse model of glaucoma [72]. *These results suggest that mammalian tissues retain a record of early epigenetic patterns that can be accessed and manipulated to reverse the record of epigenetic aging and possibly restore function to damaged tissues.*

There are few studies on reversal of epigenetic aging in humans. In a pilot study of 10 healthy men, aged 51–65 years old, Fahy et al. used a protocol to regenerate the thymus in order to investigate the effect of improved immune function on epigenetic age and risk for age-related diseases [73]. They reported a significant increase in lymphocyte-to-monocyte ratio, which is associated with reduced risk for several cancers and cardiovascular disease, less inflammation, and lower mortality, as well as significantly reduced epigenetic age using four epigenetic clocks. Averaged across all four clocks, epigenetic age in blood cells showed a maximum reduction of 2.5 years at 12 months post-treatment. From months 12–18, epigenetic age increased slightly with Horvath and PhenoAge clocks (but remained 1–2 years lower than baseline) and stayed constant with GrimAge and Hannum clocks. *These results suggest that reversal of epigenetic age may be possible in humans.*

What do these studies mean for our ability to reverse aging in humans and improve health outcomes? Although we are not yet at the point where we can therapeutically reduce a person's epigenetic age, that future may not be too distant. A seminal study in 2011 demonstrated that fibroblasts from centenarians and other senescent cells could be reprogrammed to induced pluripotent stem cells (iPSCs) [74]. Further studies showed that the rejuvenated cells could be differentiated into cell types different than the original fibroblasts [75], implying that the re-differentiated cells had no epigenetic memory of the age and state of the original cells. Marioni speculates on the importance of ongoing studies on partial reprogramming in which the cellular reprogramming is stopped at a point at which the somatic identity of the cell is maintained but at a younger epigenetic age [76]. Since epigenetic clocks are based on CpG sites that are not associated with specific age-related genes or biological pathways, the effect of experimental manipulation of these sites to reverse aging is unclear. Furthermore, since cancer is a disease in which cells live forever, we should be cautious in attempting to extend human lifespan by manipulating epigenetic age.

5. Future perspective

Epigenetic age acceleration is a mechanism to biologically embed (i.e., encode, preserve, and transmit) information from early life events throughout the life course. This biological embedding may be the mechanism by which the impacts of early life experiences are preserved throughout life and influence later life health, in accord with DOHaD tenets. This paper summarizes many studies that report EAA and EAD in association with early-life exposure to psychosocial stressors and adult health outcomes. There is often a lack of strong consensus across studies, perhaps due to different demographics of study populations, different stressors and health outcomes and different ways of measuring them, and the use of different epigenetic clocks. Additional study is required to determine where consensus exists and, particularly, which stressors and

outcomes are most strongly associated with EAA and EAD and how these associations differ based on the use of different epigenetic clocks. Future studies should also seek to determine if EAA is causally linked to age-related disorders or is simply a biomarker of biological aging.

The results summarized here also broaden the debate on human evolution, and specifically how we study adaptation vs maladaptation, and provide a template for future studies. For example, is EAA always maladaptive because it represents premature aging that leads to earlier and increased risk of aging-related disease? Can EAA function as a differential susceptibility variant in children at high risk for later-life psychopathology and exhibit an epigenetic x environment effect? Is early-life EAD an adaptive response that essentially hits the brakes to enable an optimal response to an adverse environment or is it a maladaptive response that signals children are late in meeting developmental milestones? Furthermore, it is useful to speculate on ways to use our expanded understanding of psychosocial stress and epigenetic aging to improve the human condition. Can we use EAA as a biomarker to identify vulnerable individuals at risk for poor mental health and candidates for intervention? Can we use changes in epigenetic age as a measure of the effectiveness of proposed interventions? Can we develop protocols to mitigate the effects of stress on health and possibly reverse epigenetic aging, and what possible side effects might there be? This wealth of questions makes it clear there are many fertile areas of future investigation with respect to epigenetic aging, psychosocial stress, and the impacts of childhood adversity.

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