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The embodiment of parental death in early life through accelerated epigenetic aging: Implications for understanding how parental death before 18 shapes age-related health risk among older adults

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A B S T R A C T

Parental death in early life has been linked to various adverse health outcomes in older adulthood. This study extends prior research to evaluate how parental death in early life is tied to accelerated epigenetic aging, a potentially important biological mechanism from which social and environmental exposures impact age-related health. We used data from the 2016 Venous Blood Study (VBS), a component of the Health and Retirement Study (HRS), to examine the association between parental death in early life and accelerated epigenetic aging as measured by three widely used epigenetic clocks (PCPhenoAge, PCGrimAge, and DunedinPACE). We also assessed whether some of the association is explained by differences in educational attainment, depressive symptoms, and smoking behavior. Methods included a series of linear regression models and formal mediation analysis. Findings indicated that parental death in early life is associated with accelerated epigenetic aging for PCPhenoAge and DunedinPACE. The inclusion of educational attainment, depressive symptoms, and smoking behavior attenuated this association, with formal mediation analysis providing additional support for these observations. Parental death in early life may be one of the most difficult experiences an individual may face. The elevated biological risk associated with parental death in early life may operate through immediate changes but also through more downstream risk factors. This study highlights how early life adversity can set in motion biological changes that have lifelong consequences.

1. Introduction

Death of a parent in early life has been linked to adverse age-related health outcomes later in life (Conde-Sala & Garre-Olmo, 2020; Donnelly et al., 2023; Liu et al., 2022a; Smith, 2014). Prior research has shown that those who experience a parent's death in childhood are more likely to have cardiometabolic conditions (Chen et al., 2020; Smith, 2014), develop disability (Björkenstam et al., 2017), and die prematurely (Smith, 2014). The mechanisms linking early life parental death and later life health are multiple, broadly encompassing social, psychological, and economic pathways. For example, young people who experience a parent death often engage in health risk behaviors, such as smoking and drug or alcohol use, to numb the pain of loss, and these behaviors are difficult to alter once set. Children may not perform as well in school through increased absences or greater difficulty in paying attention that, potentially leading to lifelong socioeconomic disadvantage. A parent's death can also lead to significant psychological distress that may make children more likely to experience depression throughout their lives. In sum, loss of a parent in early life is a life-altering event that can pose significant challenges that shape an individual's life trajectory. Each of the possible pathways, along with the death event itself, can lead to physiological dysregulation that underly a broader risk to age-related health outcomes. However, much of the literature examining the association between parental death in early life and later life health has focused on specific health conditions or system-specific biological risks and has yet to consider the ways that accelerated aging may link early life parental death to several later life health conditions.

Recent advancements in gerontology have led to the development of measures of biological aging. Biological aging measures are multisystem summary measures that allow researchers to assess physiological dysregulation prior to the advent of clinical symptoms (Crimmins et al., 2021a; Levine, 2013). These measurements are highly predictive of disability, morbidity, and mortality in later life (Faul et al., 2023). Additionally, social and health science researchers have used these measures to understand how faster and slower biological aging differentiates later life health risk across individuals and groups (Farina et al., 2022; Levine & Crimmins, 2014, 2018). In recent years, epigenetic clocks have been proposed as measures of biological aging at the

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molecular and cellular level. Epigenetic changes are a hallmark of aging and, thus, are thought to be fundamental to increasing risk for poor health in later life (Brunet & Berger, 2014; López-Otín et al., 2013). These changes are also strongly associated with social and environmental conditions throughout the life course (Andrasfay & Crimmins, 2023; Crimmins et al., 2021a; Oblak et al., 2021). Epigenetic clocks based on DNA methylation are now among the most studied biomarkers of aging used in social science and medical research, providing renewed insight into how biological aging processes are responsive to life events and shape health.

This study builds on prior research in two notable ways: 1) we examine the association between parental death at 18 years of age or younger and accelerated epigenetic aging in later life, and 2) we investigate whether these associations are in part attributable to educational attainment, smoking, and depressive symptoms. We use the Health and Retirement Study (HRS) Venous Blood Study (VBS) which has collected information on early life parental death and epigenetic aging. We hypothesize that respondents who had a parent die before the age of 18 will have accelerated epigenetic aging. We also expect that some of the association between early life parental death and accelerated epigenetic aging will be through educational attainment, smoking, and depression, but the association between parental death in early life and accelerated epigenetic aging will not be fully accounted for due to biological scarring associated with an early life traumatic event. Understanding how early life parental death is associated with accelerated aging will help identify potential mechanisms that link early life adversity to poor health in later life through biosocial processes.

2. Background

2.1. Biosocial pathways linking parental death to accelerated epigenetic aging

Prior research provides substantial evidence that early life conditions impact later life health risk (Ben-Shlomo & Kuh, 2002; Brandt et al., 2012; Haas, 2007; Hayward & Gorman, 2004). This phenomenon has been called the "long arm of childhood" (Hayward & Gorman, 2004) and has led to substantial scholarship seeking to understand how and why childhood conditions impact age-related health. Health researchers have found evidence of both direct and indirect effects of childhood experiences (Mustillo et al., 2021; Pakpahan et al., 2017; Pudrovska, 2014). Direct effects can refer to changes in biological functioning or structure that can put an individual at greater risk of developing health problems in later life. With regard to biological risk, prior studies on allostatic load have found that stressful life experiences, including early life conditions or events, can cause adaptations in the body that lead to "wear and tear" that elevate the risk of health complications in older adulthood (Prior et al., 2019). This perspective centers the body as a record from which to understand how life course exposures, including early life, lead to poorer health in older adulthood (Simandan, 2010). Emerging evidence from epigenetics has found that the epigenome is responsive to early life conditions, especially childhood socioeconomic adversities (Marini et al., 2020; Raffington et al., 2021). As such, from a life course perspective, early life may represent a sensitive period during which molecular changes are established, carried forward into older adulthood, and elevate age-related health risks. Thus, epigenetic changes may represent a potential biological mechanism by which the "long arm of childhood" operates.

Indirect effects are also important to consider, as early life conditions or events often place people on different social and economic trajectories in adulthood. These trajectories often shape more proximate risks of age-related conditions in adulthood, such as poor health behaviors (i.e. smoking) (Klopack et al., 2022b; Lovallo, 2013; Raposa et al., 2014), worse mental health (Merrick et al., 2017), and socioeconomic status (Pudrovska, 2014). For example, persons who experience adversity in childhood are more likely to have lower educational attainment (Duncan et al., 1998), report greater levels of depression (Merrick et al., 2017), and engage in health-damaging behaviors (Fuller-Thomson et al., 2013). Each of these factors has been associated with premature mortality and poorer health. These risk factors are among some of the most widely researched with regard to epigenetic change and have been among the most significant factors to be associated with epigenetic age acceleration (Crimmins et al., 2021a; Klopack et al., 2022b). Therefore, these potential mediators may provide some insight into how early life conditions may be linked to accelerated epigenetic aging in later life through distinct downstream pathways.

To understand how early life events or conditions impact later life health, life course researchers point to the intensity, chronicity, whether it was social or environmental, and developmental timing as key aspects to evaluate the potential impact of the stressor or event on health (Simandan, 2010). The death of parent in early life may be one of the most difficult experiences a young person can encounter. Parental death in early life often leads to considerable loss of social support and economic resources that can undermine health and well-being throughout life (Conde-Sala & Garre-Olmo, 2020; Donnelly et al., 2023a; Marks et al., 2007). While the event itself is acute, the absence of a parent is felt throughout life. People who experience parental loss in early life may be disadvantaged throughout life. It is these challenging aspects of early parental death that may increase risk for several morbidities and premature mortality (Donnelly et al., 2023a; Liu et al., 2022a; Smith, 2014).

The association of parental death in early life with multiple later life health conditions suggests that several pathways across multiple domains exist. That is, parental death in early life sets in motion cascades of risk through overlapping and multitudinous processes that impact downstream factors that make it impossible to attribute poor health in later life to one individual direct or indirect pathway. Instead, the association with poor health in older adulthood is often an accumulation of risk across several domains. In fact, prior research has found evidence of both direct and indirect pathways. Early parental death has been tied to greater depressive symptoms (Böckerman et al., 2023; Kamis et al., 2022), poor educational outcomes (Liu et al., 2022a; Prix & Erola, 2017), and higher rates of smoking (Lacey et al., 2018). These pathways are among some of the widely documented in the literature. These factors also are strongly associated with biological risk. But even after accounting for downstream risk factors, parental death in early life continues to be associated with greater health risk, which suggests that a biological mechanism directly connecting parental death in early life to later life health may exist (Smith, 2014). Moreover, prior research has shown that epigenetic changes are highly responsive to traumatic events in early life (Labonté et al., 2012; Sumner et al., 2019). As such, from both direct and indirect pathways, the loss a parent in early life may impact dynamic biological processes to create and sustain health inequalities in later life (Prior et al., 2019). However, how parental death is embodied at the molecular level remains understudied, although this approach would provide additional evidence of potential biological underpinnings of the "long arm of childhood" and provide further insight into how parental death in early life is linked to multiple health outcomes.

2.2. Accelerated epigenetic aging and life course research

With advancements in biological data collection and computational methods, several epigenetic clocks have been developed. Broadly, epigenetic clocks can be classified into two sequential groups: 1st and 2nd generation clocks. 1st generation clocks refer to a set of clocks that were designed to predict chronological age (i.e., Horvath and Hannum). These clocks are based on DNAm patterns that change with age. 2nd generation clocks were designed to predict health status in later life, using DNAm patterns that were associated with morbidity, mortality, or their risk factors (i.e. PhenoAge and GrimAge). Lastly, a new iteration of clock prediction has emerged, sometimes referred to as 3rd generation clocks, trained on trajectories of age-related health status and

biomarkers (i.e. DunedinPace). Given differences in their development, 2nd generation clocks (or later) perform better at predicting age-related health outcomes than 1st generation clocks, which have mixed results in predicting age-related conditions despite consistently predicting chronological age (Faul et al., 2023; Maddock et al., 2020).

It is also important to note that while there are clear distinctions between 1st and 2nd generation clocks, 2nd generation and later clocks may relate differently to various health conditions and social and environmental factors due to differences in their development. Specifically, 2nd epigenetic clocks were trained on different age-related health markers. For example, GrimAge was trained to predict mortality from 7 plasma proteins and smoking pack-years (Lu et al., 2019) as well as age and sex. As such, several of, but not all, CpG sites used in the GrimAge clock are strongly associated with smoking. Therefore, GrimAge may be more closely tied to mortality risk factors that are either smoking-related themselves or show similar epigenetic signatures to smoking than other epigenetic clocks. Therefore, the social or environmental risk factors as well as health-risks associated with each epigenetic clock may differ because of the way that each was developed (Oblak et al., 2021). However, understanding of differences across clocks is still emerging and scientific consensus as to the meaning of observed differences between how clocks relate to exposures and outcomes has not yet been achieved.

The differences in 2nd generation clocks point to two important considerations for social science research design when evaluating epigenetic aging. First, no "gold standard" for epigenetic aging exists. Each clock provides information on accelerated aging and different clocks are not based on the same underlying epigenetic changes and are not trained on the same health risks. Therefore, mixed findings should not be treated as contradictory but rather as complementary (i.e., significance between exposures and methylation as measured by epigenetic aging can exist for one clock but not the others and would still provide evidence of some form of epigenetic age association with exposure). Second, because no one epigenetic aging clock is accepted as standard, researchers often use several epigenetic clocks in their studies (for example: Andrasfay & Crimmins, 2023; Faul et al., 2023; Fiorito et al., 2022; Lo & Lin, 2022). The use of several clocks allows researchers to investigate underlying social and environmental impacts on epigenetic aging more broadly by accounting for different DNA methylation signatures that are predictive of several, but not completely overlapping, age-related health outcomes. Therefore, in this study, we incorporate three commonly used epigenetic clocks in social science and health research which have been designed to predict age-related health outcomes (PCPhenoAge, PCGrimAge, and DunedinPace).

Additionally, studies have shown that epigenetic clocks are tied to several risk factors across the life course. Substantial research has shown that more years of education are associated with aging deceleration, while smoking and depression are associated to aging acceleration (Beydoun et al., 2019; Crimmins et al., 2021a; Klopack et al., 2022a,b). These associations have been found across a variety of clocks, suggesting that these risk factors are robust to sample and algorithm differences in clock development. These risk factors also are among the most widely studied in population health studies to understand differences in later life health risk and may be key pathways that link parental death in early life to observed age acceleration in later life.

2.3. Study overview

This study builds on work on the early origins of later life health by examining the association of parental death with accelerated epigenetic aging. We also assessed whether these associations can, in part, be attributed to educational attainment, smoking, or depressive symptoms. We used data collected in the 2016 Venous Blood Study from the Health and Retirement Study. Overall, we hypothesize that parental death in early life will be tied to accelerated epigenetic aging; and, part of the association will be explained by differences in educational attainment, smoking, and depressive symptoms. Our research contributes to the "long arm of childhood" literature by evaluating molecular-level changes associated with parental death in early life that may indicate potential biological underpinnings that link parental death in early life to poor health in older adulthood.

3. Data and methods

To evaluate the association between early life parental death and epigenetic aging, we used data from the Health and Retirement Study (HRS). The HRS is a biennial longitudinal study of older adults ages 51 years and older that collects information on demographics, life history information, socioeconomic status, health behaviors and health, along with a significant biomarker collection. In 2016, the HRS collected venous blood, which included DNA methylation (DNAm) assays.

To participate in the Venous Blood Study (VBS), HRS respondents had to have completed a prior interview, not be living in a nursing home, not have a proxy respondent, and agree to and complete subsequent blood collection (Crimmins et al., 2017). Blood collection occurred within approximately 2 months of the 2016 core interview, with most occurring within the first 4 weeks. Licensed phlebotomists went to respondents' homes to collect 50.5 ml of blood. Blood was then shipped to the CLIA-certified Advanced Research and Diagnostic Laboratory at the University of Minnesota to process DNA methylation information using the Ilumina 850 K chip for a subsample of 4018 of the VBS respondents. More detailed information has been published elsewhere (Crimmins et al., 2017; Crimmins et al., 2021b). The sample was designed to be nationally representative with the application of sampling weights.

Reductions to the sample were made due to missing information for parental death (N = 370) and another 266 were missing information from demographic or other covariate information (primarily from smoking pack years and CESD). In total, this study included 3382 participants.

4. Measures

4.1. Accelerated epigenetic aging

To evaluate epigenetic aging, we used three DNAm aging measures that have been widely used in social science and health research (PCGrimAge, PCPhenoAge, and DunedinPACE). GrimAge was trained on 7 DNAm surrogates of plasma proteins, a DNAm surrogate of smoking pack years, chronological age, and sex (Lu et al., 2019). PhenoAge was trained on 9 blood-based markers of immune and tissue function (Levine et al., 2018). DunedinPACE was trained on changes in 19 biomarkers and health indicators that were related to healthy aging (Belsky et al., 2022). The three measures were trained on different samples with various age groups represented. GrimAge was trained using data from the Framingham Heart Study offspring cohort when respondents were 53–73 years old. PhenoAge was trained in the InCHIANTI cohort, whose respondents were Italians 21–100 years old. DunedinPACE is based on Dunedin Study respondents who were 45 years old with biomarker data collected from respondents at ages 26, 32, 38, and 45 years old. We use the principal components or 'PC' version of the GrimAge and PhenoAge clocks that have improved reliability of the estimates, which were estimated by the Levine Lab (Higgins-Chen et al., 2022).

Additionally, while GrimAge and PhenoAge are both scaled in years and are meant to capture epigenetic age at time of measurement (values range from 38 to 125), DunedinPACE was designed to capture the pace of aging and is scaled in years of epigenetic aging per calendar year (values range from 0.63 to 1.74). To estimate age acceleration based on GrimAge and PhenoAge, or whether one is aging faster or slower for a given age, epigenetic age was regressed on chronological age. From these regression models, we took the residual differences between the regression estimates and chronological age, which had positive and negative values. Positive values indicated faster epigenetic aging.

Negative values indicated slower epigenetic aging. Conversion for DunedinPACE was not necessary because acceleration or deceleration are inherent in its unit metric.

4.2. Parental death

Parental death before the age of 18 was coded as dichotomous (1 – experienced a parent die before 18 and 0 – did not experience parental death before age 18). This measure was based on 4 questions obtained in the core survey: 1) "Is your mother still living?", 2) "If not living, in what year did she die/pass away", 3) "Is your father still living?", and 4) "If not living, in what year did he die/pass away". Respondent's age at parental death was calculated using birth year and year of parental death. Additionally, we performed a sensitivity analysis evaluating different age cut points: 10 years or younger and 25 years or younger. Patterns were consistent, but for 10 years or younger the sample size was reduced and made estimates unreliable.

4.3. Education

Educational attainment was based on years of schooling and ranged from 0 to 17.

4.4. Depressive symptoms

Depressive symptoms were measured using the Center for Epidemiological Studies Depression scale (CESD), which included yes or no responses to feeling: 1) depressed, 2) everything was an effort, 3) sleep was restless, 4) happy, 5) lonely, 6) enjoyed life, 7) sad, and 8) could not "get going". Items 4 and 6 were reverse coded. Values ranged from 0 to 8.

4.5. Smoking

Smoking was measured using adult pack years. Pack years were calculated using age respondents started smoking, age respondents ended smoking, and total amount of cigarettes per day. Respondents earliest age (or age 18 for respondents who starting smoking prior to 18) was subtracted from respondents latest age to provide total number of years of smoking. Packs of cigarettes smoked per day was then calculated from the average of the number of reported cigarettes smoked per day at each wave for each respondent, and the maximum number of cigarettes smoked during the time the respondent reported smoking the most. Missing information was imputed. Detailed information on this measure has been published elsewhere (Haghani et al., 2020). The values ranged from 0 to 138.

4.6. Childhood socioeconomic adversity

Childhood socioeconomic adversity was based on a summary measure [0–4] with greater values indicating greater adversity. The summary measures came from self-reported retrospective questions on socioeconomic circumstances during childhood, mother's and father's education of less than 8 years, and father's blue-collar employment. For self-reported retrospective childhood socioeconomic circumstance, respondents were asked: "Now think about your family when you were growing up, from birth to age 16. Would you say your family during that time was pretty well off financially, about average, or poor?" Responses were dichotomized into 1- poor and 0 - not poor. Parental education was provided in years and dichotomized into 1- less than 8 years and 0 - more than 8 years. Following prior research, respondents who did not provide information on mother or father's education were assigned less than 8 years (Luo & Waite, 2005; Montez & Hayward, 2014). Father's blue-collar employment was coded as 1 – blue collar (which included employment in protective services, farming/fishing/forestry, service, construction, production, and don't know) and 0 - otherwise.

4.7. Other variables

Models were adjusted for age and sex/gender.

4.8. Analysis

To evaluate the association between death of parent before 18 and accelerated epigenetic aging, we used two approaches: 1) evaluation of the overall association and its sensitivity to confounding or downstream risk factors and 2) a formal test of the pathways. The first approach uses a series of linear regression models to evaluate the sensitivity of the association between death of a parent before age 18 and accelerated epigenetic aging. In the first model, we only included death of a parent and controls for age and sex. In the second model, we added childhood socioeconomic adversity to evaluate whether childhood parental loss may, in part, be associated with overall adverse socioeconomic conditions in childhood, which may be a result of parental loss or co-occurring with it. Next, we evaluated the sensitivity of the effect of parental loss before 18 on epigenetic aging after adjusting for three potential pathways independently: education (Model 3), smoking (Model 4), and depression Model (5). In Model 6, we include all covariates. We also presented the standardized versions of these results for ease of interpretation of the epigenetic age indicators, which are available as supplementary tables.

Next, to formally test our hypothesis regarding pathways, we used mediation analysis with 1000 bootstraps. Each pathway was tested independently but includes the adjustments for all other covariates. In other words, the underlying model for the mediation analysis is equivalent to Model 7 in the regression models, but tests for the direct and indirect effects of loss of parent before 18 b y each potential pathway independently (education, smoking, and depression).

All analysis were conducted in R using the svyglm and mediation packages. Sampling weights, provided from the HRS, were used for all analysis to account for complex sampling design.

5. Results

Weighted descriptive statistics are shown in Table 1. The average PhenoAge was 66 and average GrimAge was 77. The average DunedinePace of aging value was 1.02.11% of the sample experienced parental death before 18. The average number of socioeconomic childhood adversity conditions was 1.08. The average years of completed schooling was 13.3. The average CESD score was 1.3. The average smoking pack years was 13. Lastly, the average chronological age of the sample was 69 and 46% of the sample were men.

OLS regression results evaluating the association between parental loss before 18 and accelerated epigenetic aging are shown in Tables 2–4. Each epigenetic age measure is associated with a different table. Table 2

Table 1
Weighted descriptive statistics for analytical (N = 3382).

	Mean/%	SD	Range
PC PhenoAge	66	11	38.2–125.9
PC GrimAge	77	8	58.9–108.5
DunedinPace	1.02	0.15	0.63–1.74
Parental Death Before 18	11%		
Child Socioeconomic Adversity	1.08	1.28	0–4
Number of Years of Schooling	13.3	3	0–17
CESD Score	1.3	1.9	0–8
Smoking Pack Years	13	20	0–138
Age	69	9	56–100
Men	46%		

Table 2
Linear regression predicting accelerated epigenetic aging (PhenoAge) from parental death before 18 (health and retirement study VBS 2016; N = 3382).

	PC PhenoAge					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Parent Died Before 18	1.008*	0.803*	0.759^{+}	0.744^{+}	0.742^{+}	0.662^{+}
Childhood SES Adversity		0.409***	0.197^{+}	0.286*	0.403***	0.115
Years of Schooling			−0.236***			−0.200***
Depression (CESD)				0.412***		0.367***
Pack-Years					0.031***	0.026***
Age	0.027^{+}	0.021	0.014	0.026	0.014	0.013
Male	1.821***	1.854***	1.945***	1.989***	1.637***	1.870***

Note: $^{+}$p <0.1, *p < 0.05, **p < 0.01, ***p < .001.

Table 3
Linear regression predicting accelerated epigenetic aging (GrimAge) from parental death before 18 (health and retirement study VBS 2016; N = 3382).

	PC GrimAge					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Parent Died Before 18	0.172	0.085	0.045	0.051	−0.066	−0.113
Childhood SES Adversity		0.174*	−0.019	0.104	0.160**	−0.032
Years of Schooling			−0.215***			−0.162***
Depression (CESD)				0.235***		0.155***
Pack-Years					0.075***	0.072***
Age	0.007	0.004	−0.002	0.007	−0.014^{+}	−0.016^{+}
Male	3.104***	3.118***	3.201***	3.195***	2.588***	2.723***

Note: $^{+}$p <0.1, *p < 0.05, **p < 0.01, ***p < .001.

Table 4
Linear regression predicting accelerated epigenetic aging (DunedinPace) from parental death before 18 (health and retirement study VBS 2016; N = 3382).

	DunedinPace					
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Parent Died Before 18	0.024**	0.014	0.013	0.013	0.012	0.009
Childhood SES Adversity		0.020***	0.011***	0.017***	0.019***	0.009**
Years of Schooling			−0.010***			−0.009***
Depression (CESD)				0.011***		0.009***
Pack-Years					0.001***	0.001***
Age	0.002***	0.002***	0.002***	0.002***	0.002***	0.002***
Male	0.033***	0.035***	0.038***	0.038***	0.025**	0.032***

Note: $^{+}$p <0.1, *p < 0.05, **p < 0.01, ***p < .001.

contains PhenoAge, Table 3 contains GrimAge, and Table 4 contains DunedinPACE.

For PhenoAge (Table 2), we found that parental death before 18 was associated with approximately 1 year of accelerated epigenetic aging (Model 1). After adjusting for childhood SES, the acceleration with parental death was reduced to 0.8 years of accelerated aging but remains statistically significant. Next, we find that the association between parental death prior to 18 and accelerated aging is reduced to marginal significance with the inclusion of education (Model 3), depression (Model 4), and pack-years (Model 5). Each pathway was associated with accelerated epigenetic aging in the expected direction. Lastly, in Model 6, we include all covariates and find that the effect on epigenetic aging is reduced to 0.66 and remains marginally significant.

For GrimAge (Table 3), we found no association between parental death before 18 and accelerated epigenetic aging. All other covariates (child SES adversity, education, depression, and pack-years) were associated with accelerated GrimAge in the expected directions.

For DunedinPACE (Table 4), we found a strong association between accelerated epigenetic aging and parental death before 18 (CO: 0.02, p < 0.01). However, after adjusting for childhood socioeconomic adversity, the coefficient was reduced by half and was no longer associated with epigenetic age acceleration. All other covariates (Model 3–6) were associated with DunedinPACE in the expected directions.

Standardized results showing the same associations and reductions across epigenetic age measures are shown in Supplementary Tables 1–3. These results are provided for comparison across different epigenetic clocks on a similar scale. But differences across epigenetic clocks were not formally tested as it is not an objective of this study.

Next, we formally tested the pathways from parental loss before 18 and accelerated epigenetic aging with mediation analysis using 1000 bootstraps. Results are shown in Table 5 and only presented for PhenoAge and DunedinPACE because accelerated GrimAge was not associated with parental death before 18 as indicated by the regression models. Ancillary analysis for mediation on GrimAge confirmed this observation (results not shown).

Results for PhenoAge provided evidence of indirect effects from childhood parental death before 18 to accelerated epigenetic aging through education, depression, and smoking pack-years. The proportion mediated by education was 0.32. The proportion mediated by CESD was 0.20. The proportion mediated by smoking pack-years was 0.11. For DunedinPACE, the proportion mediated by education was 0.48. The proportion mediated by CESD was 0.22. The proportion mediated by smoking pack-years was 0.25.

6. Discussion

The present study examined the association between parental death before the age of eighteen with accelerated epigenetic aging. We also investigated potential education, depression, and smoking pathways through which parental death might lead to accelerated aging. We found

Table 5
Mediation Analysis of the Effect of Parental Death before 18 and Accelerated Epigenetic Aging (**PC PhenoAge and DunedinPace**) through Educational Attainment, Depressive Symptoms, and Smoking Behavior using 1000 Bootstraps (HRS VBS 2016, **N = 3382**).

PC PhenoAge	Education		Depressive Symptoms		Smoking	
	β	95% CI	*β*	95% CI	*β*	95% CI
Total Effect	0.43	[0.16, 1.37]	0.37	[0.13, 1.25]	0.34	[0.10, 1.27]
Direct Effect	0.30	[0.02, 1.23]	0.30	[0.02, 1.14]	0.30	[0.06, 1.23]
Indirect Effect	0.14	[0.06, 0.21]	0.07	[0.03, 0.19]	0.04	[0.01, 0.12]
Proportion Mediated	0.32	[0.07, 0.79]	0.20	[0.03, 0.80]	0.11	[-0.00, 0.42]

DunedinPace	Education		Depressive Symptoms		Smoking	
	β	95% CI	*β*	95% CI	*β*	95% CI
Total Effect	0.013	[0.002, 0.027]	0.008	[-0.001, 0.024]	0.008	[-0.000, 0.026]
Direct Effect	0.006	[-0.003, 0.021]	0.006	[-0.004 , 0.021]	0.006	[-0.003, 0.023]
Indirect Effect	0.006	[0.003, 0.008]	0.002	[0.001, 0.004]	0.002	[0.000, 0.005]
Proportion Mediated	0.48	[0.17, 2.11]	0.22	[-0.73, 2.01]	0.25	[-0.13, 1.59]

that parental death before age eighteen was associated with a 1.01 year increase in PhenoAge and 0.024 increase in DunedinPACE, but no significant association with GrimAge. Additionally, we provide evidence that educational attainment, depression, and smoking may be potential pathways that link early parental death to accelerated epigenetic aging. Although the inclusion of variables for these pathways reduced the association of early parental loss with epigenetic aging, this association remained statistically significant. The present study extends prior research to show the importance of parental death in early life for epigenetic aging—a hallmark of aging—that may put individuals at greater risk for health complications in later life, but much of the association may be from downstream risk factors which point to the potential modifiability of the health risk associated with parental death in early life.

While prior research has shown that people who experience the death of a parent in early life have a greater risk of depression, loneliness, cognitive impairment, functional limitations, poor self-rated health, and mortality in older adulthood (Donnelly et al., 2023; Kamis et al., 2022; H. Liu et al., 2022), we go further to show that this traumatic event is associated with epigenetic age acceleration – a potentially important biological mechanism that underlies age-related health risks. Research on epigenetic aging has already linked epigenetic age acceleration to disability, morbidity, and mortality (Crimmins et al., 2021; Faul et al., 2023). Therefore, while we do not directly evaluate accelerated epigenetic aging as a mechanism that links parental death in early life to poor later life health, we draw on the theoretical importance of prior research (López-Otín et al., 2013; Pal & Tyler, 2016) to show how early life experiences of parental death may become embodied and in turn affect health decades later. Thus, epigenetic aging may be one way that the "long arm of childhood" is established (Hayward & Gorman, 2004) and suggests childhood as a sensitive period (Murgatroyd & Spengler, 2011; Zhu et al., 2022) of the life course in which epigenetic changes associated with age acceleration are established. However, it is important to note that this study cannot ascertain the precise timing of epigenetic age acceleration with parental death in early life, which limits the interpretation of accelerated aging as a mechanism of aging linked to early life parental death. Future studies are needed to evaluate whether epigenetics age acceleration occurs close to the time of parental death, or if losing a parent in early life leads to years of accumulated changes that become evident in older adulthood as epigenetic signatures of accelerated aging.

We also found evidence that the association between parental death before 18 and accelerated epigenetic aging may be malleable based on the presence of significant mediators. Specifically, educational attainment, depressive symptoms, and smoking accounted for 11.4%–48.5% of the total effect of parental death before 18 on epigenetic age acceleration. As such, it could be argued that part of the association between parental death in early life and accelerated epigenetic aging results from downstream risk factors that are linked to parental death in early life. Therefore, epigenetic age acceleration from parental death in early life should not be viewed as an intractable life event that inevitably leads to elevated health risks in older adulthood. Rather, the presence of several mediators suggests that there are multiple pathways from which parental death in childhood and adolescence may shape health throughout the life course, which has also been found in other studies of mortality (Hiyoshi et al., 2021; Maier & Lachman, 2000). When considering the pathways presented in this study, it is also important to note that several of the pathways measured in this study are in themselves related to broader social, psychological, and economic factors that may lead to accelerated aging and are linked to several later life health conditions (Han et al., 2018; Klopack et al., 2022b). The aim of this study was not to fully account for the association between epigenetic aging and parental loss, but rather to provide scientific evidence that there are multiple pathways affecting this outcome. Future studies should consider how these mechanisms may overlap and correspond with other known risk factors that are key drivers of aging-related health outcomes.

Additionally, much like other studies that have evaluated accelerated epigenetic aging, we found mixed results across clocks (Klopack et al., 2022b; McCrory et al., 2021). Our results showed robust results for PhenoAge, a clock trained on mortality among older Italians, modest results for DunedinPACE, a clock trained on young to middle aged persons in New Zealand, and no results for GrimAge which was trained on older persons related to Framingham participants. Differences across clocks likely stem from differences in sampling and the phenotype these clocks were trained on – a "gold standard" that does not yet exist. For this reason, in research evaluating accelerated epigenetic aging, it is important to consider multiple clocks. Mixed findings might also be framed much like studies that evaluate different age-related health outcomes: the clocks, themselves, can be viewed as producing different signals of underlying age-related epigenetic changes that are associated with poor later life health broadly. This perspective suggests that clocks should be viewed as complementary rather than as a substitute for one another. Therefore, differences in findings would not be viewed as contradictory.

Despite research advancements linking early life hardship to accelerated aging, this study has important limitations to consider. While the epigenetic subsample of the HRS was designed to be nationally representative, selection processes may have led to more conservative estimates in this study as people who experience parental death in early life are more likely to be in poor health and die younger (Smith, 2014), which would preclude them from being in the sample. Additionally, we cannot ascertain the timing of epigenetic changes. Future studies are needed to evaluate whether DNA methylation signatures of parental death are observed shortly after the event in childhood. One way to evaluate more immediate changes would be to use samples on respondents at different ages, including younger ages, to better understand how the early life trauma of losing a parent may be directly tied to accelerated aging and how pathways may exacerbate these changes over time. Additionally, while we include education in the research design as a socioeconomic indicator, other unobserved confounders that are associated with education, such as cognitive abilities, may require

further exploration to better understand how and why education may be a pathway from which early life parental death is associated with accelerated aging. Lastly, smoking behavior, education, and depressive symptoms were chosen to represent three important pathways that are well-researched in the population health literature and are related to both the losing a parent in early life and accelerated epigenetic aging. Future research should investigate other important pathways such as marital history and loneliness.

Moreover, while it is not a limitation for this study, sociodemographic differences in the effect and pathways should be considered for future research. Prior research has shown that Black and Latinx individuals are more likely to experience parental death in early life than White individuals (Donnelly et al., 2023a; Umberson et al., 2017). Women may have greater risk of poorer health outcomes than men from parental loss in childhood (Liu et al., 2022a,b). We are unable to pursue this line of research due to sample size limitations.

The death of a parent in early life should be viewed as an important juncture in a young person's life that has the potential to cascade into a lifetime of hardship as evidenced by worse mental health, compromised physical health, and elevated mortality risk (Donnelly et al., 2023a; Liu et al., 2022a; Smith, 2014). We provide evidence that parental death in early life is associated with epigenetic changes that underlie several poor age-related health outcomes. We also find evidence of indirect effects through socioeconomic, psychological, and health behavior pathways, suggesting wide-ranging effects of parental death in early life on an individual's aging and health trajectory. In conclusion, our findings show that parental death in early life may be embodied through epigenetic age acceleration which may affect health decades later, but these findings also point to potential modifiability through multiple pathways that may weaken the link between parental death in early life and poorer health in later life.

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Ethical statement

The Health and Retirement Study received IRB approval from the University of Michigan. All respondents in this publicly available data set provide consent to the collection and the use of survey information. More information on the HRS can be found at: https://hrs.isr.umich.edu/sites/default/files/biblio/HRS_IRB_Information%28web%29_08_2018.pdf.

CRediT authorship contribution statement

Mateo P. Farina: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Eric T. Klopack:** Writing – review & editing, Methodology, Conceptualization. **Debra Umberson:** Writing – review & editing, Data curation, Conceptualization. **Eileen M. Crimmins:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

No conflicts of interest to report.

Data availability

The data are publically available through the Health and Retirement Study Website: https://hrs.isr.umich.edu/data-products. Analysis code is available at: https://github.com/mateofarina/SSMPH_ParentalLossgit.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2024.101648.

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