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Grandparents' educational attainment is associated with grandchildren's epigenetic-based age acceleration in the National Growth and Health Study

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ABSTRACT

We examined three generations (grandparents, mothers, and grandchildren) to assess the association between grandparents' educational attainment and their grandchildren's epigenetic-based age acceleration and whether the association was mediated by parental educational attainment and mothers' life course health-related factors. Mothers were recruited to the NHLBI Growth and Health Study at 9–10 years and followed for 10 years (1987–1998). Mothers were then re-contacted three decades later (ages 37–42) to participate in the National Growth and Health Study (NGHS), and health information from their youngest child (i.e., grandchildren; N = 241, ages 2–17) was collected, including their saliva samples to calculate epigenetic age. Five epigenetic-based age acceleration measures were included in this analysis, including four epigenetic clock age accelerations (Horvath, Hannum, GrimAge, and PhenoAge) and DunedinPACE. Grandparents reported their highest education during the initial enrollment interviews. Parental educational attainment and mothers' life course health-related factors (childhood BMI trajectories, adult cardiovascular health behavioral risk score, and adult c-reactive protein) are included as mediators. Grandparents' education was significantly associated with Horvath age acceleration ($b = -0.32$, $SE = 0.14$, $p = 0.021$). Grandchildren with college-degree grandparents showed significantly slower Horvath age accelerations than those without college degrees. This association was partially mediated by parental education and mothers' health-related factors, especially adult cardiovascular health behavioral risk score and CRP, but not mothers' childhood BMI trajectory. This ability to conserve the speed of biological aging may have considerable consequences in shaping health trajectories across the lifespan.

1. Introduction

Socioeconomic status (SES) is a fundamental cause of health disparities – its impact on health is consistent over time despite the remarkable advancements in medical technology and efforts to reduce disease risk factors (Link and Phelan, 1995; Phelan et al., 2004). The increased understanding of the importance of early life as a sensitive developmental period for health across the lifespan (Halfon and Hochstein, 2002) has led to a growing interest in integrating the life course frameworks to study the impact of SES on health (Ben-Shlomo and Kuh, 2002; Jones et al., 2019). Instead of solely focusing on the role of adult SES (e.g., educational attainment or current income), the focus is on the critical role of early life socioeconomic context (e.g., parental education or family income growing up) in shaping lifespan health trajectories (Cohen et al., 2010). Growing up in a low SES environment increases the likelihood of exposure to environmental and psychosocial

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stressors (Evans, 2004; Evans et al., 2013), with a potentially permanent shift in health trajectories across the lifespan (Miller et al., 2011; Shonkoff et al., 2009; Taylor, 2010). In the past two decades, there has been increasing empirical evidence on the direct association between early life SES and adult health outcomes (Cohen et al., 2010; Evans, 2016; Milaniak and Jaffee, 2019; Steptoe and Zaninotto, 2020). More recently, multiple recommendations suggest exploring the intergenerational impact of socioeconomic disadvantage on health (Drake and Liu, 2010; Jones et al., 2019). Exposure to early life social disadvantage may not only be consequential in shaping one's health trajectories across the lifespan but may also have a long-lasting impact on the offspring's health. However, there is a lack of empirical efforts to examine how exposure to social disadvantage in one generation is translated into compromised development and health of the next generation. This analysis examined how grandparents' educational attainment, a proxy of parents' early rearing socioeconomic context, can have a long-lasting impact on grandchildren's health outcomes.

Epigenetics is hypothesized to be the primary biological mechanism that links early life socioeconomic disadvantage in one generation with compromised health and well-being of their offspring (Drake and Liu, 2010; Perez and Lehner, 2019; Scorza et al., 2019). Evidence of epigenetic intergenerational transmission in humans comes from studies involving the offspring of survivors of traumatic experiences. Exposure to the Holocaust and Tutsi genocide affects the methylations of genes responsible for glucocorticoid regulation among the survivors and their offspring (Perroud et al., 2014; Yehuda et al., 2016). In addition, the Dutch famine impacted the DNA methylation status of the survivors' offspring, especially at genes implicated in growth, development, and cardiometabolic functions (Heijmans et al., 2008; Tobi et al., 2009). Exposure to environmental and psychosocial stressors in early life can lead to epigenetic changes, including DNA methylation, in gamete cells (Scorza et al., 2019). These epigenetic changes that happen long before conception can be manifested in their offspring's epigenetic makeup, given that some DNA methylation can be stably heritable through cell divisions and preserved during the maturation of the gamete cells (Hur et al., 2017). In this analysis, we were interested in understanding whether exposure to a more typical social disadvantage, namely growing up in a low SES environment, was associated with differences in the next generation's epigenetic markers, especially epigenetic age. Epigenetic age (also called epigenetic clock) is a novel DNA-methylation-based marker of aging that reflects an overall estimate of cellular or biological age relative to the chronological age (Horvath, 2013; Horvath and Raj, 2018). The epigenetic clocks are designed to predict morbidity and mortality (Dhingra et al., 2018; Horvath and Raj, 2018) and have been validated across multiple age groups, including pediatric samples (Horvath and Raj, 2018).

However, there are open questions regarding how exposure to social disadvantage in one generation can be epigenetically transmitted intergenerationally. Most of our understanding regarding the mechanisms of epigenetic intergenerational transmission of social disadvantage is based on animal studies, primarily focusing on the paternal effects to narrow down the transmission via gametes (C. Buss et al., 2017; Perez and Lehner, 2019). More recently, there has been growing interest in understanding the role of maternal effects on epigenetic transmission of social disadvantage (C. Buss et al., 2017; Scorza et al., 2019). Exposure to early social disadvantage can create epigenetic alterations in maternal germline (oocytes) that can be transmitted to the offspring (Scorza et al., 2019). However, intergenerational transmission through maternal effects can occur indirectly through maternal health-related consequences of early life social disadvantages (e.g., dysregulation of metabolic and immune systems) that alter the oocyte cytoplasm and gestational biological environment (C. Buss et al., 2017). For example, early life socioeconomic disadvantage increases the likelihood of maternal obesity (Frederick et al., 2014), which can alter oocyte cytoplasm during pregnancy and compromise fetal development (Wu et al., 2015).

In addition, maternal exposure to early life adversity is associated with immune system programming that biases function toward proinflammatory tendencies (Miller et al., 2011). This, combined with unhealthy behaviors, can alter the gestational environment toward elevated stress arousal, including higher prenatal cortisol levels (Claudia Buss et al., 2016) and placental corticotrophin-releasing hormone production (Moog et al., 2016), which can compromise fetal development. Several studies showed that maternal childhood adversity is associated with surrogate measures of intrauterine growth restriction (i.e., preterm birth and low birth weight), independent of pregnancy stressors (Margerison-Zilko et al., 2017), or as a modifying factor for the effect of prenatal psychological distress on birth outcomes (Blackmore et al., 2016). Taken together, these early findings show that early adversity is linked to maternal health pregnancy outcomes that may also influence offspring's epigenetic makeup. This indicates that it is crucial to examine the role of life course health-related consequences of early life social disadvantages on mothers that may mediate the association between maternal early life SES and their offspring's epigenetic outcomes.

Finally, research on socioeconomic inheritance and mobility in the United States indicated a strong association of education, income, and wealth across generations with restricted opportunities for upward mobility (Chetty et al., 2014; Torche, 2015). Mothers who grew up in low SES families are more likely to have lower education, income, and wealth levels than those from high SES families. Thus, the impact of maternal exposure to low SES during childhood on their offspring's epigenetic age may be mediated through the mother's own SES. However, there is a lack of empirical evidence that shows the intergenerational impact of cumulative socioeconomic disadvantages on epigenetic age.

1.1. The current analysis

The NHLBI Growth and Health Study ("Obesity and cardiovascular disease risk factors in black and white girls: the NHLBI Growth and Health Study," 1992; Tomiyama et al., 2013) and the follow-up National Growth and Health Study (NGHS) (Laraia et al., 2021, 2023) provide a unique opportunity given the availability of information from three generations, including grandparents' SES, parental education, mothers' life course health-related factors, and grandchildren's epigenetic age. The present analysis examined the association between grandparents' educational attainment and their grandchildren's epigenetic-based age acceleration. Grandparents' SES represents a proxy for mothers' early rearing experiences and their probability of being exposed to environmental and psychosocial stressors. While maternal prenatal information was unavailable, the NHLBI Growth and Health Study and NGHS included detailed information regarding maternal childhood body mass index (BMI) from age 10 to 19, adult cardiovascular health behavioral risk score, and adult inflammation, which are important factors for affecting the maternal gestational environment and fetal development (Claudia Buss et al., 2016; Margerison-Zilko et al., 2017; Moog et al., 2016; Wu et al., 2015). This analysis aimed to examine the mediating role of these factors on the association between grandparents' educational attainment and their grandchildren's epigenetic-based age acceleration. The hypothesized mediation model is presented in Fig. 1.

2. Methods

2.1. Data and participants

Data were derived from the National Growth and Health Study (NGHS), a longitudinal cohort study focusing on the lifespan development and intergenerational transmission of health among a diverse population. The NGHS study is a follow-up to the National Heart, Lung, and Blood Institute (NHLBI) Growth and Health Study (1987–1997). Details on participants' recruitment and data collection protocol of the original NHLBI Growth and Health Study have been provided elsewhere

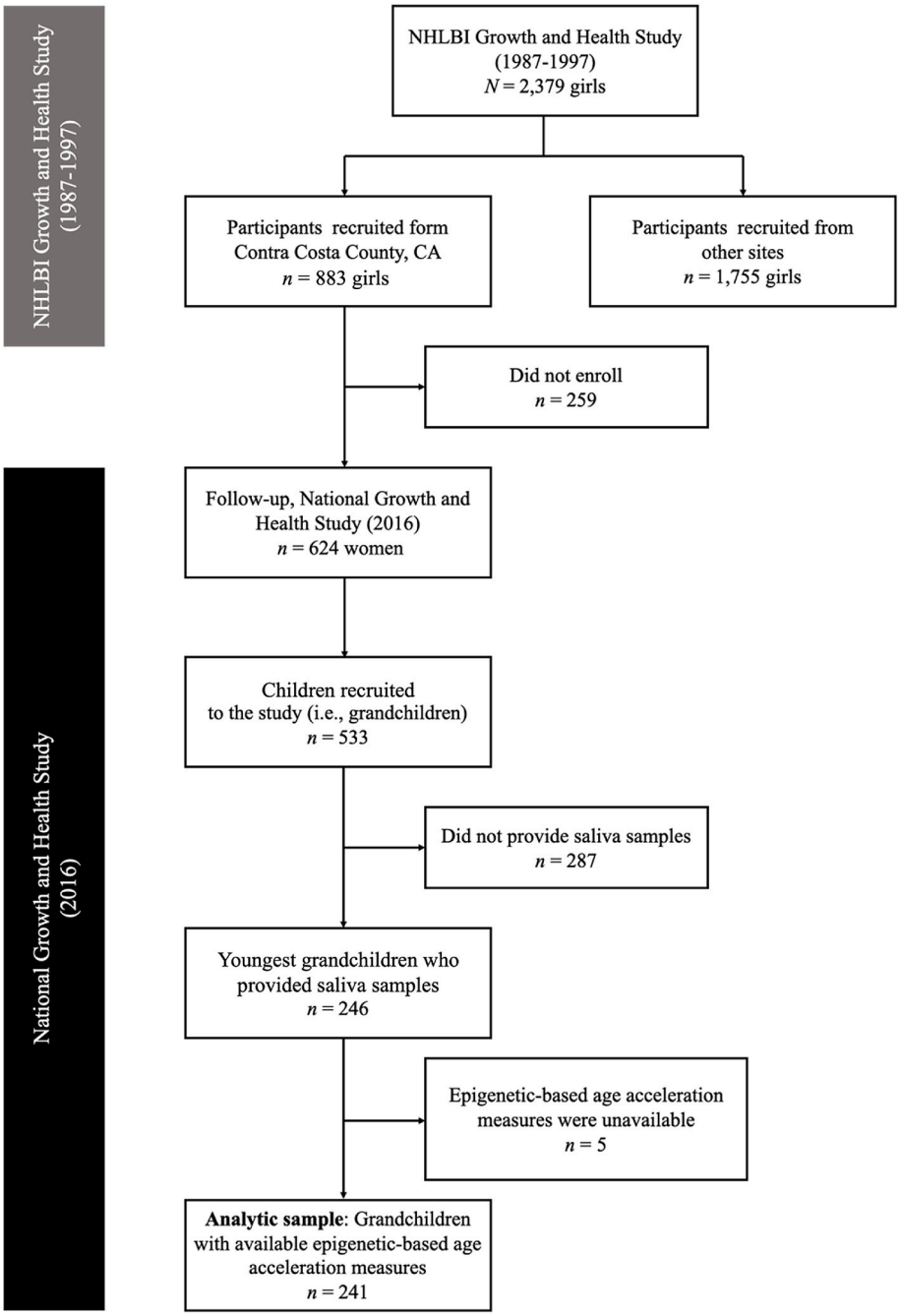

Fig. 1. Selection of the analytic sample in this analysis. Out of 533 grandchildren recruited to participate in the follow-up NGHS study, 287 did not provide saliva samples due to not being the youngest or not returning samples, resulting in 246 youngest grandchildren who provided saliva samples. The final analytic sample include 241 grandchildren with available epigenetic-based age acceleration measures.

("Obesity and cardiovascular disease risk factors in black and white girls: the NHLBI Growth and Health Study," 1992; Tomiyama et al., 2013). Briefly, 2379 Black and white girls (n Black = 1213) ages 9 to 10 were recruited from public and parochial schools (Cincinnati, OH, and Contra Costa County, CA) and families enrolled in a health maintenance organization (Washington, DC). Parents of these girls reported their highest educational attainment during the baseline survey (1987–1988). Information regarding psychosocial, behavioral, and biological factors associated with the development of obesity was collected annually for ten consecutive years, including girls' body mass index (BMI).

Almost three decades after being recruited to the NHLBI Growth and Health Study, the Contra Costa County participants were re-contacted to enroll in the NGHS. Inclusion criteria to participate in NGHS include: 1) participated in the NHLBI Growth and Health Study, 2) not being pregnant at the time of recruitment, and 3) resided in the United States and not currently incarcerated. There were 887 eligible NHLBI Growth and Health Study participants from Contra Costa County. The NHLBI Growth and Health Study participants from Contra Costa County showed similar sociodemographic characteristics relative to the rest of the participants from other study sites (see Supplemental Material 1), including racial composition (χ^2 [df = 1] = 1.08, p = 0.31), highest parental education level (χ^2 [df = 1] = 3.72, p = 0.06), and childhood family income (χ^2 [df = 1] = 2.50, p = 0.12). Among eligible Contra Costa participants, 624 (n Black = 307) enrolled in the NGHS (retention rate = 70%). Women who did not enroll in NGHS were more likely to be Black (χ^2 [df = 1] = 4.76, p = 0.03), less likely to have parents with a

college degree (χ^2 [$df = 1$] = 7.00, $p = < 0.01$), and more likely to have lower childhood income (χ^2 [$df = 1$] = 9.55, $p = < 0.01$).

The women in NGHS were in their early midlife (36–43 years) when enrolled in the NGHS, and almost three-fourths reported having at least one biological child (73.7%; *M* number of children = 1.51. *SD* = 1.25). Participants' youngest (most recently born) children, ages 2 to 17, were recruited to the study to examine the intergenerational transmission of stress and health ($N = 553$; enrollment rate = 86%). Women with and without biological children in NGHS showed similar sociodemographic characteristics based on race (χ^2 [$df = 1$] = 0.45, $p = 0.52$), highest education (χ^2 [$df = 1$] = 0.94, $p = 0.35$), household income (χ^2 [$df = 1$] = 3.76, $p = 0.06$). As expected, women with biological children were more likely to be married (χ^2 [$df = 1$] = 31.54, $p = < 0.001$).

Data collection protocol in NGHS includes completing baseline questionnaires, home visits for anthropometric measurements and saliva sampling, LabCorp visits to draw blood, and a 3-day food and physical activity diary. Fasting blood samples were collected from mothers during the LabCorp blood draw visit at UC Berkeley. Blood was collected into a green-top (heparin) tube and assayed at the nearest LabCorps clinic. The blood was spun within 1 h of drawing. Children's saliva samples were collected during in-home visits by trained staff using Oragene DNA Collection Kits (OG-500, or OG-575 with a swab for younger children). Specimens were stored at UC Berkeley until further assessment.

The analytic sample of the current analysis includes children with data on epigenetic age (see Fig. 1). Of 533 enrolled children, 246 provided saliva samples for epigenetic-based age acceleration measures based on being the youngest child. Five children were excluded from the analytic sample due to missing data on epigenetic-based age acceleration measures. The final analytic sample includes 241 children (52.7% female; $M_{age} = 8.23$, $SD_{age} = 4.01$, $range_{age} = 2–17$) with available epigenetic-based age acceleration information. The information included in this analysis came from three generations (see Fig. 2), the parents of the girls in the original NHLBI Growth and Health Study (referred to as grandparents/F0), the original girls/women participants of NGHS (referred to as mothers/F1), and the children of the NGHS women participants (refer as grandchildren).

2.2. Measures

2.2.1. Grandparents' educational attainment

Demographic and household information was obtained from the girls' parents during the baseline survey of the NHLBI Growth and Health Study (1987–1988), including parental highest education. We refer to this information as grandparents' educational attainment in this analysis. Grandparents' highest education was grouped into three categories, high school degree or less, some college, and college degree or higher. For the current analysis, the grandparents' education was dichotomized into no college degree and a college degree or higher.

2.2.2. Grandchildren's epigenetic-based age acceleration

DNA methylation analyses with saliva samples were performed at the Semel Institute UCLA Neurosciences Genomics Core (UNGC) using the Illumina Infinium Methylation EPIC BeadChip. All the saliva samples from all the participants in the NGHS study (including grandchildren and mothers) was analyzed together. Genomic DNA was isolated using temperature denaturation and subjected to bisulfite conversion, PCR amplification, and DNA sequencing (EZ DNA Methylation-Gold Kit, Zymo Research). Epigenetic clocks were calculated using the Horvath's online calculator https://dnamage.genetics.ucla.edu/, in which missing CpGs were automatically imputed and BMIQ method (Teschendorff et al., 2013) was used to normalize the data.

Four epigenetic clocks were included in this analysis: Horvath (2013), Hannum (Hannum et al., 2013), GrimAge (Lu et al., 2019), and PhenoAge (Levine et al., 2018). The Horvath and Hannum epigenetic clocks were derived from DNA methylation analysis of chronological age, while the GrimAge and PhenoAge clocks were developed from DNA methylation analysis of mortality risk. Recent studies have utilized these clocks to examine epigenetic age among pediatric samples (Etzel et al., 2022; Raffington et al., 2021). Details regarding criterion, interpretation, and discovery sample for each epigenetic clock have been summarized elsewhere (Raffington and Belsky, 2022). Epigenetic clock age

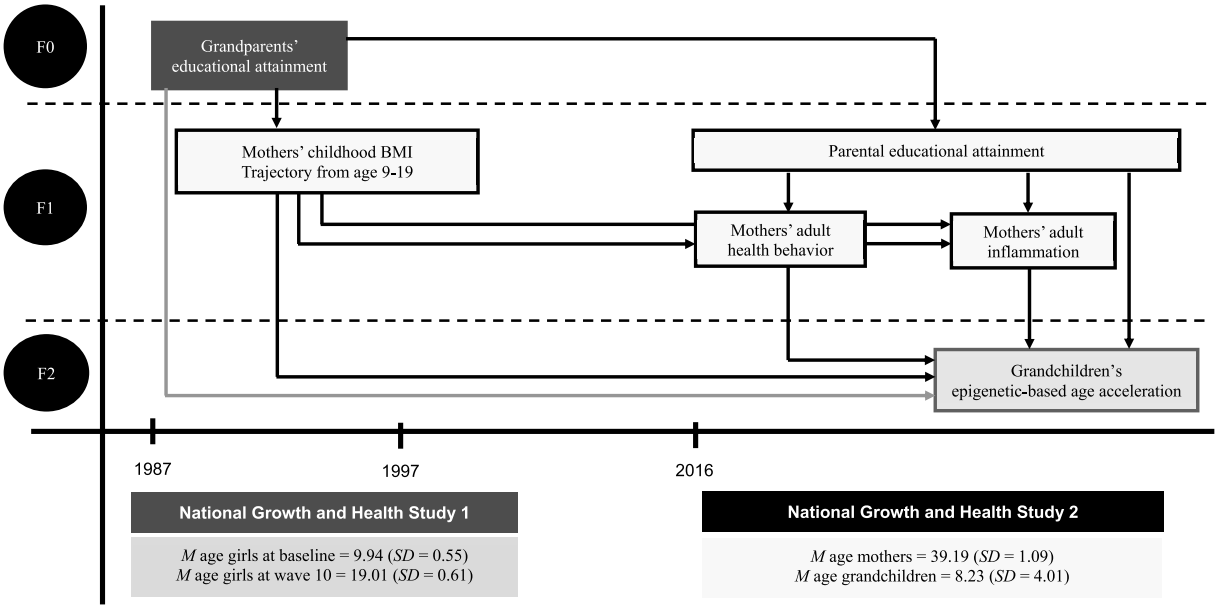

Fig. 2. Variables included in the current analysis came from the NHLBI Growth and Health study (1987–1997) and the follow-up National Growth and Health Study (NGHS). The combined information resulted in data from three-generation, including grandparents (F0), mothers (F1), and grandchildren (F2). The gray line represents the main goal of the current analysis, to examine the association between grandparents' educational attainment as a socioeconomic context of mothers' early rearing on grandchildren's epigenetic-based age acceleration. The black lines represent the hypothesized mediational model of the pathways from grandparents' education to grandchildren's epigenetic age through parental education and mothers' life course health-related factors (childhood BMI trajectories, adult cardiovascular health behavioral risk score, and adult inflammation).

acceleration was calculated by regressing the chronological age on epigenetic clocks and keeping the residuals from the model. Positive values represent higher epigenetic age than chronological age (i.e., accelerated aging) and vice versa. In addition, this analysis included DunedinPACE, which used within-individual decline across 19 biological indicators of organ-system integrity as the predicted phenotype (Belsky et al., 2022). DunedinPACE score represents years of biological aging occurring per 12 months of chronological time (Belsky et al., 2022). A recent study involving pediatric samples has used saliva-based DunedinPACE to measure the pace of aging (Perret et al., 2023). DunedinPACE scores were calculated using an R package available on GitHub (https://github.com/danbelsky/DunedinPACE/). We computed cell-count residuals of all measures of epigenetic-based age accelerations by regressing each outcome on the mixtures of buccal epithelial cells and white blood cells estimated using the *EpiDISH* package in R (Zheng et al., 2018). To ensure that all outcomes are on the same scale, epigenetic-based age acceleration measures were z-transformed.

2.2.3. Parental education and life course health-related mediators

Parental SES was based on their highest formal educational attainment. When mother and father's education were available, we used the highest education among them. Mothers' life course health-related mediators include mothers' childhood Body Mass Index (BMI) trajectories, adult cardiovascular health behavioral risk score, and adult c-reactive protein (CRP). During the ten years of the NHLBI Growth and Health Study, data on girls' BMI (kg/m^2) was collected annually. Information regarding parental highest educational attainment (high school or less, some college, or college degree and higher) was collected during the follow-up study. Parental highest education was dichotomized into no college degree versus college degree and higher. Furthermore, mothers' adult cardiovascular health behavioral risk score was the sum of Life's Simple seven behavioral factors, including physical activity, diet quality, BMI, and smoking behavior. Each behavioral factor was rated as either poor (scored as 0), intermediate (scored as 1), or ideal (scored as 2) based on the predefined criteria (possible range = 0–8; a higher score represents better health behavior) (Unger et al., 2014). Finally, the mothers' adult CRP was assayed from fasting blood specimens using an Immunochemiluminometric assay (ICMA) on the Integra 800. The intra-assay coefficient of variability (CV) was 1.3%, and the inter-assay CV was 3.1%. Due to normality concerns, the raw CRP values were transformed by natural log (*ln*).

2.3. Analytic strategy

Analyses were divided into two parts. First, the association between grandparents' education and grandchildren's epigenetic age acceleration was examined using linear regression analysis, adjusted for grandchildren's age (years) and sex (0 = male, 1 = female). Grandchildren's BMI (kg/m^2), mother's childhood family structure (0 = single parent, 1 = two parents), and mother's current marital status (0 = others, 1 = currently married) were then added as an additional covariate in the fully adjusted model. Second, multilevel structural equation modeling (MSEM) was utilized to formally examine the mediating role of mother's educational attainment and life course health-related factors, including childhood BMI trajectories, adult cardiovascular health behavioral risk score, and adult c-reactive protein (CRP). Our mediators comprised information from multiple levels of analysis. In this analysis, mothers' longitudinal childhood BMI from age 9–19 was nested within people, resulting in two levels of analysis (within- and between-person). Thus, we examined our mediational hypotheses using the multilevel structural equation modeling (MSEM) framework. MSEM framework combines the benefits of multilevel modeling and structural equation modeling in which nested data are partitioned into within- and between-person components while simultaneously testing path models such as our hypotheses. The full hypothesized mediation model is presented in Fig. S2.

Required pre-analysis steps were performed before running the hypothesized models, including extensive data assessment, cleaning, and missing data examination (Surachman et al., 2019). Data were inspected for the potential univariate (through standardized scores, $|z| \geq 3.30$) and multivariate (Mahalanobis Distance $p < 0.001$ and Studentized Deleted Residual greater than ± 4.00) outliers. We retained all the data as there was no evidence of severe or multivariate outliers. Missing data

Table 1
Grandchildren's and mothers' characteristics based on grandparents' education level ($N = 241$).

Characteristics	All Participants	Missing Data (*n*)	Grandparents' Education		
			No college degree ($n = 172$; 71.4%)	College degree ($n = 69$; 28.6%)	$\lvert t/\chi^2 \rvert$
Grandchildren's characteristics					
Mean age (*SD*)	8.23 (4.01)	–	8.42 (4.02)	7.75 (3.99)	1.16
% Female	52.7	–	54.1	49.3	0.45
Mean body mass index (*SD*)	19.85 (5.08)	–	20.19 (5.24)	19.01 (4.59)	1.63
Mothers' characteristics					
Mean age	39.19 (1.09)	–	39.17 (1.02)	39.23 (1.27)	0.33
% Black	49.4	–	56.4	31.9	11.84**
% Married/living with a partner	65.8	1	60.8	78.3	6.65*
Parental educational attainment					
% College degree or higher	41.9	–	32.0	66.7	24.34***
Mothers' mean childhood body mass index (*SD*)					
Baseline ($M_{age} = 9.94$, $SD_{age} = 0.55$)	18.47 (3.42)	2	18.57 (3.38)	18.22 (3.52)	0.71
Wave 2 ($M_{age} = 10.89$, $SD_{age} = 0.57$)	19.49 (3.89)	11	19.62 (3.85)	19.16 (3.98)	0.81
Wave 3 ($M_{age} = 11.91$, $SD_{age} = 0.60$)	20.47 (4.19)	18	20.60 (4.16)	20.15 (4.28)	0.72
Wave 4 ($M_{age} = 12.90$, $SD_{age} = 0.57$)	21.66 (4.44)	14	21.93 (4.43)	20.98 (4.44)	1.45
Wave 5 ($M_{age} = 13.90$, $SD_{age} = 0.59$)	22.66 (4.51)	21	22.96 (4.50)	21.87 (4.47)	1.61
Wave 6 ($M_{age} = 14.91$, $SD_{age} = 0.58$)	23.27 (4.70)	30	23.63 (4.73)	22.35 (4.54)	1.79
Wave 7 ($M_{age} = 15.96$, $SD_{age} = 0.57$)	23.65 (4.78)	29	24.20 (5.02)	22.38 (3.92)	2.84**
Wave 8 ($M_{age} = 16.98$, $SD_{age} = 0.58$)	23.94 (4.95)	20	24.45 (5.17)	22.65 (4.15)	2.47**
Wave 9 ($M_{age} = 17.90$, $SD_{age} = 0.59$)	24.47 (5.40)	21	25.06 (5.66)	22.98 (4.38)	2.62**
Wave 10 ($M_{age} = 19.01$, $SD_{age} = 0.61$)	24.88 (5.86)	10	25.58 (6.19)	23.08 (4.50)	3.41**
Mean change from baseline to wave 10	6.53 (4.30)	12	7.02 (4.61)	5.28 (3.08)	3.30**
Mothers' adult cardiovascular health behavioral risk score					
Mean Life's Simple 7 behavior component (*SD*)	3.94 (1.99)	3	3.62 (1.91)	4.71 (1.97)	3.90***
Mother's adult inflammation					
Ln C-reactive protein (mg/L; *SD*)	0.64 (1.17)	35	0.68 (1.14)	0.52 (1.23)	0.92

Note: *SD* = standard deviation; $\lvert t/\chi^2 \rvert$ = statistics from t-tests (for continuous variables) or chi-square tests (for categorical variables) on sociodemographic variables based on grandparents' education.

are minimal in the data set (see Table 1). Most of the missing data are related to information regarding mothers' childhood BMI and mothers' adult CRP.

We examined our mediational hypotheses by fitting the hypothesized model see Fig. 2). Mothers' childhood BMI trajectory was analyzed by fitting the random BMI trajectory slope based on the association between study wave and BMI at the within-person level. This slope represents the changes in BMI as the study progressed from baseline to wave 10. The random BMI trajectory slope was modeled at the between-level as a latent variable representing mothers' latent childhood BMI trajectory. The full mediation model was tested at the between-person level, focusing on the mediating roles of latent mothers' childhood BMI trajectory, education level, adult cardiovascular health behavioral risk score, and adult CRP on the association between grandparents' educational attainment and grandchildren's epigenetic age acceleration. Grandparents' educational attainment was hypothesized to be directly associated with parental educational attainment and mothers' latent childhood BMI trajectory. In turn, both parental educational attainment and latent childhood BMI trajectory were hypothesized to be associated with mothers' adult cardiovascular health behavior risk score. Both latent childhood BMI trajectory and mothers' adult cardiovascular health behavior risk score were hypothesized to be associated with mothers' adult CRP. Finally, grandparents' educational attainment and all the mediators were hypothesized to be associated with grandchildren's epigenetic age acceleration. Indirect effects and their associated statistical significance were tested using the MODEL INDIRECT command (Mehta and Neale, 2005). For the full mediation model, there were 8 possible indirect effects, including: 1) Grandparents' educational attainment → parental educational attainment → grandchildren's epigenetic age acceleration; 2) Grandparents' educational attainment → parental educational attainment → mothers' adult cardiovascular behavioral risk score → grandchildren's epigenetic age acceleration; 3) Grandparents' educational attainment → parental educational attainment → mothers' adult CRP → grandchildren's epigenetic age acceleration; 4) Grandparents' educational attainment → parental educational attainment → mothers' adult cardiovascular behavioral risk score → mothers' adult CRP → grandchildren's epigenetic age acceleration; 5) Grandparents' educational attainment → mothers' latent childhood BMI trajectory → grandchildren epigenetic age acceleration; 6) Grandparents' educational attainment → mothers' latent childhood BMI trajectory → mothers' adult cardiovascular behavioral risk score → grandchildren epigenetic age acceleration; 7) Grandparents' educational attainment → mothers' latent childhood BMI trajectory → mothers' adult CRP → grandchildren epigenetic age acceleration; 8) Grandparents' educational attainment → mothers' latent childhood BMI trajectory → mothers' adult cardiovascular behavioral risk score → mothers' adult CRP → grandchildren epigenetic age acceleration.

The accuracy and fit of the models were assessed using multiple criteria, including various fit indices to determine the overall goodness of fit, evaluating whether there were specific areas of strain in the solution, and examining the magnitude, significance, and interpretability of the model's parameter estimates (Mehta and Neale, 2005). The full hypothesized mediational model was then modified by removing the non-significant paths. All analyses were conducted using MPlus version 8.8 (Muthén & Muthén, 1998–2017). Throughout the analysis, we used the maximum likelihood estimation with robust standard errors to deal with missing data.

3. Results

Mothers' and grandchildren's characteristics based on grandparents' educational attainment are shown in Table 1. Grandchildren's age, sex, and BMI did not differ between grandparents' education groups. Mothers with lower parental education (i.e., grandparent's education = no college degree) tend to self-identify as Black. They are less likely to earn a college degree and marry or live with a partner. Mothers with lower parental education showed similar BMI compared to those with higher parental education when recruited to the study as girls. Significant differences in mothers' childhood BMI based on grandparents' education were evident during middle to late adolescence when they were around 15–19 years old (see Table 1). In addition, mothers with lower parental education had worse adult cardiovascular health behavioral risk score but not c-reactive protein (CRP).

3.1. Grandparents' education and Grandchildren's epigenetic age acceleration

Adjusted for grandchildren's age and sex, grandparents' education was significantly associated with Horvath age acceleration ($b = -0.33$, $SE = 0.13$, $p = 0.012$). However, grandparents' educational attainment was not associated with grandchildren's Hannum ($b = -0.21$, $SE = 0.14$, $p = 0.14$), GrimAge ($b = -0.15$, $SE = 0.14$, $p = 0.27$), and PhenoAge ($b = -0.18$, $SE = 0.14$, $p = 0.20$) age accelerations, as well as DunedinPACE ($b = 0.16$, $SE = 0.13$, $p = 0.23$). Grandchildren with college degree grandparents showed slower Horvath age acceleration, relative to those with lower grandparents' education. The associations between grandparents' education and Horvath age acceleration remained significant in the fully adjusted model (Fig. 2; $b = -0.32$, $SE = 0.14$, $p = 0.021$). Full results from regression analyses are presented in Supplemental Material 3.

3.2. Results from mediation analyses

Mediation analyses were conducted to formally examine whether parental educational attainment and life course health-related factors mediated the association between grandparents' education and grandchildren's epigenetic age acceleration. We only conducted mediation analyses with the Horvath age acceleration measures since grandparents' education was not significantly associated with other epigenetic-based age acceleration measures. The hypothesized mediation model was mostly supported when looking at parental education and life course health-related factors' role in the association between grandparents' education and grandchildren's Horvath age acceleration (described below).

3.2.1. Grandparents' education, parental education and life course health-related factors, and Horvath epigenetic age acceleration

To test the hypothesized mediation model, we fitted the full mediation model (Fig. 1). Most of the paths in the hypothesized model were statistically significant (see Supplemental Material 4). The hypothesized model was simplified by excluding the non-significant paths. We refer to the modified model as the final model. The final model showed a better fit than the full hypothesized model (Hypothesized model: $AIC = 23566.89$, $BIC = 23757.74$, Adj. $BIC = 23652.89$; Final model: $AIC = 23564.82$, $BIC = 23732.53$, Adj. $BIC = 23640.39$). The results from the final model are presented in Fig. 4A. In the final model, grandparents' educational attainment was associated with both parental educational attainment ($Est = 0.35$ $SE = 0.07$, $p < 0.001$) and mothers' childhood latent BMI trajectory ($Est = -0.16$, $SE = 0.07$, $p = 0.014$). Higher grandparents' educational attainment was associated with higher parental educational attainment and slower childhood BMI increase from ages 9 to 19. In turn, higher parental educational attainment ($Est = 1.38$, $SE = 0.24$, $p < 0.001$) and slower BMI trajectory ($Est = -0.88$, $SE = 0.30$, $p = 0.003$) were significantly associated with better adult cardiovascular health behavioral score. Slower mothers' childhood BMI trajectory was also associated with lower mothers' adult CRP ($Est = 0.86$, $SE = 0.17$, $p < 0.001$). Similarly, better mothers' adult cardiovascular health behavioral score was associated with lower mothers' adult CRP ($Est = -0.18$, $SE = 0.04$, $p < 0.001$). Finally, mothers' adult CRP was significantly associated with grandchildren's Horvath age acceleration ($Est = 0.16$, $SE = 0.05$, $p = 0.003$). Lower mothers' adult CRP was associated with slower Horvath accelerated biological age. The

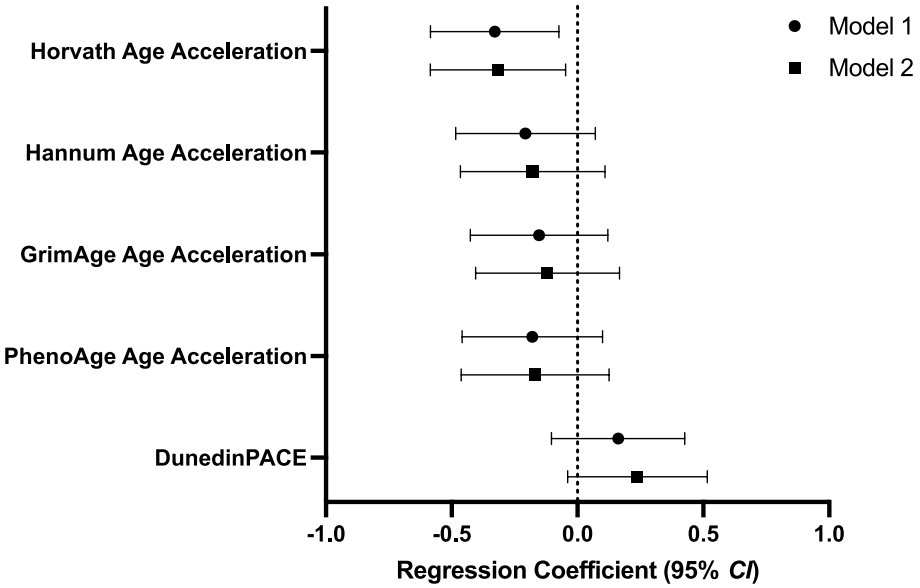

Fig. 3. The association between grandparents' education and epigenetic-based age acceleration measures (z-tranformed). In Model 1, grandchildren's age (years) and sex (0 = male, 1 = female) were included as covariates. In Model 2, the grandchildren's body mass index (BMI; kg/m^2), mother's childhood family structure (0 = single parent, 1 = two parents), and mother's current marital status (0 = others, 1 = currently married) were added as an additional covariate. Having grandparents with college degrees was associated with slower Horvath age acceleration in both minimally adjusted and full models.

association between grandparents' education and Horvath age acceleration remained significant in the final mediation model (*Est* = −0.29, *SE* = 0.13, $p = 0.023$; Fig. 3A). The total indirect effect, including all four mediators, was significant (*Est* = −0.04, *SE* = 0.02, $p = 0.028$; Fig. 4B). The only significant indirect effect of grandparents' education on grandchildren's Horvath age acceleration was through parental education, adult cardiovascular health behavioral risk score, and adult CRP (*Est* = −0.013, *SE* = 0.006, $p = 0.036$; Fig. 4B). Covariates added to the model include grandchildren's age, sex, BMI, mother's childhood family structure, and mother's marital status.

4. Discussion

This analysis was among the first to examine the impact of maternal early life SES on their offspring's (ages 2–17) epigenetic marker, specifically epigenetic-based age acceleration. Utilizing the information collected from three-generation (grandparents' education, parental education, and life course health-related factors, and grandchildren's epigenetic age), we found that grandparents' educational attainment, a proxy of socioeconomic context of maternal early rearing, was significantly associated with grandchildren's epigenetic clock age acceleration, especially Horvath age acceleration. Adjusted for sex and age, we found that grandchildren whose grandparents achieved a college degree showed slower biological age acceleration based on Horvath age acceleration measures. This significant association remained even after the adjustment for grandchildren's BMI, mothers' childhood family structure, and mothers' current marital status.

This analysis adds to the increasing number of empirical studies examining epigenetic age among children and adolescents. However, previous studies primarily focused on the impact of concurrent early life social disadvantage on accelerated biological age, including lower family and neighborhood SES (Raffington et al., 2021), early threat-related experiences (Sumner et al., 2019), and cumulative adverse childhood experiences (Tang et al., 2020). This analysis adds to the critical role of parental early life socioeconomic experience in shaping children's biological age. Our findings suggest that intergenerational socioeconomic advantage (i.e., higher grandparent education) might help slow down the biological age acceleration in early life. This ability to conserve the speed of biological aging may have considerable consequences in shaping health trajectories across the lifespan, especially in adulthood. However, more studies are needed to examine this hypothesis.

Understanding the biological and psychosocial pathways that might explain our findings is critical. We examined whether the association between grandparents' educational attainment and grandchildren's epigenetic age acceleration was mediated by parental educational attainment and life course health-related factors, including childhood BMI trajectories (age 9–19), adult cardiovascular health behavioral risk score, and adult inflammation (CRP). We found that while these factors did not fully explain the association between grandparents' educational attainment and grandchildren's epigenetic age acceleration, they were important mediators that explained 14.5% of the association between grandparents' educational attainment and grandchildren's Horvath age acceleration.

These findings raise multiple important points regarding the mechanisms of intergenerational transmission of social disadvantage and health through maternal factors. Our analysis found a moderate association between grandparents' and parental educational attainment. More importantly, we showed that these intergenerational SES contexts were associated with maternal health-related factors that may be associated with the epigenetic age of the grandchildren. First, we showed that grandparents' education was associated with mothers' BMI trajectories from age 9 to 19. This finding corroborates previous findings on the association between lower childhood SES and a higher probability of obesity (Frederick et al., 2014). In turn, we showed that steeper BMI trajectories were associated with two crucial maternal health-related factors in adulthood, adult cardiovascular health behavioral risk score and CRP. Other studies have shown similar results on the critical role of childhood BMI trajectories in shaping adult health outcomes, especially adult inflammation (Goosby et al., 2016). While we did not find a significant association between parental educational attainment and adult CRP, we showed that parental education was significantly associated with adult cardiovascular health behavioral risk score that, in turn, linked to CRP. Finally, we showed that mothers' adult CRP was directly associated with grandchildren's Horvath age acceleration. Together, these findings suggest that accumulating SES advantages and disadvantages across generations may play a critical role in the intergenerational transmission of health.

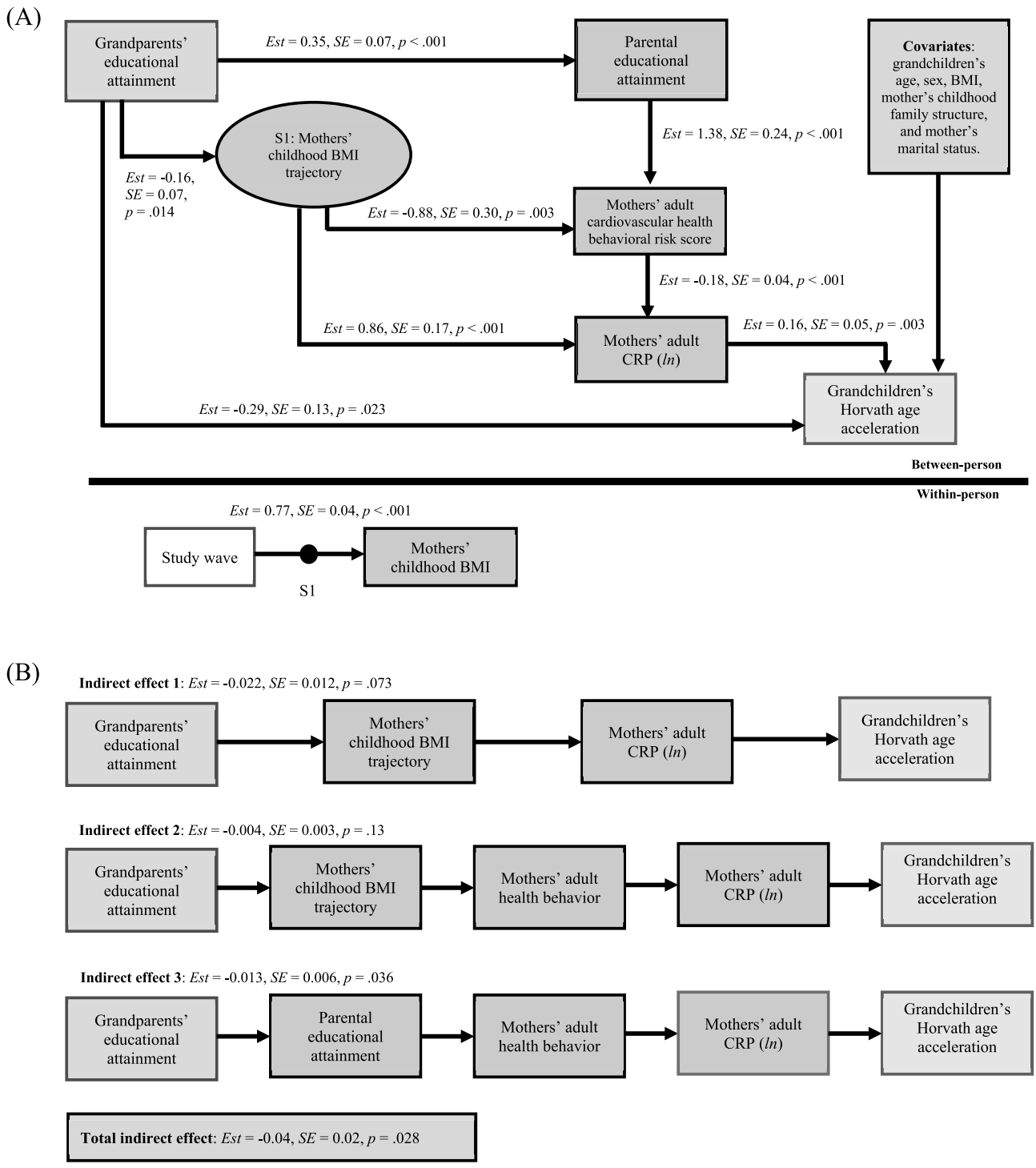

Fig. 4. A. The final model from the mediation analysis using multilevel structural equation modeling testing the mediating role of parental education and life course health-related factors on the association between grandparents' education and grandchildren's Horvath age acceleration. The circle represents a latent variable. Solid lines represent significant paths. S1 represents the random slope of the association between the study wave and mothers' childhood BMI. At the between-person, S1 represents the latent mothers' childhood BMI trajectory from age 9 to 19. Covariates added to the model include grandchildren's age, sex, BMI, mother's childhood family structure, and mother's marital status. B. Indirect effects from the final MSEM model. The total indirect effect was significant ($Est = -0.04$, $SE = 0.02$, $p = 0.028$), and the indirect path through parental education, mothers' adult health behavior, and adult CRP was also significant ($Est = -0.013$, $SE = 0.006$, $p = 0.036$).

The mechanisms for the transmission of grandparent SES to offspring epigenetics are unknown. While we showed that mothers' adult CRP correlated with their offspring's epigenetic age, this does not explain the mechanism of how DNA methylation is transmitted from mothers to their children. Here, we can only speculate. There could be direct transmission across generations of methylation patterns that are measured in the epigenetic clock composites. A likely pathway could be through fetal programming during the mother's pregnancy that influenced offspring epigenetics. Another hypothesis is that mothers' early life exposure to socioeconomic disadvantage is associated with the programming of the mother's immune system, leading to pro-inflammatory tendencies. Maternal dysregulation of the immune

system can directly impact the pregnancy environment and, eventually, the offspring's health outcomes. Furthermore, our findings show that lower early life SES was also associated with a higher risk of obesity and unhealthy behavior. These factors can also lead to chronic low-grade inflammation in adulthood, alter the biological environment during pregnancy, and compromise fetal development.

4.1. Study strengths and limitations

The growing rates of socioeconomic inequality and the persistent health disparities in the United States require a better understanding of the intergenerational impact of socioeconomic disadvantage on health. This analysis took advantage of the multi-generation design provided by the NHLBI Growth and Health Study and the follow-up National Growth and Health Study (NGHS). The historic and follow-up study's combined information provided a unique opportunity to examine an important question regarding the association between maternal early life SES and their offspring's epigenetic age. In addition, we took advantage of the longitudinal information from the historical data of the NHLBI Growth and Health Study, specifically focusing on BMI trajectories throughout the teenage years. We utilized advanced statistical modeling, namely multilevel structural equation modeling, to simultaneously examine the pathways from grandparents' educational attainment to grandchildren's epigenetic age through maternal socioeconomic and life course health-related factors. In light of these strengths, this analysis also has several limitations. While these studies included a diverse sample, they were recruited from the Bay Area, CA. Hence, the generalizability of these findings is limited. However, we showed that the Contra Costa County participants in NGHS showed similar childhood sociodemographic characteristics to the rest of the NHLBI Growth and Health Study participants from other study sites. Being a longitudinal cohort study, there were missing values among various measures. We addressed missing values through our analytical methods using robust maximum likelihood estimation with robust standard errors, which allowed us to retain the entire sample. Furthermore, we cannot differentiate maternal and paternal grandparents' educational attainment in this analysis. Future studies should prioritize replicating this study by dissecting the different pathways from maternal and paternal grandparents' education. In addition, our indicator of SES was limited to educational attainment, and future analyses should attempt to include other indicators of socioeconomic factors, including income, wealth, and subjective social status. Finally, the transmission of the socioeconomic disadvantage process is highly likely influenced by the structural factors known as crucial social determinants of health, such as residential segregation and systemic racism. Future investigation should attempt to test the role of these factors on the epigenetic intergenerational transmission of disadvantage.

4.2. Conclusion

In this analysis, we examined three generations (grandparents, mothers, and grandchildren) to assess the association between grandparents' educational attainment and their children's epigenetic age and whether the association was mediated by parental educational attainment and life course health-related factors. Grandchildren with college-educated grandparents showed significantly slower epigenetic clock age acceleration than those without college degrees. The association between grandparents' education level and grandchildren's age acceleration, especially Horvath age acceleration, was partially mediated by parental socioeconomic and health-related factors, especially parental education, mothers' adult cardiovascular health behavioral risk score, and mothers' CRP levels, but not mothers' childhood BMI trajectory. This analysis provides evidence that intergenerational socioeconomic advantages can slow down the biological age acceleration in early life. This ability to conserve the speed of biological aging may have considerable consequences in shaping health trajectories across the lifespan.

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CRediT authorship contribution statement

Agus Surachman: Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Elissa Hamlat:** Writing – original draft, Writing – review & editing, Methodology. **Anthony S. Zannas:** Formal analysis, Methodology, Writing – original draft. **Steve Horvath:** Conceptualization, Data curation, Methodology, Supervision. **Barbara Laraia:** Conceptualization, Data curation, Funding acquisition, Supervision, Writing – original draft. **Elissa Epel:** Conceptualization, Data curation, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2024.117142.

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