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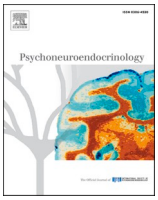

Early life adversity and age acceleration at mid-life and older ages indexed using the next-generation GrimAge and Pace of Aging epigenetic clocks

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ABSTRACT

Objective: This retrospective cross-sectional study was designed to explore whether the experience of childhood adversity was associated with epigenetic age acceleration in mid-life and older ages using the next generation GrimAge and Pace of Aging DNA methylation clocks.

Method: The study involved a sub-sample of 490 individuals aged 50–87 years of age participating in the Irish Longitudinal Study on Aging (TILDA); a large nationally representative prospective cohort study of aging in Ireland. Childhood adversity was ascertained via self-report using 5-items that were deemed to indicate potentially nefarious childhood exposures, including growing up poor, death of a parent, parental substance abuse in the family, childhood physical abuse, and childhood sexual abuse.

Results: Only childhood poverty was associated with significant epigenetic age acceleration according to the GrimAge and Pace of Aging clocks, hastening biological aging by 2.04 years [CI= 1.07, 3.00; $p < 0.001$] and 1.16 years [CI= 0.11, 2.21; $p = 0.030$] respectively. Analysis of the dose-response pattern revealed each additional adversity was associated with 0.69 years of age acceleration [CI= 0.23, 1.15; $p = 0.004$] according to the GrimAge clock. Mediation analysis suggested that lifetime smoking explains a substantial portion (>50%) of the excess risk of age acceleration amongst those who experienced childhood poverty.

Conclusions: This study adds to the growing body of evidence which implicates early life adversity, particularly deprivation as a potential precipitant of earlier biological aging, and implicates smoking-related changes to DNA methylation processes as a candidate pathway and mechanism through which the social environment gets transduced at a biological level to hasten the aging process.

1. Introduction

An extensive evidence base suggests that early life adversity (ELA) and social disadvantage are associated with increased risk of disease, disability, and premature mortality (McCrory et al., 2015; Nelson et al., 2020; Rod et al., 2020). ELA has also been shown to accelerate child-adolescent development as indicated by earlier pubertal development; more rapid development in brain regions involved with emotional processing to allow for independent emotional regulation at an earlier age; and with cellular markers of age acceleration such as leukocyte telomere shortening (Belsky, 2019; Colich et al., 2020). Evolutionary life history models hypothesise that earlier development may serve as an adaptive response to a harsh or unpredictable environment by maximising the prospects of reproduction prior to mortality – the trade-off being poorer health and shorter lifespan (Belsky, 2019). A central question that remains to be addressed is how these pernicious psychosocial influences get transduced at the biological level to hasten the aging process. One suggestion that has gained traction in recent years is that epigenetic mechanisms may partly explain the persistent effects of ELA on health in later life (Barnett et al., 2018; Vineis et al., 2017).

Alongside telomere erosion and genomic instability, epigenetic modifications represent a primary 'hallmark of aging' (López-Otín et al., 2013). Epigenetic mechanisms govern the transcription of the genome. These mechanisms include histone modifications, non-coding RNA's and DNA methylation (DNAm) (O'Donnell and Meaney, 2020), but it is

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the latter that has received most attention in the context of aging. DNAm refers to the addition or removal of methyl (-CH3) groups to Cytosine-phosphate-Guanine (CpG) sites. DNAm is important for gene regulation and gene expression, and a high level of DNAm in gene promoters is associated with transcriptional repression (i.e. gene silencing) (Champagne, 2010). DNAm is modulated by lifestyle and environmental factors, and as such, represents a plausible biological intermediary linking our social and molecular worlds (McCrory et al., 2019a, 2019b).

Horvath (2013) and Hannum (Hannum et al., 2013) were among the first to show that levels of DNAm at a small number of CpG sites across the human methylome could be used to develop highly accurate measures of chronological age. The discrepancy resulting from the regression of DNAm age on chronological age is hypothesised to represent an index of the biological aging rate. A positive residual signifies someone who is aging faster than their chronological age, whereas a negative residual indicates someone who is aging more slowly than their chronological age. The epigenetic clocks have been shown to be associated with a range of pathologies and with mortality (Horvath and Raj, 2018). Importantly, the epigenetic clock does not tick at a constant rate, but runs fastest in early childhood, slowing to a more constant rate by early adulthood, so there is reason to suspect that early life may represent a critical or sensitive period for the embodiment of adverse social exposures (Barnett et al., 2018).

An early meta-analysis involving data for nine cohorts and a total sample of 2186 participants examined associations of childhood adversity, post-traumatic stress disorder (PTSD), and lifetime trauma with epigenetic age acceleration (EAA), indexed using the Horvath and Hannum clocks (Wolf et al., 2018). Although there were no significant meta-analytic associations of childhood adversity, PTSD or lifetime trauma with EAA, moderator analysis revealed that childhood trauma as assessed using the Childhood Trauma Questionnaire, and severity of PTSD were associated with Hannum EAA. A separate meta-analytic study involving 9 studies and data for 1001 participants examined the impact of ELA - occurring prior to 18 years of age - including threat, deprivation and low socio-economic position (SEP) with biomarkers of cellular and molecular aging including leukocyte telomere length and epigenetic aging. They found that threat was associated with significantly faster EAA, but not deprivation or low SEP (Colich et al., 2020).

Studies since this time have been similarly inconsistent. A number of studies have been published using the Accessible Resource for Integrated Epigenomic Studies (ARIES) sub-sample of the larger Avon Longitudinal Study of Parents and Children (ALSPAC). The first study examined the impact of ELA and low SEP with Horvath EAA at ages 29 and 47 among ALSPAC mothers, and at age 53 in the National Survey of Health and Development (NSHD). ELA was indexed using 16 items in the ALSPAC cohort and 8 items in the NSHD cohort. Childhood sexual abuse was the only ELA associated with EAA in this study, hastening the pace of epigenetic aging by 2.74 and 3.34 years at ages 29 and 47 respectively (Lawn et al., 2018) in the ALSPAC sample. Neither childhood SEP nor a cumulative count of ELA's were found to relate to EAA in this study.

Marini et al. (2020) investigated the link between the experience of ELA, measured prospectively on at least 4 occasions between early and middle childhood, with EAA at 7.5 years of age among the children of the ALSPAC mothers using the Horvath and Hannum clocks. ELA was indexed using 7 items including neighbourhood disadvantage, financial hardship, maternal psychopathology, single-parent status, family instability, caregiver physical or emotional abuse, and sexual or physical abuse by anyone. Financial hardship was the only adversity associated with Hannum, but not Horvath EAA, when modelled using an ever vs never exposed dichotomy. When the adversities were disaggregated to examine sensitive period effects, physical abuse at 3.5 years, and financial hardship and neighbourhood disadvantage at 7 years were associated with EAA according to the Hannum clock, but the effect sizes were typically small. A subsequent study using the same cohort examined the relationship of 10 adverse childhood events measured prospectively between 0 and 14 years with EAA at 17 years using the Horvath clock, finding that emotional abuse and physical abuse were associated with ~1.2 years of EAA in girls, but not boys; and a dose-dependent association between a count of adversities and EAA in girls, which persisted after adjustment for a range of socio-demographic and lifestyle factors (Tang et al., 2020).

These studies suggest that the experience of ELA, usually operationalized as abuse or neglect, may leave epigenetic imprints, but the aforementioned studies modelled EAA using the first-generation epigenetic clocks, Horvath and Hannum, which were trained using chronological age and are not strongly related to clinical outcomes (Horvath and Raj, 2018). The development of epigenetic clocks to quantify biological aging is a rapidly evolving science and the first of the second-generation clocks, PhenoAge (Levine et al., 2018) and GrimAge (Lu et al., 2019), have already started to appear. Importantly, they are more strongly correlated with disease status, age-related clinical phenotypes, and mortality than their progenitors. The GrimAge clock seems to stand out amongst its peers (Hillary et al., 2019; Maddock et al., 2019; McCrory et al., 2021), but owing to its novelty has not been widely employed in the childhood trauma literature.

Recently, Hamlat et al. (2021) examined the relationship of ELA and precocious puberty with EAA using four epigenetic clocks among a small sample (n = 189) of pre-menopausal caregivers. Early life trauma was associated with a faster pace of biological aging according to GrimAge, but not the other epigenetic clocks. The authors speculated that these associations were only observed with the GrimAge clock because it incorporates a larger number of CpG sites in its algorithm and taps the effects of age-related molecular changes as well as endogenous and exogenous stress factors. Arguably, the first of the third-generation epigenetic clocks is already here. Belsky's Pace of Aging methylation (PoAm) clock was trained using longitudinal change in 18 blood chemistry and organ-system biomarkers and is based on levels of DNA methylation at 46 CpG sites (Belsky et al., 2020). Raffington et al. (2021) reported that PoAm was correlated with two measures of socio-economic disadvantage among a sample of 600 children aged 8–18 years, while the other epigenetic clocks, including GrimAge, were not.

Surveying the literature, a number of broad trends can be discerned. Firstly, there is no consistency in the association of any singular ELA with EAA across studies. Secondly, there is some suggestion that the associations of ELA with EAA may be more pronounced among women. Thirdly, early life socio-economic adversity does not appear to be strongly related to EAA. This study then has two primary aims: (i) to examine whether the experience of retrospectively reported ELA's, including socio-economic adversity, death of a parent, parental substance abuse during childhood, physical abuse during childhood, and sexual abuse during childhood are associated with EAA in mid-life and older ages among a sub-sample of community-dwelling older persons using the next-generation GrimAge and PoA methylation clocks, and if so; (ii) to understand the potential life course pathways through which the experience of ELA precipitates accelerated aging.

2. Material and methods

2.1. Sample

The Irish Longitudinal Study of Ageing (TILDA) study design and sample selection is described in elsewhere (Whelan and Savva, 2013). Briefly, the study involves a nationally representative sample of 8175 community-dwelling older persons aged 50 years and older at baseline. The sampling fraction is approximately 1/156 of all persons aged 50 years and over in Ireland at the time of the baseline survey between 2009/2011. Respondents complete a computer-assisted personal interview in the home and a separate self-completion questionnaire (SCQ) containing more sensitive information that is returned via post. All participating respondents are invited to attend for a detailed

clinic-based health assessment administered by trained nursing staff in either a center-based or home-based setting. The present study uses a subsample ($n = 500$) of the baseline TILDA cohort who were selected specifically to examine the impact of different life course socio-economic trajectories on the epigenetic ageing rate based on the cross-classification of their father's and their own contemporaneous social class position into 4 groups: stable high, stable low, upwardly mobile, downwardly mobile, as described in detail in McCrory et al. (2019b). Prior to selection, the sample was pre-stratified by social class trajectory and sex, and 125 cases were randomly selected from within each category. Of the total number of eligible cases within each social class trajectory, they are represented in the following proportions: stable high (125 / 457 =0.27), stable low (125 / 513 =0.24) steep upward mobility (125 / 429 =0.29), downwardly mobile (125 / 295 =0.42) with the latter group being over-represented relative to the others. Supplementary Table S1 summarises the characteristics of the included vs the excluded sample in terms of baseline characteristics. Ethical approval for the TILDA study was obtained from the Trinity College Dublin Research Ethics Committee and signed informed consent was obtained from all participants.

2.2. Exposure variables – early life adversities

Early life adversity (ELA) was retrospectively reported using five items adapted from the Stressful Life Events Inventory (Krause, Shaw & Kearney, 2004), which was designed to capture exposure to a number of threatening and potentially noxious life events. Respondents were asked to indicate whether they had experienced any of the following events before 18 years of age: (1) parental alcohol or drug abuse that caused problems in the family (2) physical abuse by either parent (3) physical abuse by anyone other than parents (4) sexual abuse by either parent (5) sexual abuse by anyone other than parents. Due to small cell sizes, responses to the two physical abuse and responses to the two sexual abuse questions were combined to create aggregate physical abuse and sexual abuse variables. Whether the respondent experienced the death of a parent before 18 years of age was ascertained from data provided elsewhere in the questionnaire. These measures were supplemented by an additional item that was designed to tap socioeconomic adversity in early life. Respondents were asked to rate the financial circumstances of the household between birth and 14 years of age on a 3-point response scale: pretty well off financially, about average, poor. A binary response was derived by setting those growing up "poor" = 1. A composite childhood adversity index was calculated by summing scores across the 5 items.

2.3. Reliability and validity of retrospective recalled early life adversity

The study relies on retrospective reports of ELA experienced decades previously, which may be subject to recall bias and misclassification (Hardt and Rutter, 2004). Potential biases include memory failures due to the length of the time that has elapsed between exposure and recall; false negatives to avoid embarrassment or distress; anchoring of retrospective recall by contemporaneous circumstances (e.g. poverty); and false positives owing to psychopathology / personality traits. A recent study involving the Dunedin cohort that explicitly examined the reliability of recall of ELA's measured prospectively at ages 3, 5, 7, 9, 11, 13 and 15 with retrospective recall at age 38 documented moderate agreement ($r = 0.47$; kappa = 0.31) between the two methods for a count of ELA's. However, the overall index of ELA's disguised considerable heterogeneity in reliability of recall for individual events which ranged from a high of $r = 0.83$ for loss of a parent, through $r = 0.22$ for household substance abuse, to $r = 0.10$ for experience of sexual abuse and $r = 0.07$ for experience of physical abuse (Reuben et al., 2016) although the lower reliabilities for interpersonal abuse during childhood may have been due to differences in the reporting source (e.g. administrative records for prospective ELA's vs self-report for retrospective ELA's). The Dunedin study did not examine reliability of recall of childhood socio-economic adversity, although Ward (2011) has reported reasonable concurrence between subjective appraisals of being better or worse off compared with others among sibling pairs (weighted kappa = 0.46). Both the Dunedin study and an earlier study involving data for the 1958 National Child Development Study (Hardt et al., 2010) found that retrospective and prospective measures of ELA were associated with midlife health suggesting that retrospective reports are a valid means for assessing the impact of ELA on later life health.

2.4. Outcome variables

2.4.1. GrimAge epigenetic age acceleration (EAA)

DNA methylation age estimation was calculated from whole blood and has been described in detail elsewhere (McCrory et al., 2019a, 2019b). Epigenetic age acceleration (EAA) was indexed using the GrimAge (Lu et al., 2019) and Pace of Aging methylation (PoAm) clocks (Belsky et al., 2020). GrimAge was developed using a 2-stage process. In the first stage, Lu and colleagues regressed levels of each of 88 plasma proteins and smoking pack years on chronological age, sex, and CpG levels, identifying CpG sites whose linear combination best predicted corresponding plasma protein levels in the training dataset. They identified 12 DNAm based surrogate biomarkers that correlated > =0.35 with their target biomarkers in the training and test datasets. In the second stage, they regressed time to death due to all-cause mortality on age, sex, DNAm pack years, and the 12 DNAm surrogate biomarkers of plasma protein levels, with the elastic net selecting 8 DNAm based biomarkers (DNAm pack years DNAm adrenomedullin, DNAm beta-2 microglobulin, DNAm Cystatin C, DNAm growth differentiation factor 15, DNAm leptin, DNAm plasminogen activation inhibitor, and DNAm tissue inhibitor metalloproteinase) across 1030 CpG sites that jointly predicted mortality risk.

2.4.2. Pace of aging methylation (PoAm) epigenetic age acceleration (EAA)

As described by Belsky et al. (2020), PoAm is qualitatively different from other methylation clocks in that it represents a rate measure (i.e. how fast a person is aging) as compared with a state measure (i.e. how much aging has occurred up until that point). It was also developed using a multi-step process. In the first stage they selected 18 blood chemistry and organ-system function biomarkers measured at ages 26, 32 and 38 years among a representative same-age cohort of participants to the Dunedin study. They modelled rate of change in each biomarker by calculating how far each individual deviates from the cohort norm and then combined the 18 personal rates of change to compute a composite score for each individual. Having established that this composite was associated with a range of age-related clinical phenotypes, they subsequently used the whole-genome methylation data collected at 38 years to derive a PoAm clock by identifying DNAm based correlates of change in the PoA measure. The resulting PoAm clock is based on levels of methylation at 46 CpG sites and has been shown to predict age 45 physical and cognitive functioning. It is expressed as a percentage score difference from a mean of 1, which corresponds to the typical rate of aging for a 38-year-old in the Dunedin cohort. For example, a score of 1.01 indicates someone aging 1% faster relative to their age-matched peer. We performed a transformation of the score to ensure that PoAm was expressed in a similar metric to GrimAge by subtracting 1 from the PoAm score, multiplying it by their chronological age in years and then taking the residuals from the regression of PoAm age on chronological age and white blood cells percentages (WBC) following Houseman et al. (2012). Different cell types in blood have different DNA methylation profiles. For the above reason, differences in DNA methylation at specific CpG sites between two (or more) groups can be driven entirely by differences in WBC proportion at the time of blood collection. Therefore, adjusting for white blood cell composition has become common in epidemiological and clinical studies analysing DNA methylation in blood to avoid false-positive associations. We utilise the intrinsic EAA

measures (adjusted for WBC percentages) as the dependent variables in our analysis and report results for the extrinsic EAA measures in the supplementary appendices.

The GrimAge DNAm clock was computed using a Python script, equivalent to using the Horvath online software at http://dnamage.genetics.ucla.edu/new, kindly shared by Dr. Ake T. Lu and Professor Steve Horvath. The Dunedin PoAm clock was computed using a freely available R package named 'DunedinPoAm38' (instruction available at https://github.com/danbelsky/DunedinPoAm38).

2.5. Covariates

We control in the base models for age (years) because the epigenetic clocks tend to underestimate age in the tissues of older persons (El Khoury et al., 2019) and to account for potential cohort differences in the reporting of adversities. We control for sex to account for sex-related differences in the experience of abuse and because menopause may accelerate epigenetic aging (Levine et al., 2016).

2.6. Mediating variables

Fiorito et al. (2019) have shown that low socio-economic position (SEP) and other lifestyle-related factors including smoking, physical inactivity, body mass index (BMI), and heavy alcohol consumption are associated with a faster pace of epigenetic aging. Highest level of educational attainment is represented as a 3-level variable: primary, secondary and tertiary. Smoking history was assessed by asking respondents whether they had "ever smoked cigarettes, cigars, cigarillos or a pipe daily for a period of at least one year?" and if so, for how many years, they had smoked altogether. Cross-classification of responses to these questions produced a five-level variable for analysis: never smoked, past smoker $<$ 30 years; past smoker $>$ =30 years; current smoker $<$ 30 years; current smoker $>$ =30 years. We chose a cut-off of 30 years because smoking typically begins in early life; so, smoking for 30 years or more in a mid-life cohort generally indicates a lifetime smoking history (Doll et al., 2004). Hazardous drinking was measured using the 4-item CAGE screening instrument which asks whether the participant has ever tried to cut-down on their drinking, been annoyed at someone for suggesting they cut-down, ever felt guilt about their drinking, and whether they needed an eye-opener to get them going in the mornings. Endorsing two or more items is considered to indicate a potentially clinically problematic profile (Ewing et al., 1984). Physical activity was indexed using the eight-item short form of the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). It measures the amount of time in minutes spent walking and engaged in moderate and vigorous physical activity, and the amount of time spent sedentary. Participants were classified into low, medium and high levels of physical activity as per the IPAQ scoring protocol. Body Mass Index (BMI) was calculated from measured height and weight. Height was measured using a SECA 240 wall mounted measuring rod and weight was measured using a SECA electronic floor scales.

The experience of trauma may compromise a person's ability to form close personal relationships (Krause et al., 2004) so we adjust for social network size using the Berkman-Syme Social Network index (Berkman and Syme, 1979); a four-item composite measure comprising different types of social connections: marital status (married vs. not married); sociability (number and frequency of contacts with children, close relatives, and close friends); church group membership (no vs. yes) and membership in other community organizations (no vs. yes). A total score ranging between 0 and 4 indicates the extent of social connections with higher scores signifying greater social connectedness. We adjust additionally for the experience of depression measured using the 8-item Center for Epidemiological Studies Depression (CESD) scale short-form because the experience of early life adversity is strongly associated with psychopathology in later life (McCrory et al., 2015), and case-control studies have reported that depression and symptom severity are associated with EAA (Laura et al., 2018). Exposure to ELA may predict continuing exposure to adversity across the life span, or increase psychological distress (Saxton and Chyu, 2020). A generalized measure of stress was obtained using the four-item short form of the Perceived Stress Scale (Cohen et al., 1983) which is designed to gauge the extent to which an individual appraises situations in his/her life as stressful. Respondents indicate how often they have felt this way in the past month on a five-point rating scale ranging from "never" to "very often." Scores range from 0 through 16 with higher scores indicating higher levels of perceived stress.

2.7. Missing cases

The epigenetic sample comprised 500 individuals. Of these, 10 individuals had missing DNA methylation data and a further 28 individuals did not return a SCQ resulting in an initial case base of 462 participants. Of those who completed an SCQ, 29 were missing data on the death of a parent and a smaller proportion of participants were missing data on some of the other childhood adversity items, reducing the effective sample size to 422 individuals. A further 26 individuals were missing information on some of the covariates resulting in a complete case base of 396 respondents. We employed multiple imputation to account for item-level non-response using all covariates in the imputation model, which was implemented in Stata using multivariate imputation by chained equations (MICE) with 20 replications.

2.8. Statistical analysis

Statistical analysis was undertaken using Stata v.15.0. The EAA measures were regressed separately on each adversity type adjusting for chronological age and sex in Ordinary Least Squares regression. We tested for effect modification by fitting sex*adversity interaction terms. We examined the extent to which the different adversity types clustered by calculating the tetrachoric correlation matrix and examined the extent to which their common correlation attenuates the association of each adversity with the others in multivariable regression. We explored dose-response relationships in the data by calculating a count of childhood adversities (range = 0–5). Having established the relationship of ELA with epigenetic age acceleration in the base models, we then examined the degree to which separate adjustment for education (model 2), lifestyle behaviours (model 3), psychosocial factors (model 4), and all covariates entered simultaneously attenuated any observed association (model 5). Karlson-Holm and Breen (KHB) (Kohler et al., 2011) mediation analysis was subsequently used to determine which of the individual mediating variables led to a statistically significant reduction in the slope of the line relating childhood adversity to EAA. We had to adjust for each variable separately as the KHB module does not support decomposition involving multiple mediators within a multiple imputation framework.

3. Results

Table 1 reports the baseline characteristics of the sample. The mean age of the sample was 62.3 years (SD=8.3) and 50.9% were female. The experience of adversity during childhood was common with 19.9% reporting that they grew up poor, 15.7% reporting the loss of a parent before 18 years of age, 8.6% and 8.0% reporting the experience of childhood physical abuse and childhood sexual abuse respectively, and 11.5% reporting parental substance abuse that caused problems in the family. The proportion of the epigenetic sub-sample reporting experience of these different adversity types is reasonably representative of the overall TILDA cohort (Supplementary Table S1), although there is some slight over-representation in terms of those reporting experience of substance abuse in the family (11.5% vs 8.8%). The childhood adversity variables were inter-correlated in the low to moderate range (Supplementary Table S2). Childhood poverty was correlated with death of a

Table 1
Characteristics of the sample.

	Variables	Mean (SD) or N (%)	N missing
Childhood adversities	Childhood poverty	92/462 (19.9%)	0
	Death of a parent	68/433 (15.7%)	29
	Alcohol / drug use in family	52/451 (11.5%)	11
	Physical abuse	39/452 (8.6%)	10
	Sexual abuse	36/451 (8.0%)	11
DNA methylation	GrimAge EAA	-0.09 (4.3)	0
	Pace of Aging	1.07 (0.08)	0
	Age (years)	62.3 (8.3)	0
	Female	235 (50.9%)	0
Education	Primary	101 (21.9%)	–
	Secondary	158 (34.3%)	–
	Tertiary	202 (43.8%)	–
	Missing		1
Smoking	Never smoked	186 (40.8%)	–
	Past smoker< 30 years	141 (30.9%)	–
	Past smoker> =30 years	53 (11.6%)	–
	Current smoker< 30 years	8 (1.75%)	–
	Current smoker> =30 years	68 (14.9%)	–
	Missing		6
CAGE	Hazardous drinking	77 (17.2%)	14
Physical activity	Low	131 (28.7%)	–
	Medium	163 (35.7%)	–
	High	163 (35.7%)	–
	Missing		5
Body Mass Index	BMI (kg/m^2)	28.8 (5.08)	1
Berkman-Syme	Social network index	2.85 (0.93)	0
CESD	Depression	4.61 (4.20)	0
	Perceived Stress Scale	4.10 (3.04)	19

parent ($r = 0.28$; $p = 0.005$). Parental substance abuse during childhood was correlated with childhood physical abuse ($r = 0.39$; $p = 0.001$) and childhood sexual abuse ($r = 0.45$, $p < 0.001$), while the latter two were correlated ($r = 0.61$; $p < 0.001$). The two EAA measures were substantially intercorrelated as estimated using Pearson's correlation coefficient ($r = 0.60$).

Fig. 1 shows the age and sex adjusted independent association of each of the childhood adversity variables with EAA. Childhood poverty was the only individual adversity type associated with EAA, hastening the rate of aging by 2.04 years (95% CI = 1.07, 3.00; $p < 0.001$) and 1.16 years (95% CI = 0.11, 2.21; $p = 0.030$) according to the GrimAge and PoAm clocks respectively. A dose-dependent relation was also observed for GrimAge, such that each additional adversity increased EAA by 0.69 years (95% CI = 0.23, 1.15; $p = 0.004$). The dose-response association was non-significant with respect to PoAm, but still positive at 0.45 years (95% CI = −0.05, 0.96; $p = 0.080$). As the different adversity types were low to moderately inter-correlated, we adjusted simultaneously for the experience of other types of adversity in secondary models (Supplementary Table S3). The association of childhood poverty with GrimAge EAA was not appreciably affected, although the association with PoAm was no longer statistically significant. The broad pattern of results was very similar using the extrinsic EAA measures (Supplementary Table S4). We tested for effect modification by fitting separate sex*-adversity interaction terms. Only one of the individual contrasts was statistically significant at the 0.05 level with growing up poor having a larger effect in women compared with men (B= 2.25, 95% CI = 0.15, 4.36; $p = 0.036$) on the POAm clock. Following a suggestion from one of the reviewer's, we explored interactions between poverty and the other childhood adversity types. We observed that the experience of childhood sexual abuse was associated with more pronounced EAA among those growing up in poverty, hastening epigenetic ageing by 5.04 [95% CI = 0.82, 9.26; $p = 0.019$] and 4.56 [95% CI = 0.10, 9.02; $p = 0.045$] years on the GrimAge and PoA clocks respectively.

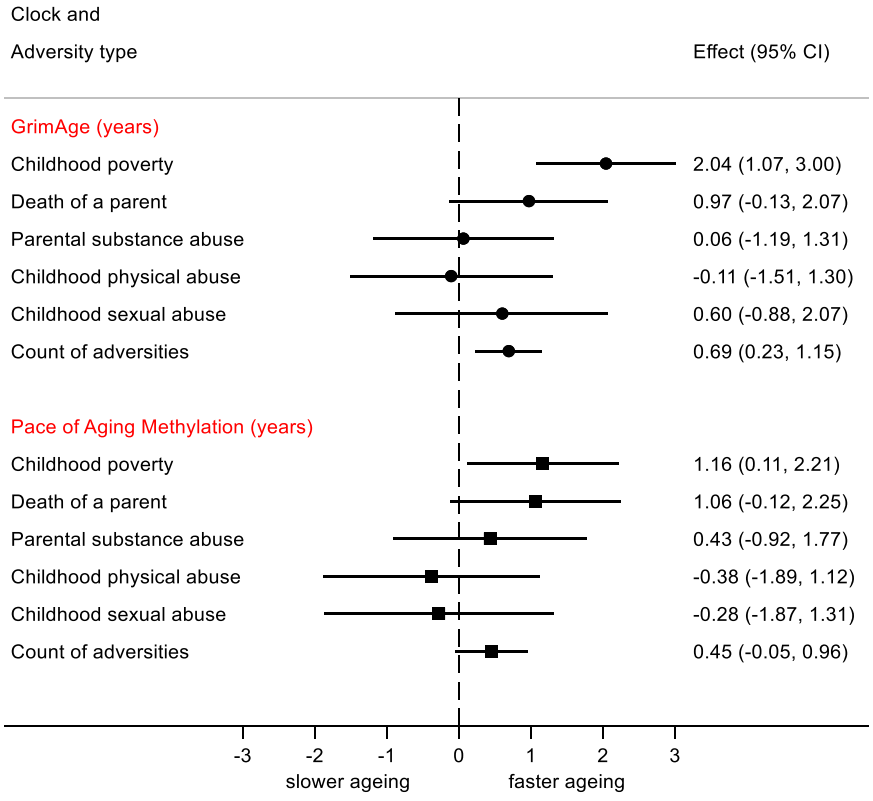

Fig. 1. Age and sex adjusted independent association of the childhood adversity measures with GrimAge and Pace of Aging epigenetic age acceleration.

Table 2
Association of the exposure variables with the mediating variables.

		Childhood poverty			Death of a parent			Parental substance abuse			Childhood physical abuse			Childhood sexual abuse		
		No	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*
Education	Tertiary	49.6%	20.7%	.001	47.4%	30.9%	.042	41.5%	69.2%	.001	43.9%	51.3%	.676	44.0%	52.8%	.480
	Secondary	34.2%	34.8%		33.4%	45.6%		35.7%	25.0%		35.0%	30.8%		34.8%	33.3%	
	Primary	16.3%	44.6%		18.6%	23.5%		22.9%	5.8%		21.1%	18.0%		21.3%	13.9%	
Smoking	Never smoked	43.4%	30.4%	.018	43.2%	32.8%	.295	39.9%	43.1%	.663	40.7%	34.2%	.046	40.9%	32.4%	.001
	Past smoker< 30 years	31.3%	29.4%		30.5%	34.3%		31.7%	29.4%		29.9%	47.4%		30.9%	35.3%	
	Past smoker> =30 years	11.0%	14.1%		11.1%	11.9%		12.2%	7.8%		12.0%	7.9%		12.2%	5.9%	
	Current smoker< 30 years	1.9%	1.1%		1.4%	4.5%		1.5%	3.9%		1.5%	5.3%		1.0%	11.8%	
	Current smoker> =30 years	12.4%	25.0%		13.9%	16.4%		14.7%	15.7%		15.9%	5.3%		15.1%	14.7%	
CAGE	Hazardous drinking	17.6%	15.7%	.684	16.3%	15.9%	.934	15.3%	33.3%	.001	16.8%	23.7%	.280	16.4%	29.4%	.054
Physical activity	Low	26.2%	38.5%	.067	28.3%	22.1%	.563	27.9%	28.9%	.678	28.1%	28.2%	.286	28.4%	22.9%	.765
	Medium	37.2%	29.7%		35.5%	39.7%		35.4%	40.4%		36.9%	25.6%		35.9%	37.1%	
	High	36.6%	31.9%		36.3%	38.2%		36.7%	30.8%		35.0%	46.2%		35.7%	40.0%	
Body Mass Index	BMI (kg/m^2)	28.7	29.0	.573	28.7	28.6	.514	28.8	28.1	.660	28.7	28.5	.841	28.7	29.4	.198
Berkman Syme	Social Network Index	2.89	2.72	.101	2.92	2.66	.029	2.86	2.77	.675	2.88	2.56	.071	2.87	2.67	.261
CESD	Depression	4.55	4.88	.497	4.47	5.03	.340	4.53	4.67	.921	4.43	6.08	.008	4.44	5.94	.056
	Perceived Stress Scale	3.93	4.82	.021	4.0	4.48	.205	4.05	4.23	.979	3.99	5.09	.047	4.03	4.49	.535

Table 3
Age and sex adjusted independent association of the mediators with GrimAge and Pace of Aging epigenetic age acceleration.

	Variables	GrimAge b (95% CI)	Pace of Aging b (95% CI)
Education	Tertiary	*ref*	*ref*
	Secondary	0.79 (−0.09, 1.67)	0.78 (−0.15, 1.72)
	Primary	2.42 (1.39, 3.46)	2.73 (1.62, 3.83)
Smoking	Never smoked	*ref*	*ref*
	Past smoker< 30 years	0.99 (0.31, 1.66)	0.96 (0.12, 1.81)
	Past smoker> =30 years	5.19 (4.23, 6.14)	3.86 (2.67, 5.05)
	Current smoker< 30 years	5.43 (3.24, 7.63)	3.71 (0.98, 6.44)
	Current smoker> =30 years	8.19 (7.33, 9.05)	7.16 (6.09, 8.23)
CAGE	Hazardous drinking	0.95 (−0.13, 2.03)	-0.03 (−1.19, 1.13)
Physical activity	Low	*ref*	*ref*
	Medium	-1.05 (−2.03, −0.05)	-0.49 (−1.55, 0.57)
	High	-1.14 (−2.15, −0.13)	-1.09 (−2.18, −0.02)
Body Mass Index	BMI (kg/m^2)	0.03 (−0.05, 0.11)	0.00 (−0.08, 0.08)
Berkman Syme	Social Network Index	-1.03 (−1.44, −0.61)	-0.80 (−1.25, −0.35)
CESD	Depression	0.13 (0.04, 0.22)	0.11 (0.00, 0.21)
	Perceived Stress Scale	0.18 (0.05, 0.32)	0.14 (0.00, 0.28)

Table 2 shows the relation of the exposure variables with the putative mediating variables using the two-sample Wilcoxon rank-sum (Mann-Whitney) test for continuous variables and chi-square tests of association for categorical variables. There are some trends in the data that are worthy of comment. For instance, childhood poverty was strongly associated with subsequent educational attainment; 44.6% of those who grew up poor have a primary level educational qualification or equivalent compared with 16.3% of those who were non-poor. However, a different pattern was observed with respect to the maltreatment variables whereby those who experienced childhood physical abuse or sexual abuse were more likely to have completed tertiary level education, replicating a pattern that has previously been observed in the larger TILDA cohort (Feeney et al., 2013). We also noted a fairly consistent trend whereby those who experienced ELA were more likely to have ever smoked and to have a hazardous alcohol consumption profile. They also tend to have smaller social support networks, and higher levels of psychological distress as indexed using the CESD-SF and perceived stress scale.

Table 3 in turn shows the association of the putative mediating variables with the two EAA measures. The primary educated were epigenetically older according to both the GrimAge and PoAm clocks compared with the tertiary educated reference group. Smoking exerts a strong influence on the epigenetic ticking rate, particularly among current smokers or those who have smoked for 30 years or more. Physical inactivity and heavy alcohol consumption were also positively associated with EAA, but BMI was not. Notably, the psychosocial variables were also linked with EAA in this study. CESD-SF depression and perceived stress were both associated with EAA, while a high level of social connectedness was associated with slower aging.

We undertook an exploratory mediation analysis in order to illuminate the potential life course pathways through which childhood poverty contributes to EAA using hierarchical entry of covariates in order to ascertain the extent to which they attenuated the association of poverty with EAA (Table 4). For completeness, results are also shown for the other childhood adversity types. Model 1 shows the base model adjusted for age and sex, while the subsequent models show the

Table 4
Minimal and multivariable adjusted associations of each adversity type with GrimAge and Pace of Aging epigenetic age acceleration.

Panel A	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
GrimAge (years)	*b (95% CI)*	*b (95% CI)*	*b (95% CI)*	*b (95% CI)*	*b (95% CI)*
Childhood poverty	2.04 (1.07, 3.00)	1.49 (0.49, 2.49)	0.87 (0.16, 1.59)	1.75 (0.79, 2.71)	0.66 (−0.08, 1.40)
Death of a parent	0.97 (−0.13, 2.07)	0.79 (−0.30, 1.88)	0.51 (−0.29, 1.31)	0.63 (−0.45, 1.71)	0.44 (−0.37, 1.24)
Parental substance abuse	0.06 (−1.19, 1.31)	0.51 (−0.73, 1.76)	-0.10 (−1.02, 0.81)	-0.02 (−1.23, 1.20)	-0.03 (−0.95, 0.89)
Childhood physical abuse	-0.11 (−1.51, 1.30)	-0.04 (−1.42, 1.34)	0.65 (−0.38, 1.67)	-0.57 (−1.96, 0.81)	0.46 (−0.57, 1.49)
Childhood sexual abuse	0.60 (−0.88, 2.07)	0.71 (−0.74, 2.16)	0.02 (−1.10, 1.15)	0.39 (−1.05, 1.83)	-0.01 (−1.13, 1.11)
Count of adversities	0.69 (0.23, 1.15)	0.59 (0.13, 1.05)	0.35 (0.01, 0.69)	0.48 (0.02, 0.95)	0.27 (−0.07, 0.61)
Panel B					
Pace of Aging (years)	*b (95% CI)*	*b (95% CI)*	*b (95% CI)*	*b (95% CI)*	*b (95% CI)*
Childhood poverty	1.16 (0.11, 2.21)	0.44 (−0.64, 1.52)	0.12 (−0.79, 1.02)	0.94 (−0.11, 1.99)	-0.32 (−1.25, 0.62)
Death of a parent	1.06 (−0.12, 2.25)	0.88 (−0.30, 2.05)	0.71 (−0.29, 1.72)	0.81 (−0.37, 1.99)	0.65 (−0.36, 1.66)
Parental substance abuse	0.43 (−0.92, 1.77)	0.93 (−0.40, 2.26)	0.42 (−0.72, 1.56)	0.37 (−0.95, 1.69)	0.63 (−0.51, 1.78)
Childhood physical abuse	-0.38 (−1.89, 1.12)	-0.31 (−1.79, 1.16)	0.30 (−0.98, 1.59)	-0.76 (−2.26, 0.74)	0.19 (−1.10, 1.49)
Childhood sexual abuse	-0.28 (−1.87, 1.31)	-0.16 (−1.73, 1.41)	-0.60 (−2.01, 0.81)	-0.46 (−2.04, 1.12)	-0.58 (−1.99, 0.82)
Count of adversities	0.45 (−0.05, 0.96)	0.33 (−0.16, 0.82)	0.20 (−0.23, 0.63)	0.29 (−0.22, 0.79)	0.11 (−0.32, 0.54)

M1: Age and sex adjusted independent association
M2: M1 + education
M3: M1 + lifestyle factors
M4: M1 + psychosocial factors
M5: M1 + M2 + M3 + M4

proportion of the total effect mediated when we adjust separately for education (model 2), lifestyle behaviours (model 3), psychosocial factors (model 4) and for all of these factors simultaneously in the full multivariable adjusted model (model 5). The relationship of childhood poverty with GrimAge was reduced by 27.0%, 57.4%, and 14.2% when adjusted for education, lifestyle factors, and psychosocial factors, respectively. The corresponding attenuation for PoAm was 62.1% (model 2), 89.7% (model 3), and 19.0% (model 4) respectively. The association of childhood poverty with GrimAge and PoAm was rendered non-significant in the full multivariable adjusted models (model 5). A similar pattern of attenuation was observed with respect to the dose-response associations.

Table 5 reports the proportion of the total effect mediated by each individual covariate in isolation. Educational attainment (27.0%) and smoking (52.5%) accounted for a substantial portion (non-additive) of the total effect of childhood poverty on GrimAge. The proportion of the total effect explained by education (62.1%) and smoking (81.0%) was even larger with respect to PoAm. The other putative mediating variables contributed little over and above that already accounted for by education and smoking. We repeated the analysis for the dose-response variable (Table 5, panel B). On this occasion, smoking and the size of the social network were the only two variables that had a substantial indirect effect.

4. Discussion

This study sought to determine whether the experience of ELA was associated with EAA as indexed using the next-generation methylation clocks. Results only partially supported the hypothesis that epigenetic mechanisms are implicated in the physiological cascade that triggers earlier disease onset and premature mortality among those exposed to adversity in early life. Only the experience of childhood poverty was associated with EAA in this study and the effects were substantive, increasing epigenetic aging by between 1.2 and 2 years, indexed using both a state and a rate measure. This is potentially an important insight because childhood socio-economic adversity has also been linked with other surrogate measures of biological aging including allostatic load burden (Evans and Kim, 2012), inflammation (Liu et al., 2017), and telomere length (Ridout et al., 2017), strengthening support for the view that privation is calamitous for health, altering methylation processes in ways that disrupt normal cellular aging. If we assume that the effects of childhood poverty on age acceleration are causal, how is it that they affect methylation patterns?

4.1. Putative mechanisms by which adversity gets under the skin

The mediation analysis suggested that much of the association was indirect and explained via differences in educational attainment and lifetime smoking. Smoking is strongly socially patterned (Hiscock et al., 2012), and one of the leading preventable causes of morbidity and mortality worldwide (U.S Centers for Disease Control, 2014). A number of epigenome wide association studies have observed that smoking induces altered DNA methylation at multiple CpG sites across the human methylome (Allione et al., 2015; Guida et al., 2015) and can disrupt biological pathways involved in cell activation, death and survival. Importantly, smoking cessation results in changes to methylation status such that former smokers more closely resemble the methylation profile of those who never smoked, indicating at least some reversibility of the effect (Dugué et al., 2020). A recent review identified 1758 genes that were differentially methylated and differentially expressed, comparing smokers with non-smokers. Functional enrichment analysis revealed that the 4 most frequently reported genes (*AHRR, GPR15, GF11* and *RARA*) were involved in biological pathways related to transcription factors, inflammation and immune cell differentiation (Silva and Kamens, 2021). Smoking-related methylation changes have in turn been associated with increased risk of cardiovascular and all-cause mortality (Morrow et al., 2020; Zhang et al., 2016), providing a plausible aetiologic pathway of linkages – poverty → low education → smoking → DNA methylation → gene expression → health – through which childhood poverty gets embedded in our cellular biology.

Of course, it could be argued that the mediation model is naïve as it does not take account of potential mediator-outcome confounding. DNA methylation surrogate markers of smoking pack years were used in the development of the GrimAge clock so it is perhaps unsurprising that childhood poverty relates to GrimAge primarily via smoking. This is a difficult conceptual problem to grapple with as smoking is one of the leading causes of premature mortality, so it is not surprising that it is afforded a heavy weight in any DNA methylation algorithm designed to detect biological age acceleration. Notwithstanding this caveat, lifetime smoking was also strongly implicated as an indirect path with the PoAm clock, which did not explicitly include smoking in its derivation, adding confidence to our primary finding that lifetime smoking is an important contributor to biological age acceleration among those growing up disadvantaged. This finding is also consistent with Belsky et al. (2020) observation in their validation study that smoking attenuated the association of low SES with PoAm by about half in the E-risk cohort at 18 years of age.

Despite this, childhood poverty is not currently included as an

Table 5
Proportion of the total effect in GrimAge and Pace of Aging epigenetic age acceleration mediated by each variable independently using the Karlson-Holm and Breen (KHB) method.

PANEL A	GrimAge				Pace of Aging			
Childhood poverty	b (se)	% mediated	z	p	b (se)	% mediated	z	p
Total effect[a]	2.04 (1.07, 3.00)	–	–	–	1.16 (0.11, 2.21)	–	–	–
Indirect effect (via)[a]								
Education	0.55 (0.17)	27.0%	3.16	0.002	0.72 (0.20)	62.1%	3.68	0.001
Smoking	1.07 (0.34)	52.5%	3.12	0.002	0.94 (0.30)	81.0%	3.16	0.002
Hazardous drinking	-0.01 (0.04)	-0.49%	-0.26	0.798	0.00 (0.01)	0.0%	0.03	0.976
Physical activity	0.11 (0.07)	5.39%	1.53	0.125	0.08 (0.08)	6.90%	1.06	0.290
BMI	0.01 (0.02)	0.49%	0.33	0.740	0.00 (0.01)	0.0%	-0.08	0.932
Social network index	0.18 (0.11)	8.82%	1.64	0.101	0.14 (0.09)	12.1%	1.55	0.121
CESD depression	0.05 (0.06)	2.45%	0.86	0.390	0.05 (0.05)	4.31%	0.83	0.407
Perceived stress scale	0.17 (0.09)	8.33%	1.86	0.063	0.13 (0.09)	11.2%	1.50	0.133
PANEL B								
Count of adversities	b (se)	% mediated	z	p	b (se)	% mediated	z	p
Total effect[a]	0.69 (0.23, 1.15)	–	–	–	0.45 (−0.05, 0.96)	–	–	–
Indirect effect (via)[a]								
Education	0.10 (0.05)	14.5%	1.89	0.059	0.12 (0.06)	26.7%	1.91	0.056
Smoking	0.33 (0.17)	47.8%	1.93	0.053	0.27 (0.14)	60.0%	1.85	0.064
Hazardous drinking	0.03 (0.03)	4.34%	1.12	0.261	-0.01 (0.02)	-2.22%	-0.25	0.803
Physical activity	0.01 (0.03)	1.45%	0.49	0.626	0.01 (0.03)	2.22%	0.27	0.785
BMI	0.00 (0.01)	0.0%	0.12	0.902	0.00 (0.00)	0.0%	-0.04	0.967
Social network index	0.14 (0.06)	20.3%	2.46	0.014	0.11 (0.05)	24.4%	2.18	0.029
CESD depression	0.06 (0.04)	8.70%	1.68	0.092	0.05 (0.04)	11.1%	1.47	0.142
Perceived stress scale	0.08 (0.04)	11.6%	1.89	0.058	0.06 (0.04)	14.0%	1.53	0.127

[a] all models estimated while holding age and sex constant

adverse childhood (ACE) event in the World Health Organisation's ACE International Questionnaire, even though studies suggest that early life deprivation structures the risk of experiencing other types of childhood adversities (Lacey and Minnis, 2020; Lewer et al., 2019), and may serve as a distal driver of the barrage of adverse health-related sequelae that have been associated with ELA. Indeed, TILDA represents an interesting test case in this context because it has a different confounding structure compared with most other studies in that the experience of inter-personal traumas such as childhood physical abuse and childhood sexual abuse are more commonly reported by those of higher education. Notably, in this study neither childhood physical abuse nor childhood sexual abuse were associated with significant EAA according to either methylation clock, even when adjusted to take account of the different socio-economic stratification by education in the TILDA cohort. This is not an entirely unexpected finding however, as other studies have also failed to observe associations of childhood sexual abuse with the first-generation clocks, while associations with childhood physical abuse have ranged in magnitude (Marini et al., 2020; Tang et al., 2020). The experience of parental substance abuse during childhood was found to be unrelated to EAA; however, loss of a parent was associated with appreciable, but non-significant, EAA across both clocks, accelerating biological ageing by ~1 year.

4.2. How reliable is retrospective recall of adversity?

In mitigation, it should be acknowledged that the study uses retrospective measures of adversity which are subject to both recall bias and misclassification (Hardt and Rutter, 2004). Moreover, the study employs a rather crude indicator of adversity, ever vs never exposed, which disguises considerable heterogeneity in the timing, intensity, and duration with which these events were experienced during childhood. Nor do we have the temporal resolution to distinguish sensitive / critical period effects as the study's cross-sectional retrospective design does not lend itself to such nuanced interpretation of results. The type and variety of adverse events experienced during childhood is also quite limited. Participants may be reluctant to disclose the experience of particular types of events such as childhood sexual abuse, leading us to under-estimate the impact of these toxic exposures on the biological aging rate. Alternatively, individuals who have experienced more severe and stigmatising forms of inter-personal trauma may be less likely to participate in a field survey of this kind.

There was a dose-response relation between the count of childhood adversities and GrimAge EAA; and again, smoking was strongly implicated as a potential pathway conferring this increased risk accounting for just less than 50% of the association. Interestingly, the size of the social network was also implicated as an important mediator in this instance. It should be acknowledged that the experience of early life trauma, particularly inter-personal violence, may erode levels of trust in others (Repetti et al., 2002) curtailing a person's ability to form close personal relationships. Over the last few decades, much research has emerged linking social integration with more auspicious health outcomes (Seeman, 1996). Consistent with this interpretation, we found that those who experienced adversity in early life had smaller social support networks, and the availability of social supports was inversely related to EAA.

4.3. Strengths and limitations

The TILDA epigenetic sample was chosen to examine the impact of life course intergenerational social mobility on the biological aging rate, so the associations observed with childhood poverty but not the other adversities may result from bias in the sample selection. The results of the mediation analysis should also be interpreted with caution because the exposure, mediators and outcome were assessed at the same time-point so we cannot rule out the possibility of reverse causation, even if we believe that lifestyle behaviours causing EAA is more theoretically tenable than the converse. In a similar vein, it could be argued that the temporal relationship between the mediators is theoretically opaque. For example, childhood poverty contributing to higher levels of lifetime stress (distal cause) may cause someone to smoke at a higher intensity (proximal cause), so the causal model might be more complex than that suggested here, as our modelling strategy involved sequential adjustment for covariates and did not test these types of structural models. It should also be acknowledged that the PoAm clock is a relatively new biomarker that was developed in a younger age cohort compared with TILDA so it may be less well calibrated for use in older cohorts compared with GrimAge which was developed using cohorts more comparable to TILDA in terms of age profile.

These limitations are countered by a number of strengths. This is the first study of its type to examine the impact of ELA on EAA, indexed

using the most recent epigenetic clocks, in a mid-life cohort where diseases of aging are highly prevalent, allowing us to assess the long-run impacts of ELA on precocious aging. As an omnibus study of aging and development, TILDA collects data on a range of variables - sociodemographic, lifestyle-related, psychosocial - operating at different levels of a person's ecological context, allowing us to illuminate the potential life course pathways through which ELA gets embodied in our cellular and molecular biology, crystallising as disease, morbidity and premature mortality. The insights provided can help inform the development of hypotheses to be tested in prospective cohort studies of child development such as ALSPAC, which benefit from prospective measurement of the exposure, mediators and outcomes at earlier stages of the life course.

5. Conclusions

This study adds to the growing body of evidence which implicates childhood deprivation as a precipitant of earlier biological aging, although the precise molecular mechanisms through which this occurs have yet to be fully elucidated. The epigenetic clocks describe an endpoint (i.e. age acceleration) but there is a requisite need to go deeper to understand how differential methylation (hypo or hypermethylation) of specific gene regions leads to the type of specific or multi-organismal damage that portends hard clinical outcomes (Neves et al., 2019) among those growing up impoverished. This study indicates that smoking-related changes to DNA methylation processes represents a candidate pathway and mechanism through which the experience of social adversity in early life gets biologically embedded at a cellular and molecular level to hasten the aging process.

Authorship declaration

C.M.C. conceived the paper, conducted the statistical analyses and wrote the initial draft of the paper. G.F., A.O.H. and S.P. contributed to the development of methods used in this paper. All authors critically revised the manuscript and contributed important intellectual content. C.M.C. takes responsibility for the paper. C.M.C. holds all datafiles and analysis files to enable replication of results.

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Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105643.

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