Exploring the Interplay of Childhood Adversity and Epigenetic Ageing: A Structured Life Course Modelling Approach

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Abstract

Much research has been dedicated towards studying the enduring efforts of adverse childhood experiences on a range of outcomes in adulthood. A growing strand of research finds that early life stressors are detrimentally associated with an accelerated pace of epigenetic/cellular ageing relative to one's chronological age in adulthood. Such epigenetic accelerated ageing (EAA) is in turn, associated with various deleterious outcomes, such as heightened mortality and morbidity risk. Among these studies however, much less attention has been paid to EAA during earlier age periods more proximate to one's exposure to adverse events; and even fewer studies have attempted to disentangle temporal effects from the cumulative effect of adversity exposure.

This study attempts to complement existing literature by examining the effect of adverse childhood experience on one's epigenetic pace of ageing during young adulthood, when epigenetic 'scars' resulting from adverse childhood experiences remain clearly visible. Using data from the Fragile Family and Child Wellbeing Study (FFCWS), I utilise a statistical learning method to investigate how various types of adverse childhood experiences (material hardship; instability; deprivation; maltreatment) are related to EAA in young adulthood, and which of the three life course hypotheses – sensitive periods; recency; and cumulative risk – best explain this relationship when all three frameworks are considered together. I find the sensitive period hypothesis to be the strongest predictor of EAA across almost all types of adverse experiences. Gender-stratified analyses yielded similar findings. This suggests that the timing of exposure (considered across ages 1-9 in this study) matters most for one's EAA in young adulthood,

compared to the recency of exposure or the total number of adverse events ever encountered by an individual (i.e., the cumulative risk model).

I further adopt a causal mediation analysis to examine if risk factors commonly identified in the literature – depression; externalising behaviour; internalising behaviour; smoking behaviour; alcohol abuse; drug abuse; BMI – similarly mediate the relationship between childhood adversity and EAA in young adulthood. Results were surprising: almost all mediators had a negative mediational effect, suggesting that they suppressed rather than contributed to the deleterious impact of adverse childhood experiences on one's epigenetic ageing process. This result differs starkly from literature investigating adulthood EAA outcomes, suggesting that pathways linking adversity experience to EAA may be vastly different across the life course. Possible reasons for such a disparity are discussed further. Results were similar in analyses stratified by gender, although most mediators were found to be non-significant for female-only analysis. Altogether, my results reiterates the importance of disentangling between life course hypotheses when investigating the relationship between childhood adversity and EAA, and suggests that pathways linking adversity to EAA may be vastly different during earlier age periods compared to adulthood.

1 Introduction

In this thesis, I investigate the longitudinal links between exposure to adverse childhood experiences (ACEs) and epigenetic ageing – a recently developed biomarker of mortality risk and other age-related diseases. Rather than treating ACEs as a singular entity, I uncover the heterogeneity underlying the relationship between ACEs and epigenetic ageing by investigating how specific *types* of ACEs are differentially linked to epigenetic ageing; and whether such links are mediated by the same social factors and behaviours.

The enduring effects of ACE exposure on various physical and mental health outcomes have been widely documented. Such early life stressors have been demonstrated to be associated with health risks such as depression (Dunn et al., 2018; Gajos et al., 2022), cardiovascular diseases (McCrory et al., 2015), as well as obesity in adulthood (Danese & Tan, 2014; Quilliot et al., 2019). Crucial to this strand of research pertains to the notion of the *long arm of childhood* hypothesis pioneered by Hayward & Gorman (2004), which posit that early life experiences have enduring effects on later-life outcomes. Events experienced in early life may have an impact on outcomes as late as one's health in adulthood (Monnat & Chandler, 2015), and even affect one's life expectancy (Jia & Lubetkin, 2020). More significantly, such effects may even extend intergenerationally to affect the health and behavioural outcomes of offsprings far removed from the events experienced by their predecessors (Lê-Scherban et al., 2018; Schickedanz et al., 2018).

Much less studied however is whether and how early life stressors get 'under the skin' to affect

later life outcomes. Whilst scarce, epidemiological studies have found significant associations between ACE exposure and DNA methylation (DNAm), which have been found to be linked with various outcomes such as earlier sexual debut and age at first birth (Schlomer, 2024), as well as increased risk of cardiovascular disease and cognitive impairment (Vidrascu et al., 2019). Such studies hint at the potential for biological factors to serve as mid-stream mechanisms intervening between early life adversity and later life outcomes. More recently, scholars have increasingly pivoted towards studying the biosocial outcomes of *epigenetic ageing*, otherwise perceived to be cellular scarring or rusting due to stress exposure. Put more precisely, epigenetic ageing results from the culmination of biological processes that regulate the ageing processes, such as DNA methylation, histone modification, and RNA modification (Wang et al., 2022). Thus, one's epigenetic age also serves as an indication of his/her risk of being afflicted by age-related diseases. Much important work has established linkages between epigenetic ageing and various age-related diseases such as depression, obesity, and a broad range of neurodegenerative diseases (Colită et al., 2024; Fransquet et al., 2019; J. K. Kim et al., 2023; Saul & Kosinsky, 2021). Such research are however largely concerned with uncovering the downstream effects of epigenetic ageing. An objective of this dissertation, then, aims to complement existing efforts by shifting the focus upstream, to examine how early life stressors (i.e., ACE exposures) may affect epigenetic ageing.

Several issues in existing literature motivate this study. First, existing findings are not robust because earlier studies largely rely on data collected retrospectively, leading to recall bias that may impair the internal validity of its findings (Hardt & Rutter, 2004). This is especially

important considering that most existing studies are concerned with adulthood outcomes, for whom childhood ACEs happened a long time ago. Present circumstances, such as one's current mental health, may also affect the accuracy of their memories when they self-report ACEs encountered in childhood. This highlights a need to utilise data collected prospectively, which minimises reporting error and enables longitudinal analyses.

Second, the bulk of existing studies adopt a cross-sectional approach in examining links between ACE exposure and epigenetic ageing. By adopting a cross-sectional approach, researchers may miss out on crucial information regarding the temporal sequence and causal pathways linking ACE exposure to epigenetic changes over time. A longitudinal approach, on the other hand, offers a more comprehensive and nuanced understanding of the interplay between ACE exposure and epigenetic aging. For instance given the heightened sensitivity of individuals to their social environments during childhood (Dunn et al., 2018), insights gleaned from longitudinal investigations can elucidate the existence of sensitive periods during which children are particularly susceptible to the adverse effects of ACE exposure. Alternatively, such elevated plasticity towards environmental adversities may suggest that accumulative exposures to adversity (i.e., cumulative risks) could culminate in deleterious outcomes. Otherwise, it is also possible that biological indicators such as epigenetic age may predominantly reflect the recency, rather than specific timings or the accumulation of ACE exposure. This temporal examination thus advances our understanding about the interrelationships between ACE exposure, developmental timing, and epigenetic ageing, informing inquiries relating to its underlying mechanisms and targeted interventions.

Third, most existing studies are primarily concerned with adulthood outcomes induced by childhood adversity, but overlooks developmental outcomes occurring during the earlier phases of one's life course. Examining such proximal outcomes is important because adolescence represents a unique developmental phase marked by rapid cognitive and emotional changes. It is during this pivotal period that the effects of childhood adversity may first become apparent, shaping developmental trajectories in profound ways. Furthermore, epigenetic processes are transient and may grow less visible over time in adulthood. By shifting our focus to examine epigenetic outcomes in adolescence rather than exclusively in adulthood, we can glean valuable insights into the early manifestations of ACEs on one's epigenetic alterations, which may be crucial for future life course trajectories.

Fourth and finally, very limited studies have attempted to examine the exact mechanisms that link ACE exposure to epigenetic ageing. Where available, such studies typically focus on adulthood rather than earlier life periods. Mechanisms may however differ across the life course, because novelty-seeking behaviours usually adopted to cope with stress may differ between adolescence and adulthood. The direction and strength of such mediation effects may also differ across the life course, given the unique phase of adolescence as a period of heightened plasticity and susceptibility to environmental influences. Developing a keener understanding of mechanisms during adolescence is therefore essential for designing targeted interventions aimed at mitigating the long-term consequences of ACEs.

In this dissertation, I analyse longitudinal panel data to explicate the link between childhood adversity and epigenetic ageing; as well as the mediators that intervene between the two.

Specifically, I aim to uncover which of the three life course models –*recency*, *cumulative risk*, or *sensitive periods*– best explain this link between childhood adversity and epigenetic ageing in young adulthood. Thus, this dissertation is primarily concerned with three research questions:

1. *Which of the three theoretical models – recency; cumulative risk; sensitive period –'best' explains the link between childhood experience (ACEs) and accelerated epigenetic ageing (EAA) in young adulthood?*
2. *How does this link between ACEs and accelerated epigenetic ageing differ by the types of ACEs?*
3. *Which risk factors mediate the relationship between ACE exposure and accelerated epigenetic ageing in young adulthood?*

I begin by discussing in Chapter 2 about epigenetic ageing and its links with various kinds of ACE exposures. Importantly, I further elaborate on the three life course models frequently discussed in the literature, and their significance in the relationship between ACE exposure and epigenetic ageing. In Chapter 3, I outline the measures and methods used in my study to answer my research questions above. I then document my findings and further discuss my results in Chapters 4 and 5 respectively. Finally, I summarise the key takeaways from this study and highlight several implications for the field in Chapter 6. I further discuss the strengths and limitations of my study, and suggest potential avenues for future research in this chapter.

2 Literature Review

2.1 The Long Arm of Childhood

The notion that early life adversities may have enduring effects on later life outcomes is commonly referred to as the 'long arm of childhood' hypothesis. Early research has found adverse childhood experiences (ACEs) to contribute to inequalities in adult mental health, such as disparities in depression and anxiety risk (Gajos et al., 2022; Schilling et al., 2008), life satisfaction (Hughes et al., 2016); as well as other mental health disorders (Ford et al., 2011; Gilman et al., 2015; Pirkola et al., 2005). Physical health conditions too, may be reflective of the effects of exposure to early childhood adversities. For instance, individuals exposed to childhood adversities were more likely to be obese (Grilo et al., 2005); and exposure to environmental stressors such as early socioeconomic hardship were also inversely associated with body mass index (BMI) among adults above 26 years old (Poulton et al., 2002). Such effects persist across the life course, with prolonged exposure to poverty correlating with an accelerated weight gain trajectory (Wells et al., 2010). Evidence linking ACEs to various forms of later life disadvantages also appear to be robust: various meta-analyses find childhood maltreatment to be associated with elevated risks of developing obesity over the life course (Danese & Tan, 2014), recurrent depression and anxiety (Li et al., 2016; Nanni et al., 2012), as well as increased substance abuse (Dube et al., 2001; Felitti et al., 1998; Schilling et al., 2008; Shin et al., 2018). Ultimately, these studies suggest that ACE exposure is associated with overall negative consequences for one's future outcomes.

A recent development in this field pertains to epidemiological research concerned with DNA methylation (DNAm). In technical terms, DNAm refers to an epigenetic alteration involving the addition of a methyl group to a cytosine nucleotide at a cytosinephosphate-guanine (CpG) site (Schmitz et al., 2023). On a practical level, DNAm influence gene expression over time, contributing to particular profiles of developmental pace, (mental) health outcomes, and behaviours (Essex et al., 2013). Existing studies have documented for instance, increased DNA methylation in the glutamate receptor NMDA type subunit 2b (*GRIN2B*) gene in response to childhood adversity (Engdahl et al., 2021), which are in turn associated with impaired mental and cognitive development, and is more prominent within schizophrenia patients (Fachim et al., 2019). Such findings have been replicated widely, finding an association between ACE exposure and DNAm in other genes as well (Heijmans et al., 2008; McGowan et al., 2008; Oberlander et al., 2008; Terry et al., 2008). Effects of ACE exposure may therefore be biologically embedded and manifest through methylation patterns within individuals.

2.2 DNA Methylation and Epigenetic Clocks

In examining DNAm patterns, one recent development has found biomarkers of ageing based on DNAm data to be highly predictive of age estimates for human tissues across the life course. DNAm age acceleration, or epigenetic accelerated ageing (EAA), then results when the age of one's human tissues is observed to be older than his/her chronological age. Some studies propose that adversity exposure are linked to the accelerated ageing of these tissues (i.e., EAA), which contribute to multi-morbidities and deterioration of bodily function (D.

W. Belsky et al., 2017). In this model, social stressors lead to changes in cellular processes associated with accelerated ageing (Miller et al., 2011) and heightened systemic inflammation, which is often treated as a regulator of mood and a pathway to various physical ailments (Slavich & Irwin, 2014; Wiss & Brewerton, 2020). Such epigenetic ageing in recent research are quantified through epigenetic clocks, which are subsets of DNAm markers (CpG sites) that accurately predict chronological ageing and DNAm-predicted age relative to chronological age (Hannum et al., 2013; Horvath, 2013, 2015). Put simply, epigenetic clocks can be thought to represent the pace at which the body ages (or risk of being infected by age-related diseases) independent of one's actual number of years lived. Unlike chronological age which increases at the same rate for all individuals however, epigenetic clocks measure one's *biological age* which may vary even among individuals born at the same time.

Recent efforts dedicated to measure biological age through DNAm data have resulted in three 'generations' of epigenetic clocks. Such epigenetic clocks are built using supervised machine learning methods incorporating penalised regressions (i.e., LASSO or elastic net techniques) trained against chronological age to identify relevant epigenetic markers (Bell et al., 2019). *HorvathAge* and *HannumAge* are two examples of first generation clocks which are highly predictive of one's chronological age and all-cause mortality at a population level. These predictions are however less accurate at an individual level, and demonstrate weak associations with physiological conditions (Horvath & Raj, 2018), even after accounting for known risk factors (Chen et al., 2016). Subsequent efforts directed at improving its predictive power then gave rise to second- and third-generation clocks, which are trained on age-related phenotypes

and diseases as well as chronological age (Bell et al., 2019). The predictive performance of these clocks are found to have significantly improved, as shown by its robust associations with various age-related diseases (Fransquet et al., 2019). An example of such a clock is the *PhenoAge* clock, which was able to capture tobacco-driven DNA methylation – an observation not captured by first generation epigenetic clocks (Horvath & Raj, 2018). Another example pertains to the recent development of the *GrimAge* epigenetic clock trained on smoking-related DNA methylation changes, which was shown to strongly predict lifespan and health span (Lu et al., 2019).

In recent years, EAA has been found to be associated with ACE exposure. Children encountering elevated parental depression at age 11 were found to experience accelerated ageing even nine years later at 20 years of age (Brody, Yu, et al., 2016). Children encountering various forms of maltreatment such as violence (Jovanovic et al., 2017; Sumner et al., 2019), sexual/emotional abuse, and neglect (Lawn et al., 2018; Wolf et al., 2018) were similarly found to predict advanced EAA. On the other hand, EAA were also found to contribute to various later life outcomes such as cardiovascular disease (Roetker et al., 2018), cancer (Durso et al., 2017), and all-cause mortality (Marioni et al., 2018). Theoretically, this suggests the possibility of EAA as a midstream mechanism mediating the relationship between ACE exposure and poorer life outcomes as commonly documented in various sociological studies. Childhood experiences may therefore extend its 'long arm' to affect social outcomes, in part, through biologically mediated mechanisms such as epigenetic ageing. Inequalities in ACE exposure during childhood then, may translate into the unequal distribution of population outcomes in

adulthood.

It is notable however that findings of adversity-induced accelerated ageing varied by the kinds of epigenetic clocks used within each study. ACE exposure were typically associated with accelerated ageing when using second- or third-generation clocks designed to capture mortality and disease risk, (Copeland et al., 2022; Sumner et al., 2019), but not when using first-generation clocks designed to predict chronological age (Fiorito et al., 2017; Marini et al., 2020; Simons et al., 2016). Part of the reason could be that epigenetic biomarkers (i.e., CpG sites wherein DNA methylation happens) associated with chronological age are largely independent from those associated with mortality and disease risk. Childhood adversity effects on biological age may thus differ depending on which epigenetic clock is used in the study. Newer epigenetic clocks may be more relevant in investigating the role of accelerated ageing as a biosocial pathway linking ACE exposure and EAA, given its ability to better predict time-to-death and other health-related phenotypes (Lu et al., 2019).

2.3 Mechanistic explanations of stress-mediated epigenetic ageing

Comprehending the biological mechanisms that underpin both stress responses and biological aging is crucial to elucidating the interplay between psychosocial stress and epigenetic aging. A core mechanism that relates to such stress-mediated epigenetic ageing pertains to *epigenetic regulation*, which refers to a series of processes that impact gene expression and function without altering the underlying DNA sequence (Gassen et al., 2017). Put otherwise, a key role of the epigenome is to serve as an interface between environmental exposures such as life

stressors on the one hand (Telese et al., 2013; Zannas & West, 2014), and the regulation of gene expression and function on the other (Brunet & Berger, 2014). Among the broad range of biological processes constituting epigenetic regulation, studies have typically paid attention to DNA methylation within CpG sites related to ageing, with the aim of uncovering relationships between life stressors and epigenetic ageing (Gassen et al., 2017). Indeed a plethora of studies have demonstrated that early life stressors can provoke such DNA methylation both in the short and long term (Boks et al., 2015; Brody, Yu, et al., 2016; Brody, Miller, et al., 2016; Klengel et al., 2013), potentially serving as a pathway between stress and epigenetic ageing.

A key component underlying epigenetic processes of stress response is the hypothalamic-pituitary-adrenal (HPA) axis. When faced with stressful situations, the HPA releases cortisol, commonly referred to as the 'stress hormone'. This triggers a process called glucocorticoid signaling, where cortisol binds to glucocorticoid receptors within cells and interacts with specific regions of DNA, thereby regulating gene activity. Importantly, this binding process has been observed to induce lasting changes in DNA methylation at CpG sites that are highly relevant to epigenetic clocks (Klengel et al., 2013; Zannas et al., 2015), potentially influencing one's biological age. Stress-induced alterations in DNA methylation and other epigenetic modifications may increase the susceptibility of stress-related genomic sites to environmental influences, ultimately contributing to accelerated epigenetic aging. Indeed, research supports this idea, showing that older individuals who have experienced higher levels of lifetime stress demonstrate more pronounced effects of epigenetic ageing (Zannas et al., 2015). This suggests that environmental stressors have an amplified ageing effect on the epigenome beyond that pre-

cipitated by the natural ageing process (Zannas et al., 2015). Instead, it indicates a synergistic relationship between life stressors and advancing age in influencing epigenetic aging.

Furthermore, research has also demonstrated the consequential impact of chronic stress exposure on the epigenome, particularly concerning DNA methylation patterns within stress-responsive genes. For instance, genes central to the stress response, such as the NR3C1 gene, exhibit altered DNA methylation profiles following chronic stress exposure (Cecil et al., 2020; Martín-Blanco et al., 2014). Otherwise, DNA methylation within the FKBP5 gene has been identified as a potential mediator of the relationship between childhood trauma and the onset of epigenetic ageing (Klengel et al., 2013). Recent advancements have further elucidated the intricate interplay between aging, stress, and FKBP5 DNA methylation, unveiling synergistic effects that exacerbate risks of inflammation and cardiovascular diseases (Zannas et al., 2019). Where psychiatrical studies have elucidated to a great extent the mechanistic processes linking life stressors and epigenetic ageing however, lesser known are whether and how specific *types* or *timing* of environmental stressors affect such age-related phenotypes. I turn to the available but limited range of studies examining these issues next.

2.4 Types of ACEs

Given that ACEs are often multifaceted, studies have found that different *types* of adversity have differential impacts on EAA (among other outcomes). For instance among ten different kinds of ACE exposure, Tang et al. (2020) found only emotional and physical abuse to be associated with DNAm age acceleration in UK children. Sumner et al. (2019) similarly

found only experiences of childhood threat to be associated with accelerated biological ageing in children and adolescent, but not that of deprivation. Similar findings exist beyond studies relating to EAA. Among various kinds of ACEs, Farkas & Jacquet (2023) found only childhood deprivation to explain accelerated BMI growth over time. In another study, Lanier et al. (2018) also found poor socioeconomic circumstances to best predict health risk relative to other forms of physical and emotional abuse. This suggests that specific types of chilhood adversities may lead to divergent downstream mechanisms, contributing to differentiated outcomes over time.

Decomposing ACEs into specific subtypes also have the advantage of uncovering contradictory effects that specific ACE events have on individual outcomes This is demonstrated by the finding that interpersonal (e.g., violence) and community-related (e.g., parental depression) adversity types were associated with lower BMI z-score; but deprivation and (socio)economic adversity were contrastingly associated with greater BMI z-score (Schuler et al., 2022). To further understand the heterogeneous effects of different ACE types on EAA, I elaborate on the dominant forms of childhood adversities commonly discussed in the literature.

2.4.1 Childhood Maltreatment

Most scholarly attention have focused on childhood maltreatment, usually comprised by various dimensions of abusive behaviours. Most commonly employed dimensions of childhood maltreatment are those relating to sexual abuse, physical, and emotional abuse, as well as (parental) neglect, often measured by the Parent-Child Conflict Tactics Scales (CTSPC)

(Straus et al., 1998). Across studies, childhood maltreatment have largely been found to correlate with EAA. Focusing on a sample of children with internalising disorder, Dammering et al. (2021) found those exposed to maltreatment to correlate with an accelerated pediatric buccal (PedBE) epigenetic clock, but not among those unexposed. Children exposed to sexual abuse, and especially those with repeated exposures, were also found to have increased methylation (Lang et al., 2020). Other kinds of ACEs, and especially childhood physical abuse, have also been found to correlate with elevated methylation in candidate genes associated with stress response (e.g., *NR3C1*, *FKBP5*, *OXTR*) (Cecil et al., 2020; Martín-Blanco et al., 2014). Genome-wide approaches have too been adopted recently to examine such associations, finding significant links between childhood maltreatment and DNAm patterns across numerous genes (Cecil et al., 2020; Sosnowski et al., 2018).

Within the childhood adversity literature more broadly, ACE exposure has been associated with various detrimental later life health outcomes. Controlling for various stressors and psychosocial factors, respondents who reported severe sexual abuse in childhood had significantly elevated body weight; while less severe forms of sexual abuse had non-significant effects (Williamson et al., 2002). Victims of physical and emotional abuse, as well as childhood neglect were also reported to be at a greater risk of higher adiposity in adolescence (Fleischer et al., 2021; Thomas et al., 2008). Such effects persist many years later into adulthood, with individuals exposed to childhood physical abuse experiencing significantly higher risks of severe obesity compared to those unexposed (Richardson et al., 2014; Rohde et al., 2008).

Heterogeneity may exist however, even among the different kinds of childhood maltreatment

exposure. Cecil et al. (2016) found DNAm ageing to differ in extent depending on the kinds of childhood maltreatment experienced. This is because different kinds of abuse and neglect are linked to varying kinds of epigenetic signatures, which in turn exert differential impacts on one's neural development and brain function associated with DNAm (Lang et al., 2020). Unique DNAm signatures exist, for instance, in individuals who developed PTSD as a result of childhood abuse rather than other forms of trauma (Mehta et al., 2013). In examining how combinations of childhood abuse affect BMI trajectories, Sacks et al. (2017) also found latent classes characterised by neglect and physical abuse to correlate with faster BMI gain, as compared to standalone latent classes or those involving emotional abuse.

Existing research also suggests that the influence of child maltreatment on stress response may vary according to gender. Notably, exposure to physical and sexual abuse has been shown to exert a more pronounced effect on methylation at the OXTR gene among females compared to males (Gouin et al., 2017). Additionally, trauma resulting from abuse appears to regulate the hypothalamic-pituitary-adrenal (HPA) axis responses more prominently in women (De-Santis et al., 2011), indicating that girls may exhibit greater susceptibility to the impact of maltreatment on stress-related biomarkers. Yet interestingly, within-gender analyses revealed that maltreated girls tend to display reduced methylation at the aldehyde dehydrogenase 2 gene (commonly associated with digestive tract cancer and metabolism) compared to non-maltreated girls, in contrast to maltreated boys who demonstrate elevated methylation relative to their non-maltreated counterparts (Cicchetti et al., 2016). This suggests that gender dynamics may differ according to specific biomarkers, thus illustrating the need for a nuanced

understanding of how gender interacts with various biological mechanisms in response to child maltreatment.

Beyond biomarkers of stress response, gender is also commonly found to moderate the effects of ACE exposure on mental health. Female adolescents were found to suffer magnified mental health problems and internalising symptoms relative to their male counterparts in response to emotional maltreatment (Hagborg et al., 2017). Sexual abuse too, was found to be uniquely associated with internalising problems among girls and externalising problems among boys (Vahl et al., 2016), signalling gender differences in stress response behaviours. Furthermore, where child maltreatment predicted the early onset of behavioural problems that diminished over time among boys, initial detection of behavioural problems were not evident among girls, but intensified and became pronounced over time (Godinet et al., 2014). Ultimately, these distinct patterns suggest the presence of gender-specific responses towards ACE exposure, underscoring the importance of conducting gender-stratified analyses.

2.4.2 Material Hardship

Another strand of research has also focused on the detrimental effect of early socioeconomic-linked deprivation on later outcomes. Often measured in terms of family-linked income/occupation or poverty levels, research indicates that early life socioeconomic adversity is significantly linked to accelerated biological ageing. A study pertaining to older aged individuals (50-87 years old) found older GrimAge and DunedinPoAm DNAm epigenetic clocks to be associated with individuals who reported growing up poor, but not with other ACEs such

as childhood maltreatment or parental drug abuse (McCrory et al., 2022). Children living in disadvantaged families and neighbourhoods also exhibited accelerated pace of ageing, with higher levels of disadvantage for Latinx-identifying children compared to White- and Latinx White-identifying children (Raffington et al., 2021). Because early childhood represents a crucial development phase for individuals, socioeconomic disadvantage may therefore be thought to translate into early life stressors in the form of resource deprivation crucial to one's growth.

But recent findings restrict the validity of such a suggestion. While some studies have found signficant relationships between childhood socioeconomic status and later EAA, effect sizes are notably small (Fiorito et al., 2019), suggesting that material circumstance play a limited role in influencing epigenetic age. Furthermore, such findings of a significant relationship are also not unanimous. K. Kim et al. (2023) found early SES circumstances to no longer be significant once the number of ACEs experienced by individuals are controlled for; while meta-analyses and systematic reviews also concluded that SES was unrelated to epigenetic age or other stress-related biomarkers in children (Colich et al., 2020; Wood et al., 2020). Evidence for gender differences are also rather equivocal, with some studies demonstrating a stronger SES-EAA relationship among men than women (Avila-Rieger et al., 2022), but other studies failing to detect significant gender effects (Fiorito et al., 2019). Further research is therefore needed to establish how SES differentially affects epigenetic ageing by gender.

Such mixed findings could be due to the retrospective research design employed especially in older studies. Participants' reports of their past experiences may be subjected to recall

bias, since current mental health status may influence one's ability to accurately recall their past adverse experiences (Hardt & Rutter, 2004). In particular, participants afflicted with poorer health (e.g., depression) may be more disposed to recall, or exacerbate their ACE exposure in contrast to those unaffected. This may in turn contribute to greater rates of false positives/negatives, resulting in biased estimates when measuring the association between ACEs and EAA outcomes. On the other hand, recent studies which tend to employ prospective cohort study designs, may obtain estimates less affected by recall bias, and thus differ in their conclusions from older studies.

2.4.3 Early Life Instability

Apart from material hardship, less studied are the effects of early life instability, where turbulent environmental changes generates uncertainty or unpredictability regarding one's short- or long-term future. Emerging studies emphasise the importance of studying the effects of unpredictability on later-life health outcomes because such uncertainty were associated with greater functional disability and health-related quality of health, even after controlling for poverty and other ACEs (Maner et al., 2023). Indeed, Simons et al. (2022) find unstable childhood events –such as parental divorce; changing schools; and residential moves– to be significant predictors of epigenetic age. J. K. Kim et al. (2023) provided further evidence of such findings, although only for the older cohort within his study.

Childhood instability in the broader literature have further been found to correlate with various detrimental outcomes. In neurobiological studies, functional magenetic resonanace imaging

(FMRI) scans reveal significant changes to neurological structure and function for those exposed to unpredictable childhood environments (Luo et al., 2024). Such alterations in turn affect DNAm patterns that influence gene expression, and which translate into behavioural risks that contribute to poorer social outcomes in adulthood (Berens et al., 2017). Unstable environments may therefore serve as an upstream risk factor with enduring effects for one's epigenetic age and other outcomes. Epidemiology research commonly propose a life history theory perspective to explain this link – exposure to unpredictable environments inculcate in individuals a fast life-history strategy, characterised by impulsivity and a focus on short-term rewards. This may translate into detrimental behaviours and outcomes associated with EAA, such as binge-eating and obesity (Ben-Shlomo & Kuh, 2002; Simpson et al., 2012). A direct examination of this theory indeed found that exposure to childhood unpredictability is predictive of a fast life-history strategy; and which is further predictive of dysregulated weight-management behaviour associated with obesity and having a high BMI (Maner et al., 2017). Such findings have been widely replicated in other studies as well, finding a fast life-history strategy to be associated with EAA-linked outcomes such as a lower age at menarche and age at first birth (AFB) (Schlomer, 2024; Sýkorová & Flegr, 2021).

Environmental instability during childhood may exert gender-differentiated effects on one's later life outcomes as well. While no study has so far examined such effects on epigenetic age, existing studies are unanimous in finding that familial instability poses greater socioemotional risks to boys compared to girls (Capaldi & Patterson, 1991; Cavanagh et al., 2008; Cavanagh & Huston, 2008). In particular, boys who experienced more parenting transitions

were likelier to report greater amounts of antisocial behaviours (Capaldi & Patterson, 1991; Cavanagh & Huston, 2008), as well as poorer mental well-being and social development in elementary school (Cavanagh et al., 2008). Such an association is mediated in part by their greater likelihood of having antisocial mothers with poor parental skills, which translate into externalising behaviours and impaired competencies at forming social relationships (Cavanagh & Huston, 2008).

2.4.4 Familial Deprivation

A final ACE domain commonly studied pertains to family deprivation, often referring to dysfunctional parenting styles or the absence of affection during one's childhood. Evidence finding support for a significant relationship between familial deprivation and EAA is scarce. Among the limited number of studies available, only one study's findings was suggestive of a link between family environment and EAA. In particular, Mrug et al. (2024) finds familial environments to significantly moderate the effect of neighbourhood adversity on one's epigenetic age, although the sample size is relatively small ($n = 343$). Other studies however report the opposite: Cole (2023) reports no signfiicant association between parenting behaviour and DNAm outcomes; while a direct examination of this link finds no association between early life deprivation and EAA development (Colich et al., 2020).

Literature in the broader ACE literature however finds direct links between familial environments and subsequent life outcomes. Individuals exposed to single-parent status in childhood, for instance, were more likely to be overweight and have higher BMI than those with dual-

parent households (Gibson et al., 2016; Huffman et al., 2010). Insecure parenting styles in childhood, characterised by the use of regulatory practices and the inability to make children feel safe, were also found to be a significant risk factor for subsequent obesity (Mazzeschi et al., 2014). Positive parenting in childhood, characterised by cultivating a supporting and warm environment for growth, also predicted later AFB among youths (Arends, 2011). Mechanisms proposed to explain such links commonly relate to the development of self-regulation strategies resonant with the fast life-history strategy mentioned earlier: children who encounter unsafe upbringing environments during their developmental phase are likelier to develop an inclination for risky behaviours and short-term rewards. This inculcates in children a proclivity to turn to maladaptive self-regulation strategies, such as binge eating (DeOliveira et al., 2005; Solomon & George, 1999) and a lower threshold to act on one's sexual desires (Sýkorová & Flegr, 2021).

Broadly, existing research also indicates that negative maternal parenting styles tend to correlate with poorer sociobehavioural outcomes specifically among girls, while negative paternal parental styles are more likely to be associated with detrimental outcomes among boys. High levels of maternal control, for instance, are shown to be be linked to later life anxiety and substance abuse only in girls, while similarly high paternal control is correlated with substance abuse only among men (Barton & Kirtley, 2012; Eun et al., 2018). Furthermore, paternal control is found to be associated with nine mental disorders in men, compared to only one in women, demonstrating a strong alignment between parental parenting styles and male outcomes (Eun et al., 2018). No existing study have examined how the effects of family deprivation

vary according to gender.

2.5 Theoretical Perspectives of ACE Exposure

Several life course theoretical perspectives have been studied in the relationship between ACE exposure and subsequent life outcomes. Specifically, three models have been broadly proposed in the ACE literature: *recency; cumulative risk; and sensitive periods.* The *recency model* suggests that health outcomes are most associated with proximal, rather than distal exposures to ACEs (Shanahan et al., 2011). In other words, recent exposures to ACEs better account for one's outcomes, compared to those occurring a longer time ago. The notion of *cumulative risk*, meanwhile, is most directly examined in the accumulation of risk model. This model posits an additive relationship in which each additional ACE exposure is correlated with increased risk of a particular outcome, regardless of one's timing of exposure (Evans, 2004). This contrasts directly against the *sensitive period hypothesis*, which proposes that outcomes are shaped substantially by the specific timing during which individuals are exposed to ACEs. Specifically, ACEs are presumed to have the largest effect on an individual's long term outcome during one's developmental phase, when they experience the greatest maturation and neurological plasticity (Bailey, 2001; Knudsen, 2004). ACEs encountered during this phase therefore exert the greatest effect on one's later life circumstances, rather than the recency or accumulation of such exposures.

Within the broader ACE literature, various studies have found support for the recency hypothesis. More recent exposures to ACEs for instance, are associated with greater harmful

effects on mental health, with the recency of exposure explaining the greatest variation of psychopathological symptoms in boys and girls exposed to physical/sexual abuse, and in girls exposed to caregiver physical/emotional abuse (Dunn et al., 2018). Adversity effects on adult depression are also found to be elevated if they occur within the same month (Kendler et al., 1999) or year (Dunn et al., 2012), suggesting that the proximity of ACE exposure matters for one's later outcomes. Epidemiological studies found mixed support for this hypothesis. In particular, the recency of ACE exposure significantly explained alterations in vagal reactivity[1] (Wesarg et al., 2022), but not DNA methylation (Dunn et al., 2019; Lussier et al., 2023a) or epigenetic age measured by first generation clocks (Marini et al., 2020). With the exception of Dunn et al. (2018) who demonstrated sex-differentiated responses towards ACE exposure, it is crucial to note that no studies have examined the recency effect of ACE exposure broken down by sex or the type of ACE event.

Most support have been found for the sensitive period hypothesis. In contrast to its recency, the timing of exposure appears to exert a greater impact on life outcomes if it occurs during sensitive periods. Studies for instance, found variation in DNA methylation to be explained more by ACE exposures in early childhood (approximately age 3-5) rather than by its recency of exposure (Dunn et al., 2018; Lussier et al., 2022; Lussier et al., 2023b). Exposure to maltreatment or socioeconomic disadvantage in early and middle childhood (age 3-7) were also found to best explain variability in epigenetic age measured by first-generation clocks (Marini et al., 2018; Marini et al., 2020). Other sensitive periods proposed include middle-late

[1]Vagal reactivity refers to the responsiveness of the vagus nerve that affect can affect bodily functions, and is linked to how the body responds to stress

childhood, as well as in adolescence (Gerke et al., 2018; Wesarg et al., 2022).

Studies within the broader ACE literature also demonstrate support for these sensitive periods. Emotional neglect during middle-late childhood (age 6-12) for instance, is associated with an increased risk of depression (Schalinski et al., 2016); while gene-environment interactions (GxE) regulating depression risk was particularly prominent during sensitive periods of age 1-5 years. Notably however, different kinds of ACE exposure may vary in their sensitive periods in predicting the same outcome. Khan et al. (2015) find for instance, that suicide ideation among young adults is most strongly predicted by parental verbal abuse during middle childhood (age 5), but only late childhood (age 14) for non-verbal emotional abuse and peer emotional abuse. Sensitive periods therefore vary by the kinds of ACE exposure in question, suggesting that adversity at different developmental phases may contribute towards distinct consequences in later life. This highlights the importance of conducting domain-specific exposure to ACEs in investigating the relevance of the sensitive period (and other) hypothesis (Gabard-Durnam & McLaughlin, 2019).

Finally, many studies have examined the relevance of accumulative ACE exposure in influencing later life EAA. Examining a sample of children with extremely low birth weight, Mathewson et al. (2021) found risk factors to be related to DNAm age in an additive fashion – for each additional risk factor experienced, biological age was observed to increased by 2.16 years in adulthood (age 32). A linear change in DNAm age was also found to pattern with every point increase in the cumulative adversity index summing up ACEs across various dimensions (Copeland et al., 2022). Such a trend was also observed to hold when ACE exposure was

summed longitudinally across time periods (Shenk et al., 2022). Evidence of such a link is however not robust. Cumulative risks were not found to be significantly associated with cellular ageing in adolescence (age 10) (Beijers et al., 2023) nor adulthood (Lawn et al., 2018; McCrory et al., 2022). Such mixed findings may potentially be attributed to how cumulative risk is operationalised within these studies. Studies that found support for the cumulative risk hypothesis appeared to sum up ACE exposure *across* several ACE domains; whereas those which found little support for the hypothesis tended to examine cumulative ACE exposure *within* a single domain. Noting that ACE domains may be differentially associated with epigenetic ageing (Gabard-Durnam & McLaughlin, 2019), cumulative risk effects observed in the former may simply be driven by exposure to certain kind(s) of ACE domains highly associated with EAA. Contrastingly, the latter approach may fail to observe significance because the ACE domains examined in those studies are less predictive of later life EAA. Thus, a subsequent inquiry along this strand of research could be to establish 1) if cumulative risk applies within *domain-specific* ACE exposure, and 2) across *which* domains does this hypothesis hold true. No study has examined this yet.

2.6 Linking the literature to this study

Research so far has established robust links between ACE exposure and epigenetic ageing in later life, as well as varying levels of support for different life course models (i.e., cumulative risk; recency; sensitive period). Various gaps are however present within this literature. First, although studies have established support that all life course models explain to some extent

the relationship between ACE exposure and EAA, no research has examined which of these models still stand when all of them are considered altogether. Relevant research considering relationships between ACEs and later-life psychopathological symptoms found for instance, only the sensitive period to hold when all life course models are considered altogether (Dunn et al., 2018). Only one other study have attempted to collectively examine all life course models with respective to EAA, using only first generation epigenetic clocks (Marini et al., 2020). But first generation epigenetic clocks are only designed to measure chronological age, which is less influenced by social environments (Horvath & Raj, 2018). Newer epigenetic clocks meanwhile are more predictive of outcomes highly influenced by social factors, such as health and mortality outcomes. Utilising newer epigenetic clocks may therefore uncover novel insights pertaining to the relationship between ACE exposure and epigenetic ageing, as well as other relevant phenotypes. Reiterating my first research question, I therefore ask: which theoretical model best explains the link between ACE exposure and epigenetic ageing as measured by newer epigenetic clocks?

Existing studies posit that individuals in early childhood (ages 1–5) undergo a sensitive period during which they experience elevated neurodevelopmental plasticity, compared to middle-late childhood (ages 6-12) (Bailey, 2001; Knudsen, 2004). This developmental phase constitutes a core phase of their growth, and has an enduring impact of later life outcomes. Thus, although the accumulation of ACEs and the recency of exposure are likely to affect adolescent EAA outcomes, I expect exposure to ACEs during the sensitive period to account for most variation in EAA across all ACE domains.

Second, studies have not attempted to examine if such links remain robust when childhood adversity are broken down into respective ACE domains. Considering the potential heterogeneity across ACE dimensions and its differentiated effects on subsequent outcomes within the literature, my second research question is therefore concerned with the question of how the relationship between ACE exposure and EAA differ by ACE domains. Because associations between the different kinds of ACEs and epigenetic age outcomes are complex and multifaceted, I do not attempt to predict how life course hypotheses differ by the ACE domain in question. Instead, I delineate below the circumstances under which a particular life course hypothesis is more adept at elucidating certain ACE domains while potentially being less applicable to others.

Sensitive periods for particular kinds of ACEs may arise because children within sensitive periods are highly susceptible to events which deprive them of *expected* familial/environmental inputs (Gabard-Durnam & McLaughlin, 2019). Additionally, given the enhanced neurodevelopmental plasticity experienced during sensitive periods, children may be additionally susceptible to highly dysfunctional environments inflicting direct harm to them. From an attachment theory perspective, such abuses are contrary to inherent expectations of safety and nurturance from their caregivers, thus promoting avoidance- rather than approach-based techniques in response to stressful experiences (e.g., aggression, frustration), which are in turn related to accelerated ageing (J. Belsky et al., 1984). Thus, ACEs which are best explained by a sensitive period hypothesis may refer to those in which there is a rift between a child's expected and immediate environments.

Meanwhile, a cumulative risk hypothesis best explains ACEs which are chronic and accumulative, rather than those that are more sporadic in nature. Under the cumulative risk perspective, ACEs are thus conceptualised as cumulative burdens that accrue over time and are more persistent in nature. This is in contrast to the sensitive period hypothesis, in which sudden unexpected exposures during vulnerable periods are sufficient for inducing long term ramifications, even if children are not consistently exposed to such ACEs. A cumulative risk hypothesis may therefore be better suited to explain socioeconomic circumstances, such as parental social class and income, which are likely to be stable over time and unlikely to fluctuate across time periods.

The application of a recency model, on the other hand, emerges as a compelling framework for understanding ACEs characterised by prolonged states rather than discrete events. In such instances, ongoing processes such as parent-child relationships, are better explained by a lens that prioritises a continual state of development rather than historical occurrences. Parent-child relationships, for example, represent an evolving and continuous development where children are significantly influenced by the prevailing conditions of their relationship, rather than that of the past or events that occured at a particular period of time. Thus, children experiencing parental absence for instance, may experience distress regardless of historical periods of positive interaction.

Finally, although existing studies have attempted to identify significant predictors of EAA, there is a dearth of literature investigating the pathways linking ACE exposure to later life EAA. It is against this lack of research that my third research question asks: which risk factors

mediate the relationship between ACE exposure and EAA? As mentioned above, because many studies have found ACE exposure to significantly predict risky health behaviours (e.g., smoking and binge eating) as well as worsened mental health outcomes (e.g., depression and anxiety), such stressors may serve as midstream mechanisms that regulate later life EAA. Thus, I expect risk factors examined in this study – depression; internalising and externalising behaviour; smoking; alcohol abuse; drug abuse; and BMI z-scores – to mediate the relationship between ACE exposure and EAA.

3 Data and Methods

3.1 Data

I perform my analysis on data derived from the Future of Families and Child Wellbeing Study (FFCWS). The FFCWS utilises a stratified multistage sampling methodology, comprising a sample of 4898 children born between 1998-2000 and their families. Notably, births to unmarried mothers were intentionally oversampled at a ratio of 3 to 1, ensuring comprehensive representation across various demographic groups, including Black, Hispanic, and low-income households. Initial interviews were conducted with mothers shortly after childbirth, while father/paternal interviews were conducted either in hospital settings or via telephone. The FFCWS follows participants across 7 waves, corresponding to the focal child's age at birth, 1, 3, 5, 9, 15, and 22 years. Further information is provided within the FFCWS public documentation (FFCWS, 2023).

Several surveys and data types exist within the FFCWS. Pertinent to my analysis are 1) the primary caregiver (PCG) survey; 2) the core mother's survey; 3) the core father's survey; 4) the child survey; and 5) the biomarker data. The PCG surveys are conducted with the primary caregiver of the focal child (typically the mother) from wave 3 onwards, and are typically concerned with data about the child's upbringing (e.g., disciplinary measures; parent-child relationship). The core mother and father's survey are conducted across all waves (1-6), and collects data pertaining to the personal circumstances of both parents (e.g., legal troubles; substance abuse). The child survey is collected in both waves 5 and 6, and is concerned with the personal circumstance of the focal child, such as his mental health and educational attainment. Finally, the DNA sampling data is also collected in waves 5 and 6, and consists of biomarker data of the focal child such as telomere length data and DNAm age data.

3.2 Measures

3.2.1 Epigenetic Clock

Epigenetic accelerated ageing, obtained through the DNA collection exercise in wave 6, serves as the outcome variable in this study. The DNA extraction process was carried out within one to two weeks after receiving saliva samples by participants. The entire sample was utilised for DNA extraction using the Oragene prepIT.L2P Laboratory Protocol for Manual Purification of DNA provided by DNA Genotek. Subsequently, the extracted DNA samples underwent bisulfite conversion using the EZ-96 DNA Methylation Kit. Genome-wide methylation profiles were then generated using either the Illumina Infinium Human Methylation450K (450K) or

Illumina Infinium MethylationEPIC (EPIC) array. These DNA methylation data were then used to create various epigenetic clocks used in this study. Further information is provided within the FFCWS public documentation (FFCWS, 2023).

I utilise one new generation epigenetic clock for my analysis collected in the Year 15 (Wave 6) of the FFCWS restricted data: GrimAge. To reduce the number of missing cases, I combine DNA methylation age data generated by both Illumina 450K and EPIC arrays, in line with present recommendations (Fernandez-Jimenez et al., 2019; Toro et al., 2023). GrimAge (Variables *k6me_grim/k6mk_grim*) measure one's epigenetic age. To ascertain if an individual is biologically older or younger than his/her chronological age (i.e., accelerated vs decelerated epigenetic ageing), one's epigenetic age is frequently compared against his/her chronological age. If one's epigenetic age is older than their chronological age, then this individual is said to experience accelerated ageing. In this study, accelerated ageing is derived by residualising one's epigenetic age with respect to his/her chronological age. Thus,

$$EAA = Age_{epigenetic} - Age_{chronological}$$

This allows me to examine how much variation in one's epigenetic age can be explained by external factors beyond one's chronological age. Positive and steeper residual values reflect greater extents of accelerated ageing; while negative values indicate the contrary. A residual value of 0 reflects that an individual's epigenetic age directly corresponds with his chronological age – i.e., that he/she is not experiencing accelerated or decelerated ageing.

3.2.2 Childhood Adversity Events

In line with the literature, four domains of adversity events are examined in this study: *Childhood maltreatment; Material Hardship; Early Life Instability; and Familial Deprivation.* These data were extracted from waves 2 to 5 of the parent-specific and PCG survey.

The first ACE domain –childhood maltreatment– measures the extent to which children were subjected to abuse behaviours by their parents/caregivers. Variables used to construct this ACE domain were similar for waves 3-5 (ages 3, 5, 9), while wave 2 (year 1) variables were carefully picked to match those in the later waves. For the year 1 data, childhood maltreatment was treated in terms of whether children were spanked by their mother or father. Caregivers who reported any values other than 'No' were treated as having engaged in childhood maltreatment. Childhood maltreatment from waves 3 to 5 were obtained using the subscales from the modified Parent-Child Conflict Tactics Scale (CTSPC) within the PCG survey. In particular, the modified CTSPC eliminated eight questions relating to severe physical maltreatment within the original CTSPC (Straus et al., 1998), and included the CTSPC's supplementary scale of *Neglect* (FFCWS, 2018). Questions within this modified CTSPC asked caregivers to report the frequencies of which they have inflicted physical or emotional harm to the focal child within the past year, including actions such as shaking, slapping or swearing at their child. The specific variables included in the analysis are documented within the appendix. Responses to these questions were rated on a 8-point scale based on the frequency of exposure (0 indicating *this has never happened* and 7 indicating *more than 20 times*). For all variables within the CTSPC, children were treated as being exposed to matlreatment if PCGs reported

any value other than 0.

The second ACE domain –material hardship– represents if children suffered socioeconomic disadvantage in their childhood. This is calculated using the poverty ratio calculated within the FFCWS across all waves. Mothers reported household incomes and the number of members within the family. Poverty ratios are then calculated by dividing the household income by year- and family-composition specific poverty threshold established by the US Census Bureau. Across all waves considered in this study, children were treated as having suffered material hardship if mothers reported being in poverty (i.e., poverty ratio < 1).

The third ACE domain –early life instability– indicates if children were faced with instability and changes linked to their familial environments. While early life instability has been operationalised in varied ways across the literature, I adopt the measure utilised by Doom et al. (2023), which considers changes in maternal romantic status across waves in the FFCWS. Mothers reported across all time points about their romantic relationship with the child's father. Relationship statuses reported include values such as still married; cohabiting; visiting; friends; or hardly/never speaking to each other. Parents who were still married, or were cohabiting were recoded as 1, and assigned a value of 0 otherwise. I then compared Year t romantic relationships with that in Year $t-1$. Children were treated as experiencing early life instability for that wave if the romantic relationship status of their mother was different from that a year earlier.

The final ACE domain –family deprivation– represents if children were exposed to parenting styles associated with a lack of affection or emotional unavailability. Similar to the above,

I adopt the measure utilised by Doom et al. (2023). For year 1, variables comprising this measure were not part of an existing scale within the FFCWS, but were chosen to reflect the growth environment and parent-child relationship. At year 1 of the survey, I chose six variables relating to maternal engagement and one variable relating to the child's food security. With respect to the former, researchers asked mothers the frequency with which they 1) engaged with their child (e.g., through games); 2) sang songs or nursery rhymes; 3) read stories to their child; 4) told stories to their child; 5) played using toys with their child; 6) demonstrated physical affection for their child. In the latter, mothers also reported if their child has ever went hungry within the past year. For the remaining waves 3 to 5, I derive five question from the CTSPC relating to the frequency with which mothers 1) were unable to express love to their child; 2) left their children alone; 3) unable to provide for their child medically; 4) provide food for them; and 5) too drunk to care for them. Across all waves, children were treated as being exposed to family deprivation if mothers reported a value other than 0 (never subjected their children to these behaviours in the past year).

3.2.3 Mediator Variables

To observe pathways linking ACE exposure and EAA, I examine six mediator variables. One mediator variable pertains to the mental health outcomes of the focal child in wave 6 of the FFCWS – Depression. Depression is measured by the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), as completed by the focal child in the child survey. Rather than the full 20-item CES-D, the modified 5-item scale was utilised given findings of better

cross-cultural comparability (Perreira et al., 2005). Specifically, the five questions inquired respondents about their feelings within the past week. Respondents rated each statement below on a four-point scale (1 = strongly agree; 4 = strongly disagree):

- I feel I cannot shake off the blues, even with help from my family and my friends (Variable *k6d2c*)
- I feel sad (Variable *k6d2n*)
- I feel happy (Variable *k6d2s*)
- I feel life is not worth living (Variable *k6d2x*)
- I feel depressed (Variable *k6d2ac*)

With the exception of *k6d2s*, I reverse code all variables such that a higher score reflects greater degrees of depression (1 = strongly disagree; 4 = strongly agree). I then take the mean of these variables up to create a scale of depression ranging from 1 to 4.

The second mediator variable pertains to the externalising behaviour of the focal child, as measured by the Child Behavioural Checklist (CBCL) Subscales within the Wave 6 PCG survey. PCGs were asked to rate on a 3-point scale how often the focal child engaged in problematic behaviours across various behavioural, emotional and social domains (0: Not true; 3: Often true). In line with the FFCWS documentation, measures of externalising behaviours were taken from the *aggressive* and *rule-breaking* subscales (FFCWS, 2023), and calculated as a mean of all variables involved. The aggressive subscales asked whether:

- Child is cruel, bullies, or shows meanness to others (Variable *p6b35*)

- Child destroys things belonging to the family or others (Variable *p6b37*)
- Child is disobedient at school (Variable *p6b38*)
- Child gets in many fights (Variable *p6b41*)
- Child physically attacks people (Variable *p6b42*)
- Child is stubborn, sullen, or irritable (Variable *p6b43*)
- Child has temper tantrums or a hot temper (Variable *p6b44*)
- Child threatens people (Variable *p6b45*)
- Child is unusually loud (Variable *p6b57*)
- Child argues a lot (Variable *p6b59*)

The rule-breaking subscale asked whether:

- Child doesn't seem to feel guilty after misbehaving (Variable *p6b49*)
- Child hangs around with others who get in trouble (Variable *p6b50*)
- Child lies or cheats (Variable *p6b51*)
- Child runs away from home (Variable *p6b60*)
- Child sets fires (Variable *p6b61*)
- Child steals at home (Variable *p6b62*)
- Child steals outside the home (Variable *p6b63*)
- Child swears or uses obscene language (Variable *p6b64*)
- Child vandalizes (Variable *p6b67*)

The third mediator variable relates to the internalising behaviours of the focal child. This was also calculated using the CBCL Subscales, and more specifically that of the *anxious/depression*

and *withdrawn* subscales. Measures of internalising behaviour was taken as the mean of the variables involved in these subscales. Specifically, the anxious/depression subscale asked if:

- Child cries a lot (Variable *p6b36*)
- Child feels worthless or inferior (Variable *p6b40*)
- Child is nervous, high-strung, or tense (Variable *p6b52*)
- Child is too fearful or anxious (Variable *p6b53*)
- Child feels too guilty (Variable *p6b54*)
- Child worries (Variable *p6b68*)

while the withdrawn subscale asked if:

- Child is underactive, slow moving, or lacks energy (Variable *p6b65*)
- Child is unhappy, sad or depressed (Variable *p6b66*)

The remaining mediators consider if the focal child has ever smoked (Variable *k6d40*) or engaged in alcohol abuse (Variable *k6d48*). Additionally, the focal child is considered to have engaged in substance abuse if he/she reported consuming either marijuana (Variable *k6f63*) or other drugs (Variable *k6f68*). The final mediator considers the tendency with which the focal child has engaged in adiposity-related behaviours such as binge eating, and is measured through self-reported BMI z-score in wave 6 (Variable *ch6bmiz*).

3.2.4 Covariates

Several demographic variables serve as covariates in this study. Research has found ethnicity and gender to be associated with both epigenetic ageing trajectories and the likelihood of ACE exposure (McCartney et al., 2019; Philibert et al., 2020), potentially confounding the relationship between the two. I include both measures as covariates. *Gender* (*cm1bsex*) is treated as a binary variable (*1 = male; 0 = female*), and ethnic categories (*ck6ethrace*) are included as nominal variables (*1 = White only, non-hispanic; 2 = Black/Af. American only, non-hispanic; 3 = Hispanic/Latino; 4 = Other only, non-hispanic*). Potential confounders suggested by other studies are also included within my analyses, including mother's race (*cm1ethrace*), mother's age at birth (*cm1age*), and mother's education levels (*cm1edu*) (Dunn et al., 2018). Mother's education is treated as four ordinal categories, with a higher score reflecting higher educational attainment:

1. Less than high school
2. High school or equivalent
3. Some college
4. College or graduate

3.3 Analyses

3.3.1 Structured Life Course Modelling Approach (SCLMA)

To adjudicate between the three theoretical models selected for this study, I adopt a two-stage Structured Life Course Modelling Approach (SCLMA) originally conceived by Mishra et al. (2009). In contrast to traditional longitudinal regression analyses, an advantage of SCLMA is in its ability to compare across multiple life course hypotheses simultaneously, and select the most parsimonious model in a structured and unbiased manner. I outline the various procedures undertaken in conducting my analysis.

Prior to conducting the SCLMA analysis, I operationalise the three proposed life course hypotheses in the following manner. In considering the cumulative risk hypothesis, exposures to any of these ACE events were summed together to construct a cumulative adversity index across all waves. Thus, the scores for the cumulative adversity index ranges from 0 (never exposed to any ACEs throughout all waves) to 16 (exposed to all four ACE domains throughout all 4 waves). An ACE-domain specific cumulative adversity index was also created by summing up ACE exposures across all waves *within a particular domain*. The minimum and maximum score for this cumulative adversity index is therefore 0 (never exposed to this ACE domain across all waves) and 4 (exposed to a particular ACE domain for all four waves) respectively.

To test the recency hypothesis, year-specific ACE exposures were weighted by the recency of their ACE exposure to calculate a recency index. This is achieved by multiplying the number of ACEs that the children were exposed to by their age when they were interviewed.

For instance, if children were exposed to 1 ACE during year 1 (wave 2 of the FFCWS), and 2 ACEs during year 9 (wave 5), then said child would have a recency score of $(1\times1)+(2\times9) = 19$. Recency scores *within particular domains* were also calculated in a similar fashion to create a domain-specific ACE recency index.

Finally, the sensitive period hypothesis is tested by calculating year-specific counts of ACEs that they were exposed to. This allows me to test if ACE exposures within particular sensitive periods/ages can explain variability in subsequent EAA outcomes. Sensitive periods of ages 1, 3, 5, and 9 years (corresponding to wave 2, 3, 4, and 5 of the FFCWS) were considered in this study. Ages 1 and 3 were treated as proxies for early childhood; age 5 as representing middle childhood; and age 9 as late childhood. Similar to the above, such scores are also additionally calculated within specific domains, to examine if sensitive periods exist/differ across different ACE domains. I summarise the three hypotheses in Table 1.

Table 1: Summary of tested life course models and how their treatment in analyses

Life Course Model	Definition	Calculation Method
Cumulative Risk	Sum of ACE exposures across all years and domains	sum(ACE count)
Recency	Sum of ACE exposures multiplied by focal child age	sum(ACE count × age at wave)
Sensitive Period	ACE exposures within each particular wave	ACE count at each wave

The creation of these variables then represents each of the three life course models proposed above. Before passing these models into the two-stage SCLMA pipeline however, I adjust for confounding to maximise the internal validity of my findings. I adhere to the Frisch-Waugh-Lovell (FWL) theorem (Lovell, 2008), which involves regressing both the key variables of interest and the outcome variables on the confounders. Residuals are then passed into the statistical model in place of the original unresidualised variables. This reduces the chances that any associations found are due to measured confounders (Zhu et al., 2021). Additionally, other studies have also found such adjustments to improve statistical power and variable selection when utilising statistical learning methods for model selection (Smith et al., 2022; Zhu et al., 2021).

After adjusting for confounders, I pass the variables associated with each life course model, as well as its covariates, into a Least Angle Regression (LARS) (Efron et al., 2004). Specifically, the LARS procedure can be thought to resemble a classic model selection method called Forward Stepwise Regression, in which variables that are the 'most useful' by some metric would be added to the model until a termination criteria is met. I have opted for the LARS algorithm over alternative statistical learning procedures, such as traditional LASSO methods, because it is commonly found to be more computationally efficient than its counterparts (Efron et al., 2004), and more widely used in the SCLMA literature (Dunn et al., 2018, 2019; Smith et al., 2022; Zhu et al., 2021). In conducting the analysis, this LARS procedure then identifies several life course models, or combination of life course models that best support the data. This eventual model selected by LARS then represents the most parsimonious model for the

exposure-outcome relationship.

I briefly describe the intuition underlying how the LARS procedure is conducted. As mentioned above, LARS can be understood as a procedure that loosely adopts a forward stagewise selection procedure. Procedurally, the LARS procedure starts off with a model where all coefficients of predictor variables are assumed to be zero, with only an existing intercept (β_0). A predicted value ($\hat{y}$) is obtained from this intercept, and a residual r is calculated by subtracting the $\hat{y}$ from the observed response variable (y). Next, a predictor variable most correlated with the residual, say X_{j1}, is selected and inserted into the model. As before, a predicted value $\hat{y}$ is computed from the newly selected predictor ($\hat{y} = \gamma X_1$), and a residual is obtained by deducting the updated $\hat{y}$ values from the observed y values.

$$r = Y - \gamma X_1$$

The coefficient γ is then increased from 0 to a certain value until a second predictor, say X_{j2}, has just as much correlation with residual r relative to X_{j1}. This second predictor then enters the model, and an updated $\hat{y}$ is obtained and subtracted from y. As usual, the coefficient of this second predictor, γX_2, is then updated until a third predictor variable of equal correlation to the residual is identified, and so on.

Thus, the above procedure can summarised pictorially in Figure 1 below. Assume a scenario with two predictor variables, $X1$ and $X2$. Point O represents the prediction $\hat{y}$ initially, when all coefficients are set to 0 with only an intercept present in the model. From here on, assume

that the model identifies $X1$ as the variable most correlated with the residual. $X1$ then enters the model, and the coefficient γX_1 is increased from 0 to a certain value in the direction of Point A. Beyond a certain point, say point B, another variable ($X2$) will equal the correlation between $X1$ and the response variable, and thus inserted into the model. From here on, the LARS regression will then 'shift' from path A to path C, where line C is the predicted value $\hat{Y} = \gamma_1 X_1 + \gamma_2 X_2$. Thus, point B can be said to be the point at which line BC will bisect the angle ABD, resulting in angle DBC being equiangular to angle ABC. Coefficients present in the model are then increased from 0 to certain value, until a third variable is found to be equally correlated with the residual and inserted into the model, and so on.

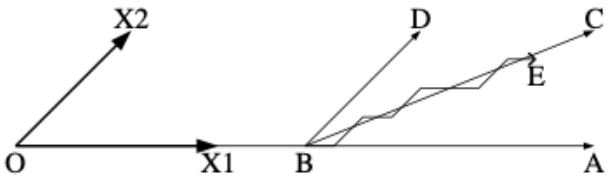

Figure 1: LARS Representation

The LARS procedure is then terminated after the number of steps needed to minimise the C_p statistic, as given by the following:

$$C_p = (1/\hat{\sigma}^2) \sum_{i=1}^{n} (y_i - \hat{y}_i)^2 - n + 2k$$

where n equals the number of observations, k represents the number of steps taken, and $\hat{\sigma}^2$ represents the estimated residual variance. The resulting variables selected then constitute the most parsimonious model that describes the relationship between the predictor(s) and

outcome variable.

Where the first stage of the SCLMA procedure constitutes fitting the LARS model with the relevant life course hypotheses, the second stage is concerned with selecting the 'best' model produced by SCLMA. Here, I adopt two complementary approaches. First, I produce an elbow plot that identifies the four best models, as well as the improvements in R^2 values associated with each model. The chosen model is typically one in which the 'next best' model yields declining marginal returns in its R^2 value. This is often represented by the model in which a sharp decline in the elbow plot is observed, indicating little improvement in the R^2 value for the subsequent life course model. As observed in Figure 2 for example, the best selected theoretical model is that of a sensitive period framework at age 36 months (3 years), given the sharp decrease in R^2 value in the next life course model produced by the SCLMA procedure. If the optimally selected model is one which involves 2 (or more) variables, then a *compound hypothesis* combining multiple life course frameworks is the best proposed model explaining the exposure-outcome relationship (Smith et al., 2022).

The second approach applies post-selection inference methods to choose the best model based on statistical criteria such as effect estimates, standard errors and p-values. The adoption of post-selection inference methods is crucial because model selection based simply on the elbow plot is inadequate to establish if the resulting parsimonious model is indeed significantly predictive of EAA. While it is possible to check for predictive power by fitting a linear regression with the proposed life course model and covariates, such an approach have been found to introduce bias into its estimates (Smith et al., 2022). On the other hand, post-selection

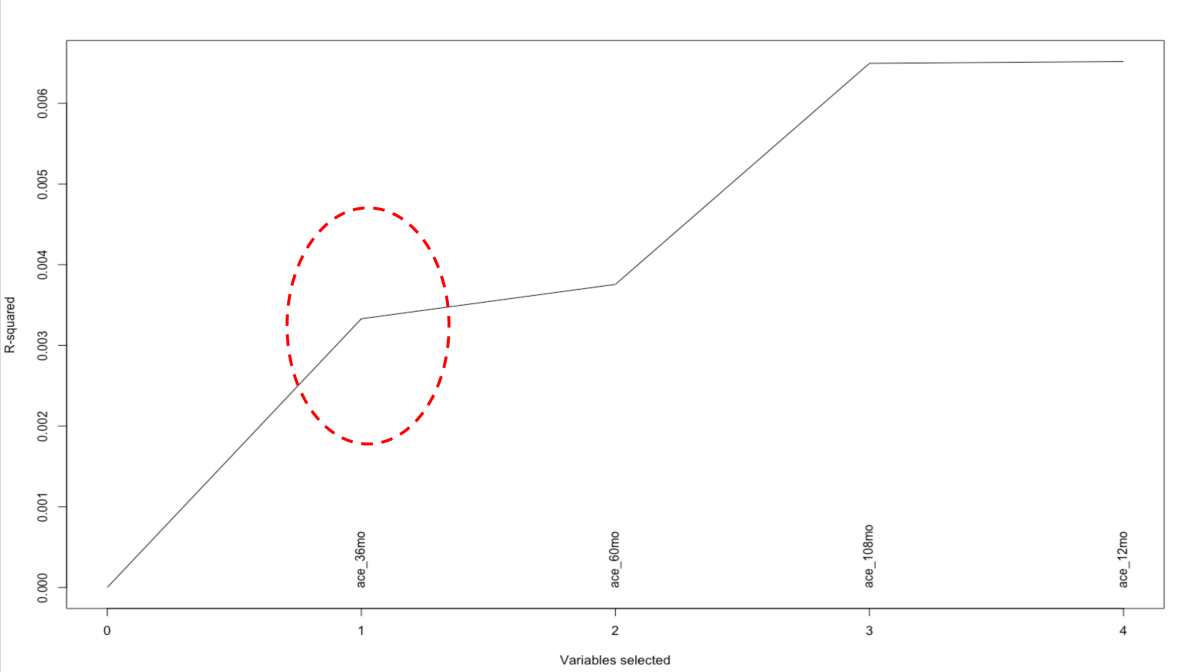

Figure 2: Example of an elbow plot

inference methods can be used to derive unbiased estimates because it accounts for the multiple hypothesis testing that happens when the LARS procedure works iteratively to choose the variable(s) most strongly associated with the outcome (Zhu et al., 2021). Four post-inference methods are typically deployed in such studies: 1) Bonferroni correction; 2) covariance test; 3) the max-|t|-test; and 4) selective inference. I adopt the selective inference method as my selection criteria in view of its ability to yield moderate statistical power and minimise the familywise type I error rate (FWER) (Zhu et al., 2021).

After obtaining the best model proposed by SCLMA, I fit the proposed life course model and its covariates into multivariable linear regression analaysis to examine the relationship between ACE exposure and EAA. This was further conducted for sex-stratified and domain-specific

analyses. In line with extant recommendations, multiple imputation was applied using the *Amelia* R package to maximise statistical power for this SCLMA procedure (Dunn et al., 2018; Smith et al., 2022; Zhu et al., 2021).

3.3.2 Causal Mediation Analysis

To identify if risk behaviours mediate the relationship between ACE exposure and EAA, I also conduct a causal mediation analysis for each of the proposed mediators mentioned above. To be clear, causal mediation – as conceived by Hicks & Tingley (2011) – differs from the traditional mediation analysis approach originally conceptualised by Baron & Kenny (1986). In the latter, the analysis is executed by comparing two linear regression models: one without the mediator, and another with the mediator. Partial mediation effects are then said to be present if the coefficient of the exposure variable in the earlier model is observed to decrease after including the mediator variable. Full mediation effects on the other hand, describes a situation where the addition of a mediator results in the loss of statistical significance of the exposure variable. Under both scenarios, the coefficient of the exposure in the mediator model is known as the direct effect (DE); while the difference in the coefficient of the exposure before and after inclusion of the mediator variable is often referred to as the mediated or indirect effect (IE). This is known as the *difference* method. An alternate approach known as the *product* method adopts a similar framework, with the exception of IE being taken as the product of the coefficients of the exposure and mediator variables within the mediator model (Figure 3).

While the use of these mediation models are widespread, recent studies have established severe

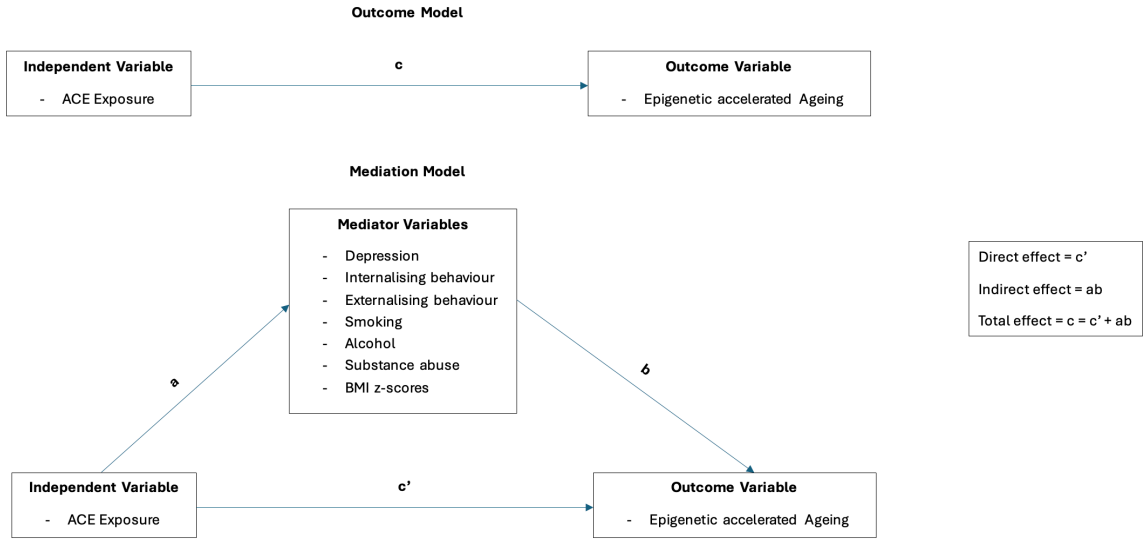

Figure 3: Mediation Framework using the product method

limitations associated with these earlier models. One such limitation is expressed diagrammatically through Figure 4. Namely, while traditional mediation models do establish controls for confounders C associated with the 1) exposure-outcome relationship; 2) exposure-mediator relationship; and 3) mediator-outcome relationship, they typically tend to overlook the fact that mediator-outcome confounders L may themselves be affected by exposure X, expressed by the red arrow in Figure 4. Overlooking this confounding effect can have serious repercussions on the estimation of direct and indirect effects, because it implies that L itself also mediates the relationship between exposure X and outcome Y; and that the mediator-outcome relationship is itself confounded by L. In studies in which such confounding is severe, mediation analysis has found the traditional approach to contribute to misleading results, such as antidepressants being positively associated with worsened depression (Strong et al., 2008). Such confounding may also be present in my study – for instance, genetic factors related to the likelihood of

smoking may also have horizontal pleiotropic[2] effects on accelerated epigenetic ageing, thus confounding the relationship between two of them. Taking this view, I have chosen to adopt the causal mediation approach, for which the main benefit over the traditional approach lies in its ability to conduct sensitivity analyses to produce standard errors and confidence intervals.

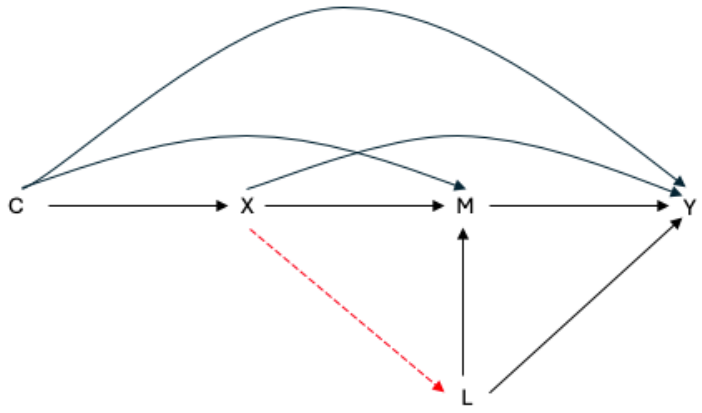

Figure 4: Mediator-Outcome confounder L affected by exposure X

To ensure robustness, I adopt a percentile bootstrap method with 1000 resamples. In this procedure, the observed data is resampled 1000 times with replacement. Both mediator and outcome models are then fitted for each bootstrapped sample, and the quantities of interests are computed. A boostrap distribution is then obtained by repeating this many times to obtain the average direct effect (ADE), the average causal mediation effect (ACME), and the total effect. The percentiles of these bootstrap distribution are then used as 95% confidence intervals to determine the significance of the ACME (Imai et al., 2010). Mediators which reduce the ADE of the exposure variable (ACE exposure) to non-significance can be said to

[2]Horizontal pleiotropy occurs when a genetic variant associated with a trait is simultaneously associated other traits.

have achieved full mediation effect, while partial mediation effect is achieved if both the ADE and average mediation effects (AME) remain significant.

4 Results

4.1 Sample Characteristics

Descriptive statistics are presented in Table 2 and Table 3 below. Table 2 illustrates the distribution of covariates across the various life course hypotheses considered within this study. It can be observed that the analytic sample (n = 4897) has an almost equal distribution of male (52%) and female (48%) focal children. Families of marginalised ethnicities were oversampled, with non-white focal children (45%) and black mothers (48%) comprising the bulk of the sample. Most mothers did not attend or graduate from college – only 11% attended or graduated from college, and a majority of mothers have less than a high school education (35%).

Males and females were, on average, exposed to approximately similar amounts of cumulative ACE exposures (mean = 5.91 – 5.92) across all waves. White focal children were noticeably exposed to the least amount of cumulative ACE events (mean = 4.55), while black children were observed to suffer the greater mean number of cumulative ACEs across all waves (mean = 6.55). Similar disparities can be observed for children with mothers of differing ethnicities. Children of white mothers experienced the least amount of cumulative ACE events (mean = 4.74), while those with black mothers had the most severe cumulative ACE exposures (mean

Table 2: Distribution of covariates by life course adversity exposure

	Total Sample		Cumulative Risk		Recency score	
	N	%	Mean	SD	Mean	SD
Gender						
Female	2342	48	5.91	2.46	25.48	12.04
Male	2555	52	5.92	2.41	25.08	11.71
Ethnicity						
White	880	18	4.55	2.09	19.77	10.23
Non-White	2199	45	6.55	2.40	27.78	11.62
Hispanic/Latino	1300	27	5.34	2.27	25.54	11.80
Other non-Hispanic	236	4.8	5.34	2.54	22.16	12.38
Multi-racial	282	5.8	5.64	2.41	24.18	12.01
Maternal Ethnicity						
White	1032	21	4.74	2.16	20.77	10.76
Black	2332	48	6.55	2.39	27.71	11.60
Hispanic	1339	27	5.89	2.30	25.17	12.00
Others	194	4	4.84	2.37	20.49	11.23
Maternal Education						
Less than high school	1700	35	6.88	2.29	29.10	11.68
High school or equal	1482	30	6.14	2.35	26.05	11.68
Some college	1191	24	5.22	2.18	22.59	10.86
College or graduate	524	11	3.75	1.70	16.72	9.01

	Sensitive. Period Age 1		Sensitive. Period Age 3		Sensitive. Period Age 5		Sensitive. Period Age 9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gender								
Female	1.80	0.92	1.36	0.89	1.30	0.89	1.46	0.91
Male	1.87	0.93	1.35	0.91	1.28	0.87	1.42	0.90
Ethnicity								
White	1.35	0.85	1.07	0.80	0.99	0.75	1.14	0.81
Non-White	2.05	0.82	1.50	0.83	1.44	0.88	1.56	0.90
Hispanic/Latino	1.83	0.85	1.33	0.86	1.30	0.91	1.47	0.94
Other non-Hispanic	1.78	0.96	1.19	0.95	1.13	0.91	1.24	0.89
Multi-racial	1.76	0.93	1.31	0.90	1.16	0.83	1.41	0.95
Maternal Ethnicity								
White	1.38	0.86	1.09	0.81	1.03	0.75	1.22	0.86
Black	2.07	0.82	1.50	0.82	1.43	0.88	1.55	0.89
Hispanic	1.84	0.84	1.33	0.87	1.27	0.82	1.44	0.85
Others	1.53	0.82	1.15	0.82	0.98	0.79	1.18	0.82
Maternal Education								
Less than high school	2.15	0.89	1.59	0.92	1.51	0.82	1.62	0.93
High school or equal	1.92	0.92	1.41	0.91	1.33	0.86	1.47	0.91
Some college	1.60	0.85	1.78	0.84	1.22	0.81	1.32	0.87
College or graduate	1.11	0.68	0.82	0.64	0.81	0.65	1.01	0.72

= 6.55). Across the range of maternal educational levels, children whose mothers acquired higher levels of education were generally less exposed to cumulative ACEs compared to their counterparts whose mothers had less education. The average number of cumulative ACE events experienced by children whose mothers did not complete high school is 6.88, while that of children whose mothers went to college was approximately half (mean = 3.75).

Apart from the cumulative number of ACEs experienced, there is little difference in average recency scores (i.e., ACE exposure weighted by recency of exposure) between male (mean = 25.08) and female (mean = 25.48) focal children. In line with earlier trends, white children also have the lowest recency scores (mean = 19.77) compared to other ethnicities, although this could be driven by the overall lower number of ACE events faced by white children. Non-white children on the other hand possessed the highest average recency scores (mean = 27.78), which reflects increased exposure to more proximal ACE events. Similarly, the recency scores of children having white (mean = 20.77) and black mothers (mean = 20.77) respectively were the lowest and highest among the analytic sample. Recency scores also decrease in tandem with rising maternal education levels – children whose mother attended or graduated college have the lowest mean recency score of 16.72; while those belonging to the lowest educational category had the highest mean recency score of 29.10.

Across all sensitive periods of age 1 to 9, the average number of ACE exposures do not appear to differ much by gender. Females however appear to be at a greater risk of ACE exposure, given overall higher number of ACEs in all sensitive periods except age 1. Compared across all age periods and both genders, most ACEs appear to be inflicted onto children at the

earliest sensitive period (mean = 1.80 – 1.87), and the least during age 5 (mean = 1.28 – 1.30). In comparing ethnic subgroups, non-white children appear to consistently experience greater numbers of ACEs across all age groups relative to other ethnicities. In contrast white children are observed to have the lowest exposures to ACEs across all sensitive periods. This is in line with trends established earlier, in which non-white children appear to be at the greatest risk compared to all ethnicities. Compared to white children, hispanic and children of other ethnicities, too, are exposed to a greater average number of ACE events across all sensitive periods. When looking at maternal education, children of mothers with lower education appear to be at a greater risk than those with higher education. Across all sensitive age periods, children of mothers who have graduated college experienced the least average amount of ACEs, compared to those with less than a high school qualification whose children experience the highest mean number of ACEs.

Table 3 illustrates the distribution of covariates across mediators and the outcome variables included in this study. Females appear to on average experience greater depression scores (mean = 1.65) compared to male children (mean = 1.52). Across all ethnicities, white children appear to have the lowest mean depression scores (mean = 1.54), especially compared to the highest scores obtained by Hispanic (mean = 1.61) and other non-Hispanic children (mean = 1.62). This disadvantage is similarly reflected by one's maternal ethnicity, in which children with Hispanic mothers exhibits the highest depression scores (mean = 1.54). In contrast, children of White and other ethnicities have the lowest average depression score (mean = 1.54 – 1.55). Not surprisingly, average depression scores also patterned by maternal education: those

Table 3: Distribution of covariates by mediators and outcome

	Depression		Externalising		Internalising		Drug Abuse	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gender								
Female	1.65	0.62	1.19	0.24	1.26	0.32	0.24	0.43
Male	1.52	0.59	1.22	0.27	1.24	0.30	0.26	0.44
Ethnicity								
White	1.54	0.63	1.19	0.23	1.31	0.34	0.19	0.39
Non-White	1.58	0.60	1.23	0.28	1.22	0.29	0.26	0.44
Hispanic/Latino	1.61	0.62	1.18	0.23	1.26	0.31	0.27	0.45
Other non-Hispanic	1.62	0.58	1.19	0.25	1.23	0.32	0.27	0.44
Multi-racial	1.59	0.60	1.21	0.25	1.27	0.30	0.24	0.43
Maternal Ethnicity								
White	1.55	0.63	1.19	0.23	1.33	0.35	0.20	0.40
Black	1.58	0.60	1.23	0.27	1.22	0.29	0.26	0.44
Hispanic	1.62	0.61	1.17	0.23	1.25	0.30	0.28	0.45
Others	1.54	0.55	1.20	0.25	1.25	0.28	0.16	0.37
Maternal Education								
Less than high school	1.62	0.61	1.24	0.28	1.26	0.30	0.30	0.46
High school or equal	1.61	0.62	1.21	0.26	1.26	0.32	0.26	0.44
Some college	1.53	0.60	1.18	0.22	1.22	0.30	0.21	0.41
College or graduate	1.48	0.56	1.14	0.20	1.25	0.30	0.15	0.35

	Cigarette use		Alcohol abuse		BMI z-score		Epigenetic Ageing	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gender								
Female	0.06	0.24	0.20	0.40	0.73	1.02	0.19	4.30
Male	0.09	0.29	0.21	0.40	0.60	1.14	-0.39	4.44
Ethnicity								
White	0.10	0.30	0.20	0.40	0.39	1.10	1.29	4.22
Non-White	0.05	0.22	0.17	0.38	0.72	1.07	-0.83	4.48
Hispanic/Latino	0.09	0.28	0.25	0.43	0.76	1.06	0.18	4.00
Other non-Hispanic	0.13	0.34	0.22	0.42	0.55	1.08	-0.44	4.43
Multi-racial	0.11	0.31	0.18	0.39	0.69	1.07	0.08	4.56
Maternal Ethnicity								
White	0.11	0.31	0.22	0.41	0.43	1.09	1.33	4.18
Black	0.05	0.23	0.17	0.38	0.73	1.07	-0.95	4.47
Hispanic	0.09	0.29	0.24	0.43	0.76	1.05	0.15	4.02
Others	0.07	0.25	0.17	0.38	0.30	1.10	0.54	4.52
Maternal Education								
Less than high school	0.09	0.29	0.23	0.42	0.76	1.08	-0.34	4.31
High school or equal	0.07	0.26	0.19	0.39	0.77	1.03	-0.36	4.48
Some college	0.07	0.26	0.19	0.40	0.55	1.12	0.07	4.39
College or graduate	0.04	0.21	0.15	0.36	0.27	1.06	0.93	4.18

with mothers who graduated college have the lowest depression scores (mean = 1.48), compared to those in the lower educational categories. Children whose mothers did not graduate high school exhibited the highest average depression scores (mean = 1.62).

In line with existing literature, boys were found to be more prone to externalising behaviours (mean = 1.22) compared to girls (mean = 1.19). Comparing ethnicities revealed very slight differences in their average externalising scores, with the highest among non-white children (mean = 1.23) and the least among Hispanic/Latino children (mean = 1.18). Similarly, children of black mothers were observed to have the highest average externalising score (mean = 1.23),and the lowest among children with Hispanic mothers (mean = 1.17). In line with earlier findings, average externalising scores appear to decrease systematically as maternal education increases. Children whose mother did not attend high school displayed the highest average externalising score (mean = 1.24), and those who did attend or graduated college demonstrated the lowest externalising score (mean = 1.14).

In contrast to externalising behaviours however, girls had a higher average internalising behaviour score compared to boys ($mean_{girls} = 1.26$, $mean_{boys} = 1.24$). Interestingly, white children appeared to have the highest average internalising score (mean = 1.31), while non-white children had the lowest mean scores (mean = 1.22). This departure from the regular trend established earlier also persisted for one's maternal ethnicity: children of white mothers had the highest average internalising score (mean = 1.33), and the lowest among children with black mothers (mean = 1.22). When considering maternal education, children whose mother did not attend high school had the highest average internalising score (mean = 1.26), while

those who attended some college had the lowest scores (mean = 1.22).

In assessing one's drug abuse, males had greater likelihoods of using drugs (mean = 0.26) compared to girls (mean = 0.24). White children were much less likely to use drugs (mean = 0.19) compared to all other ethnicities (mean = 0.24 – 0.27). Of all maternal ethnicities, children with Hispanic mothers were the most likely to use drugs (mean = 0.28), while maternal ethnicities other than White, Black, or Hispanic mothers were the least likely to use drugs (mean = 0.16). Drug use appear to decrease as mothers educational level increases: children whose mothers belonged to the lowest educational category had the highest drug use (mean = 0.30), while those who attended or graduated college had the lowest drug use (mean = 0.15).

Descriptive statistics for cigarette use are similar to that for drug abuse. Males (mean = 0.09) are more likely than girls to use cigarettes (mean = 0.06). Other non-Hispanic children were most likely to indulge in cigarettes (mean = 0.13), while black children were the least likely (mean = 0.05). Children with White mothers were the most likely to smoke (mean = 0.11), while those with Black mothers were the least likely (mean = 0.05). Cigarette use also decreased along the education spectrum: those whose mothers did not attend high school had the highest cigarette use (mean = 0.09), while whose whose mothers attended or graduated college had the least cigarette use (mean = 0.04).

Meanwhile, males were only slightly more likely to drink (mean = 0.21) compared to girls (mean = 0.20). Hispanic/Latino children were also most likely to drink (mean = 0.25), while non-White children were the least likely (mean = 0.17). Similarly, those with Hispanic mothers drank the most (mean = 0.24), compared to those with Black mothers (mean = 0.17). In line

with earlier findings, mothers with the highest education level drank the least (mean = 0.15), compared to those whose mothers did not attend high school (mean = 0.23).

The final mediator, BMI z-score, is observed to be highest for girls (mean = 0.73) rather than boys (mean = 0.60). Hispano/Latino children were observed to have the highest BMI z-score (mean = 0.76) compared to White children (mean = 0.39). Similarly, those with Hispanic mothers also had the highest BMI z-scores (mean = 0.76), while those with mothers who are other than White, Black, or Hispanic ethnicities have the lowest average BMI z-scores (mean = 0.30). Education structured BMI z-scores in line with earlier trends: children whose mothers attended or graduated college had the lowest BMI z-scores (mean = 0.27), compared to those who did not attend high school (mean = 0.76) or only had a high school qualification (mean = 0.77).

Finally the outcome variable, epigenetic ageing, appears to be more prevalent among girls (mean = 0.19) than boys (mean = -0.39). Interestingly however, White children appeared to be the most vulnerable to epigenetic ageing (mean = 1.29), while black children were the least vulnerable (mean = -0.83). This is reflected similarly by one's maternal ethnicity, in which those with White mothers experienced the greatest average epigenetic ageing (mean = 1.33) compared to those with Black mothers (mean = -0.95). This trend is even more marked when comparing maternal education: children whose mothers belonged to the highest educational category experienced the greatest average epigenetic ageing (mean = 0.93), compared to those who did not attend high school (mean = -0.34) or have a high school qualification (mean = -0.36).

Table 4: Pearson correlations of ACE exposures across time points

Age	year 1	year 3	year 5	year 9
year 1	1	---	---	---
year 3	0.29	1	---	---
year 5	0.24	0.34	1	---
year 9	0.20	0.28	0.27	1

Table 5: Pearson correlations of exposures across ACE domains

	poverty	instability	maltreatment	deprive
poverty	1	---	---	---
instability	0.14	1	---	---
maltreatment	0.04	-0.08	1	---
deprive	0.12	0.01	0.04	1

ACE exposures across various time points are found to be moderately correlated with each other (Table 4). When ACE exposures are broken down into specific types of ACE events, ACE domains are shown to be very weakly correlated with each another (Table 5). When specific ACE domains and exposure timings are considered together, wave-specific ACE exposures are only moderately correlated for the ACE domains of poverty and maltreatment, but weakly correlated for all others (Table 6). This suggests that both socioeconomic disadvantage and childhood maltreatment are the only enduring early life stressors that persist throughout all waves, while exposures to other kinds of ACEs fluctuate substantially across time periods.

To examine correlations between ACE exposures and respective covariates, I plot a heatmap (Figure 5) in which dark red shades indicate strong positive correlations while dark blue hues

Table 6: Pearson correlations of exposures across ACE domains and time points

Poverty					**Instability**				
Age	year 1	year 3	year 5	year 9	Age	year 1	year 3	year 5	year 9
year 1	1	---	---	---	year 1	1	---	---	---
year 3	0.45	1	---	---	year 3	0.16	1	---	---
year 5	0.40	0.46	1	---	year 5	0.07	0.13	1	---
year 9	0.32	0.36	0.40	1	year 9	0.07	0.07	0.13	1
Maltreatment					**Deprivation**				
Age	year 1	year 3	year 5	year 9	Age	year 1	year 3	year 5	year 9
year 1	1	---	---	---	year 1	1	---	---	---
year 3	0.07	1	---	---	year 3	0.05	1	---	---
year 5	0.06	0.40	1	---	year 5	0.04	0.15	1	---
year 9	0.09	0.33	0.37	1	year 9	0.05	0.12	0.12	1

represent strong negative correlations. Paler shades of red or blue indicate correlation coefficients close to 0. Covariates such as mother's education level (*m_edu*) and mother's age at childbirth (*m_age*) are observed to be negatively correlated with exposures across various ACE domains and time period. Other covariates, such as child and mother ethnic identity (*ethnic* & *m_race*), as well as child's gender (*male*) do not appear to have strong correlations with their exposures to adverse experiences.

4.2 Which theoretical model best explains the link between ACEs and EAA?

4.2.1 All-inclusive ACE exposure and EAA

I begin by examining the relationship between all-inclusive ACE exposure (i.e., undifferentiated by specific ACE domains) and EAA in young adulthood. In each of my following analyses,

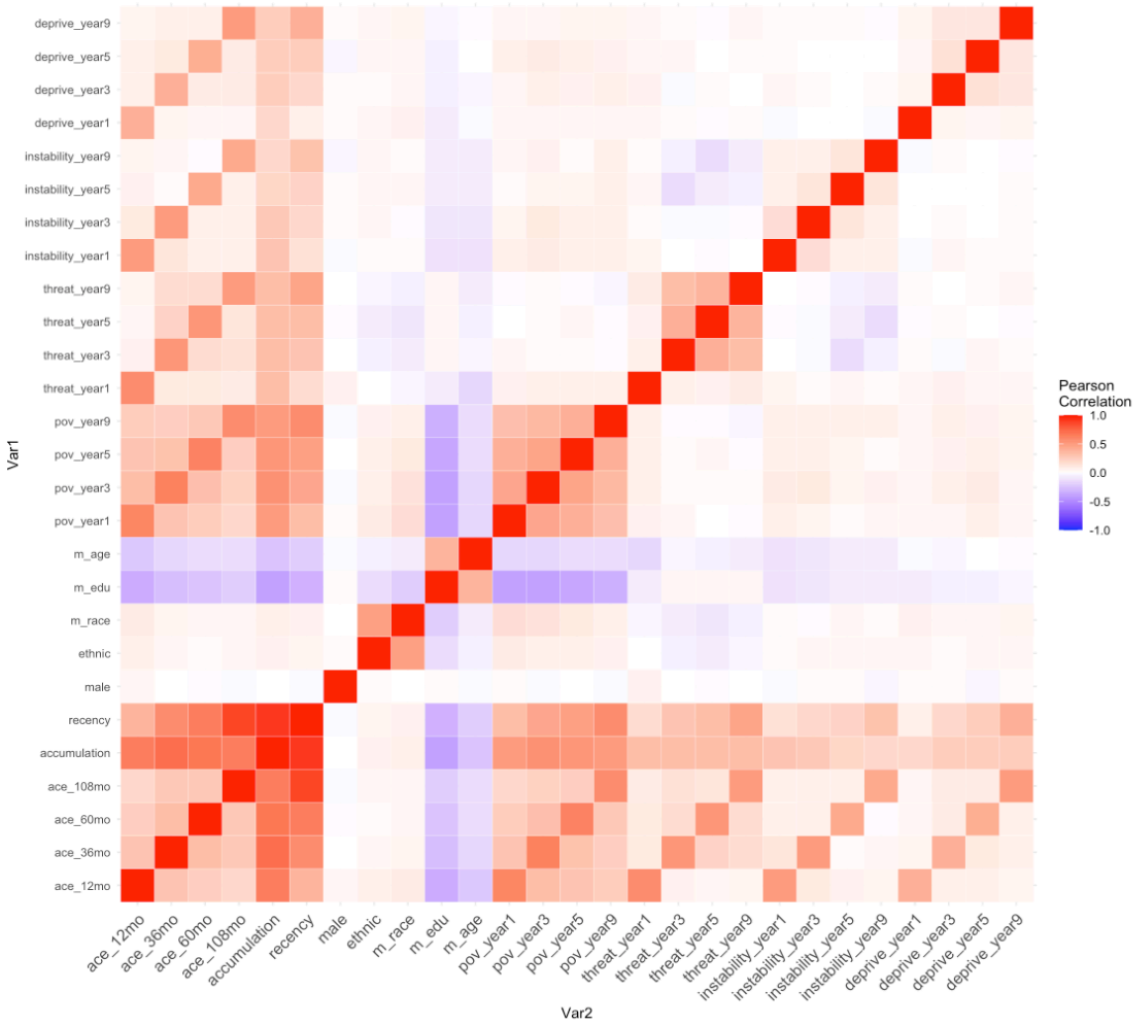

Figure 5: Correlations between ACE exposure and covariates

I first identify the 'best' hypothesis selected by the SCLMA procedure and then conduct a selective inference test to determine its statistical significance. To measure the effect of the life course hypothesis after adjustment for covariates, I enter the selected model into a multivariable OLS regression to examine how ACE exposure at this sensitive period predicts later life EAA. Results for all-inclusive ACE exposure are displayed within Table 7. My first model estimates the pooled effects of all-inclusive ACE exposure on EAA across both genders; while my second and third model reflects male- and female-specific analyses respectively. All models are inclusive of covariates[3], although not reflected within the tables below for brevity.

Table 7: Estimating all-inclusive ACE exposure effects

	Pooled	Male	Female
(Intercept)	1.31*** [0.62, 2.00]	0.55 [-0.41, 1.51]	1.95*** [0.96, 2.95]
Age 3 sensitive period	0.32*** [0.18, 0.46]	0.36*** [0.16, 0.55]	0.38*** [0.17, 0.59]
Age 5 sensitive period			-0.24* [-0.45, -0.03]
Age 9 sensitive period			-0.17 [-0.37, 0.03]
Num.Obs.	4897	2555	2342

***p < 0.001; **p < 0.01; *p < 0.05

For my pooled analysis, the elbow plot suggests that a sensitive period at age 3 (see Figure S1 in the appendix) best explains the relationship between my exposure and outcome of interest. Conducting a selective inference test also provides support for this life course hypothesis, finding the sensitive period at age 3 to be statistically significant ($p < 0.001$). Entering the

[3]Covariates include the focal child's gender, ethnicity, mother's race, mother's age at childbirth, and mother's education level.

selected model into a multivariable regression analysis finds the age 3 sensitive period model to be significantly associated with EAA in young adulthood. In particular, every additional ACE exposure at age 3 is associated with an increase in EAA by 0.32 years ($p < 0.001$). This suggests that children who experience ACEs at age 3 are likely to age faster than those who do not.

Sex-stratified analyses convey similar results, finding the sensitive period hypothesis to best explain links between ACE exposure and EAA. SLCMA analysis reveals a sensitive period for boys at age 3 ($p < 0.001$), and a compound hypothesis comprising sensitive periods of age 3, 5, and 9 for girls (see Figure S2 & Figure S3 in the appendix). A selective inference test however only establishes statistical significance for sensitive periods age 3 ($p < 0.001$) and age 5 ($p < 0.05$) for females, but not age 9. As above, I fit the selected life course models into a multivariable regression below for boys and girls to measure the effect of ACE exposure after adjusting for covariates.

For boys, the age 3 sensitive period was found to significantly predict epigenetic ageing among boys, once covariates have been adjusted for (Table 7, column 2). In particular, a single increase in ACE exposure during age 3 was associated with a 0.36 increase in one's accelerated epigenetic pace of ageing in young adulthood ($p < 0.001$). Girls, on the other hand, appeared to have a more vulnerable age 3 sensitive period given its larger coefficient ($\beta = 0.38$; $p < 0.001$). The age 5 sensitive period was also found to be a significant predictor, although ACE exposure during this age period appeared to be associated with a reduced pace of epigenetic ageing instead ($\beta = -0.24$; $p < 0.05$). Notably, the age 9 sensitive period was not found to be a

significant predictor of EAA after adjusting for covariates. This is in line with results from the selective inference test, which also found the age 9 sensitive period to be non-significant ($p > 0.05$).

In answering my first research question, the examined models consistently indicate compelling evidence regarding a sensitive developmental period at the age of 3, evident across both male and female cohorts. Furthermore, among females, additional sensitive periods emerge at ages 5 and 9, although selective inference examinations reveal the latter to lack statistical significance as a predictor of EAA. Noteworthy is the divergence in the directional impact of these sensitive periods on accelerated ageing among females. Specifically, while each ACE event encountered during early childhood (age 3) is associated with an expedited epigenetic aging process by 0.38 years, ACE occurrences during age 5 are conversely associated with a decelerated pace of ageing by -0.24 years. This disparity suggests the presence of distinct mechanisms operative during various stages of childhood development.

4.3 How do links between ACEs and EAA differ by the type of ACEs?

Next, I turn to investigate how life course hypotheses differentially explains the relationship between different types of ACEs and EAA. Findings from my SCLMA analyses are summarised in Table 8, alongside p-values derived from the selective inference tests. The dominance of the sensitive period hypothesis appeared to persist even when considering domain-specific ACEs.

With the exception of maltreatment for boys and material hardship for girls, sensitive periods at various ages appeared to explain the relationship between ACE exposure and accelerated

Table 8: Summary of results

	Pooled (n = 4,897)		Male (n = 2,555)		Female (n = 2,342)	
	Selected Model	**P-value**	**Selected Model**	**P-value**	**Selected Model**	**P-value**
Domain-specific ACE						
Material Hardship	Recency	0.970	Sensitive Period (age 1)	0.016**	Recency	0.005**
	Sensitive Period (age 1)	0.008**	Sensitive Period (age 3)	0.070		
	Sensitive Period (age 9)	0.016**	Sensitive Period (age 9)	0.023*		
Instability	Sensitive Period (age 3)	0.000***	Sensitive Period (age 3)	0.003**	Sensitive Period (age 3)	0.147
Deprivation	Sensitive Period (age 1)	0.226	Sensitive Period (age 5)	0.050*	Sensitive Period (age 1)	0.008**
			Sensitive Period (age 9)	0.019*	Sensitive Period (age 3)	0.061
Maltreatment	Sensitive Period (age 3)	0.006**	Cumulative Risk	0.380	Sensitive Period (age 3)	0.030**
			Sensitive Period (age 3)	0.471		

Notes: ***p<0.001, **p<0.01, *p<0.05. P-values are derived from selective inference tests.

ageing. Material hardship at sensitive periods of ages 1 and 9 contributed significantly to EAA for boys, while the recency of material hardship appears to matter more for girls. Meanwhile, the SCLMA procedure has selected a sensitive period of age 3 for instability-related ACEs, but selective inference only finds this to be statistically significant for boys but not girls. Deprivation-related ACEs appear to exhibit distinct sensitive periods across boys and girls: boys appeared to be more sensitive to deprivation during middle childhood (ages 5 and 9), while girls appeared to be more vulnerable in their early childhood during age 1. Finally, girls appeared to have a sensitive period of age 3 with respect to maltreatment-related ACEs, but none of the life course hypotheses explained the relationship among boys.

In answering my research question, it can therefore be discerned that a sensitive period hypothesis best explains the relationship between almost all ACE categories and EAA. The single exception pertains to the category of material hardship among girls, for which the recency

hypothesis is selected by SCLMA to be the better hypothesis. I elaborate further on each ACE category in the following subsections.

4.3.1 Material Hardship

I begin by analysing the relationship between material hardship and EAA without differentiating by gender subgroups, then conduct gender-stratified analyses. As above, I insert the selected model into a multivariable regression whilst controlling for covariates. Findings are shown in Table 9 – model 1 contains results for the pooled analysis, while models 2 and 3 reflects results for the male- and female-specific analyses respectively. Similarly, covariates –focal child's gender, ethnicity, mother's race, mother's age at childbirth, and mother's education level– are included in the analysis but are not shown in the table for brevity.

Table 9: Regression Estimates for Material Hardship

	Pooled	Male	Female
(Intercept)	2.22*** [1.54, 2.89]	1.38** [0.44, 2.32]	2.38*** [1.46, 3.31]
Recency	0.00 [-0.04, 0.05]		-0.05*** [-0.08, -0.02]
Age 9 sensitive period	-0.49+ [-1.05, 0.06]	-0.48* [-0.86, -0.09]	
Age 1 sensitive period	-0.41** [-0.71, -0.10]	-0.53* [-0.93, -0.12]	
Age 3 sensitive period		0.43* [0.02, 0.84]	
Num.Obs.	4897	2555	2342

***p $<$ 0.001; **p $<$ 0.01; *p $<$ 0.05

When males and females are considered together, the SCLMA procedure selected a compound hypothesis comprising sensitive periods of age 1 and 9, as well as the recency model as the most parsimonious model (Figure S4 in the appendix). Selective inference checks however, indicate only both sensitive periods to be statistically significant, but not the recency model. This suggests that the recency of one's exposure to material hardship matters less for predicting young adulthood EAA. Findings from the regression analysis echoes results from the selective inference checks. Once covariates have been adjusted for, only the age 1 sensitive period remain significant. In particular, exposure to material hardship during age 1 is associated with a 0.41 years decrease in one's EAA during young adulthood ($p < 0.01$).

I further stratify this analysis by gender. For males, the SLCMA procedure find a compound model comprised of age 1, 3, and 9 sensitive periods to best explain the relationship between ACE exposure and EAA (Figure S5 in the appendix). Selective inference suggests that only year 1 and 9 sensitive periods are statistically significant, but not the year 3 sensitive period. I fit this compound hypothesis into a multivariable regression model. Results from the regression analysis show that all sensitive periods – ages 1, 3, 9 – are significant predictors of EAA in young adulthood after adjusting for covariates. Specifically, every additional ACE exposure at ages 1, 3, and 9 are associated with a changes in EAA by -0.53, -0.48, and 0.43 years respectively ($p < 0.05$). Thus, only material hardship experienced at age 3 are associated with faster epigenetic ageing compared to those who did not experience financial troubles; while socioeconomic disadvantage at other sensitive periods are associated with decelerated ageing. Consistent with earlier findings, the opposite direction of these effects suggest that exposure

to ACEs triggers mechanisms that operate disparately across distinct stages of childhood development.

For girls, the best model selected by SCLMA is a recency hypothesis ($p < 0.01$, Figure S6 in the appendix). Multivariable regression analysis found the recency hypothesis to be statistically significant even after including covariates ($p < 0.001$). An increase in recency score by 1 unit is associated with a decrease in EAA by 0.05 years. Because recency scores are treated as the number of ACE exposures multiplied by its year of exposure, an additional ACE exposure in years 1, 3, 5 and 9 would therefore be associated with a decrease in EAA by 0.05, 0.15, 0.25, and 0.45 years respectively.

Analyses so far therefore point to distinct mechanisms driving the link between material hardship and EAA for boys and girls. Where boys were particularly sensitive to socioeconomic disadvantage during the ages of 1, 3, and 9, girls appeared to be influenced more by the proximity of which they experienced poverty. Interestingly, nearly all the selected life course hypotheses for boys and girls demonstrated a negative association with EAA. This suggests that socioeconomic disadvantage encountered in childhood may decelerate rather than accelerate epigenetic ageing in young adulthood. Potentially, this may reflect an acclimatisation effect where early financial hardship may inculcate resilience among children, thus buffering against the impacts of future stressors on their epigenetic age.

4.3.2 Instability

Next, I examine the ACE domain of instability. Results are reflected in Table 10. When males and females are considered together, SCLMA analysis and selective inference finds a sensitive period of 3 years to best explain the link between family environment turbulence and EAA ($p < 0.001$, Figure S7 in the appendix). Regression analysis finds the age 3 sensitive period to be statistically significant (column 1, $p < 0.01$), in which every additional ACE experienced domain during age 3 is associated with an increase in EAA by 0.7 years (column 1).

Table 10: Regression Estimates for Instability

	Pooled	Male	Female
(Intercept)	1.64*** [0.98, 2.29]	0.88+ [-0.03, 1.79]	1.81*** [0.90, 2.72]
Age 3 sensitive period	0.70*** [0.39, 1.00]	0.91*** [0.49, 1.33]	0.45* [0.02, 0.89]
Num.Obs.	4897	2555	2342

***p < 0.001; **p < 0.01; *p < 0.05

For males, SCLMA and selective inference similarly finds a sensitive period of age 3 to best account for variation in later life EAA ($p < 0.01$, Figure S8 in the appendix). Regression analyses find this life course hypothesis to significantly predict EAA, even after controlling for confounders (column 2, $p < 0.001$). Specifically, experiencing an additional unstable ACE event when boys were 3 years old is associated with a 0.91 increase in EAA in young adulthood.

Findings for females were similar to males, in which the age 3 sensitive period was also selected

by the SCLMA procedure to be the most parsimonious model (Figure S9 in the appendix). Selective inference test however revealed no significant association between this hypothesis and EAA. Significance is established however once covariates have been controlled for in the regression model (column 3, $p < 0.05$). Every additional ACE event experienced at age 3 in the instability domain is associated with a 0.45 increase in EAA at young adulthood.

The analyses conducted thus far corroborate age 3 as a notably vulnerable developmental juncture for both male and female individuals experiencing unpredictable and unstable circumstances, thereby manifesting deleterious effects on their epigenetic age. Gender-stratified analyses suggest that boys rather than girls are more susceptible to turbulent events during this sensitive period and suffer greater EAA in young adulthood. Notably, estimates for boys are about twice that of girls ($\beta_{boys} = 0.91$; $\beta_{girls} = 0.45$), reflecting a period of markedly higher vulnerability to instability-related ACEs. These findings underscore the importance of investigating gender-differentiated mechanisms underlying the relationship between instability and EAA.

4.3.3 Deprivation

Thirdly, I examine the effects of deprivation on EAA in young adulthood. Results are shown in Table 11. When male and female children were considered together, SCLMA analysis selected the age 1 sensitive period as the optimal life course hypothesis (Figure S10 in the appendix). Selective inference however revealed this hypothesis to be non-significant. Nonetheless, I fit the hypothesis into a multivariable regression model. After controlling for covariates, it is

observed that the selected model is statistically significant (column 1, $p < 0.05$). Specifically, an additional ACE experienced at age 1 is associated with a 0.42 increase in EAA in young adulthood.

Table 11: Regression Estimates for Deprivation

	Pooled	Male	Female
(Intercept)	1.50*** [0.79, 2.21]	1.09* [0.18, 2.00]	1.26* [0.28, 2.25]
Age 1 sensitive period	0.42* [0.07, 0.77]		0.74** [0.25, 1.22]
Age 9 sensitive period		0.50* [0.10, 0.91]	
Age 5 sensitive period		-0.58* [-1.13, -0.03]	
Age 3 sensitive period			0.62* [0.10, 1.15]
Num.Obs.	4897	2555	2342

***p < 0.001; **p < 0.01; *p < 0.05

Breaking down this relationship by gender, SCLMA analyses selected a compound hypothesis comprised of sensitive periods at age 5 and 9 as the most parsimonious model for boys (Figure S11 in the appendix). Selective inference checks revealed both life course hypotheses to be significant ($p < 0.05$). Fitting the above hypotheses into a regression model, both selected hypotheses were still found to be significant predictors of EAA in young adulthood, after controlling for covariates and alternate sensitive periods. Specifically for every deprivation-related ACE experienced at age 9, boys are estimated to experience EAA by an additional 0.5 years (column 2, $p < 0.05$). Interestingly, the age 5 sensitive period appears to operate in the opposite direction, predicting a decrease in epigenetic ageing by 0.58 for every ACE

experienced during 5 years old (column 2, $p < 0.05$).

In contrast to boys, the SCLMA analysis identified a parsimonious compound model comprised of age 1 and 3 sensitive periods for girls (Figure S12 in the appendix). Selective inference however only found the age 1 sensitive period to be statistically significant, but not the age 3 sensitive period. In fitting the compound hypothesis into a regression model, both sensitive periods are found to be significant across all models (column 3) after controlling for covariates. Every deprivation-related ACEs experienced during age 1 is associated with a 0.74 increase in EAA for girls in young adulthood ($p < 0.01$); while each ACE experienced during age 3 was associated with an EAA increase by 0.62 years ($p < 0.05$).

Within the domain of ACEs pertaining to deprivation, analyses unveiled distinct life course models elucidating the relationship between ACE exposure and EAA across genders. Notably, boys exhibited heightened susceptibility to ACEs solely during middle to late childhood (ages 5 and 9), whereas girls manifested sensitive periods during early childhood (ages 1 and 3). Furthermore, while both sensitive periods identified in girls were associated with adverse effects on their epigenetic age, ACE exposure for boys appears to elicit effects operating in opposite directions, underscoring the presence of gender- and age-specific mechanisms. Consequently, girls may therefore experience more pronounced repercussions in their later life epigenetic age from ACEs associated with deprivation.

4.3.4 Child Maltreatment

Finally, I analyse the relationship between childhood maltreatment and EAA in young adulthood. Results are reflected in Table 12. When boys and girls are examined together, SLCMA analysis identified a sensitive period of age 3 as the most parsimonious life course model (Figure S13 in the appendix). Selective inference checks indicate this to be statistically significant ($p < 0.05$). Similar to the above, I fit this hypothesis into a multivariable regression model whilst controlling for covariates.

Pooled regression analysis finds the age 3 sensitive period to significantly predict EAA, even after covariates have been added to the model (column 1). For every experience of childhood maltreatment experienced during age 3, individuals were subjected to an accelerated epigenetic age of 0.43 years (column 1, $p < 0.001$).

Table 12: Regression Estimates for Childhood Maltreatment

	Pooled	Male	Female
(Intercept)	1.53*** [0.85, 2.21]	0.75 [-0.22, 1.72]	1.63*** [0.69, 2.56]
Age 3 sensitive period	0.43*** [0.18, 0.68]	0.25 [-0.24, 0.74]	0.43* [0.08, 0.79]
Cumulative Risk		0.09 [-0.11, 0.28]	
Num.Obs.	4897	2555	2342

***p < 0.001; **p < 0.01; *p < 0.05

In conducting gender-stratified analyses, SCLMA analysis identified a compound model comprised of an age 3 sensitive period and a cumulative risk hypothesis to be the most parsimonious

model for boys (Figure S14 in the appendix). Selective inference however finds neither of these two hypotheses to be statistically significant after adding covariates to the regression model (column 2), suggesting that male EAA is not affected by ACEs related to maltreatment. Findings however appear to differ for females. An age 3 sensitive period hypothesis was selected as the best model for girls (Figure S15 in the appendix), and was found to be statistically significant by selective inference. Multivariable regression analysis also found this sensitive period to signficantly predict EAA, even after adjusting for covariates (column 3). In particular, every additional maltreatment-related event girls experienced at age 3 was associated with an accelerated epigenetic age by 0.43 years ($p < 0.05$).

Considered together, boys and girls therefore appeared to differ in their susceptibility to maltreatment-related ACEs overall. While girls were found to be particularly vulnerable during age 3, neither a sensitive period or cumulative risk hypothesis was found to significantly predict EAA in young adulthood for boys. These results deviate from the bulk of studies indicating an early childhood sensitive period for both boys and girls. Potentially, this is because existing studies typically examine life course models *independently* from each other. But as my findings suggest, such significant effects may disappear once alternate life course models have been controlled for.

4.4 Which risk factors mediate the relationship between ACE exposure and EAA?

Having identified the most parsimonious model suggested by the SCLMA procedure, I turn to my third research question and examine possible pathways that mediate the relationship

between ACE exposure and EAA. Namely, I investigate the role of six mediators: depression; externalising behaviour; internalising behaviour; smoking; alcohol abuse, drug abuse, and BMI z-scores. I begin by first conducting mediation analyses in the relationship between all-inclusive ACE exposure and EAA, then decompose them into respective ACE domains. I further stratify my analyses by gender to investigate if stress response mechanisms differ between males and females.

4.4.1 All-inclusive ACE exposure and EAA

I report all mediation pathways with significant average causal mediation effects (ACME) in Table 13. The significance of all indirect effects were tested using percentile bootstrapping procedures with 1000 resamples, and 95% CIs were obtained by calculating indirect effects at the 2.5% and 97.5% percentiles. Of all mediators studied, only three mediators were found to be statistically significant. Specifically, the effect of all-inclusive ACE exposure on EAA was partially mediated through alcohol abuse, externalising behaviour, and internalising behaviour. For alcohol abuse, the ACME was 0.006 (95%CI [0.00, 0.01]), representing approximately 1.7% of the total effect of ACE exposure on EAA. Externalising and internalising behaviours had negative ACME values of -0.018 (95%CI [-0.033, -0.00]) and -0.020 (95%CI [-0.040, -0.010]), representing approximately 5% and 6% of the total effects for externalising and internalising behaviour respectively. Interestingly, it is observed that these ACME values operate in the opposite direction of the direct effect of ACE exposure on EAA. In particular, the negative ACME values imply a suppressing effect of these mediators, in which the deleterious effects of

Table 13: Statistically significant indirect pathways for all-inclusive ACE exposure and EAA

Indirect Pathways	ACME	Prop. Mediated	95%CI
All-inclusive ACE Exposure → Alcohol → EAA	0.006*	0.017	[0.00, 0.01]
All-inclusive ACE Exposure → Externalising Behaviour → EAA	-0.018**	0.054	[-0.033, -0.00]
All-inclusive ACE Exposure → Internalising Behaviour → EAA	-0.020**	0.060	[-0.04, -0.01]

Note: **p<0.01; *p<0.05

ACE exposure are partially counteracted and reduced by one's engaging in externalising and internalising behaviours. In other words, these behavioural responses weakened the adverse consequences of ACE exposure on one's epigenetic age. This is contrary to findings from various studies examining *adulthood* outcomes, in which such behaviours resulted in accelerated rather than decelerated epigenetic ageing. I discuss possible explanations in the subsequent chapter.

When broken down into gender-specific ACE exposure, only males had significant but partial mediation effects (Table 14). Internalising behaviour had an ACME of approximately -0.023, with 95%CI ranging from -0.05 to -0.01. This represented about 7% of the total effect. Similar to the above, the coefficient for this ACME was negative, suggesting that internalising behaviour reduces the harmful effects of ACE exposure on one's EAA. None of the mediators investigated were found to be significant for females. Next, I examine these mediating effects broken down by respective ACE domains.

Table 14: Statistically significant pathways for all-inclusive ACE (Male) and EAA

Indirect Pathways	ACME	Prop. Mediated	95%CI
All-inclusive ACE Exposure → Internalising Behaviour → EAA	-0.023**	0.065	[-0.05, -0.01]

Note: **p<0.01; *p<0.05

4.4.2 Material Hardship

Of all mediators studied, only three mediation pathways were found be significant in the relationship between material hardship and EAA. Alcohol consumption, cigarettes, and drug abuse were found to have indirect effects of -0.011, -0.032, and -0.021 on EAA respectively. Indirect effects for alcohol consumption at 2.5% and 97.5% percentiles were -0.03 and -0.00 respectively, which represents approximately 2.6% of the total effect that material hardship exerts on EAA. 95%CI for cigarette use range from -0.06 to -0.01, representing about 7.3% of the total effect; while that for drug abuse is between -0.05 and -0.00, which is approximately 4.9% of the total effect. All mediation effects operate in the same direction as the material hardship-EAA relationship, indicating that the impact of socioeconomic disadvantage on epigenetic ageing are partially mediated through these mediators. I summarise these results below in Table 15.

Gender-stratified analyses reveal only cigarette use and internalising behaviour as significant mediators for boys (Table 16). About 10.7% of the effect of ACE on EAA is partially mediated through cigarette use, with an ACME of about -0.056. 95%CI of this indirect effect ranges from -0.11 to -0.02. Meanwhile, about 4.4% of the total effect was effected through internalising

Table 15: Statistically significant pathways for material hardship and EAA

Indirect Pathways	ACME	Prop. Mediated	95%CI
Material Hardship → Alcohol → EAA	-0.011*	0.026	[-0.03, -0.00]
Material Hardship → Cigarettes → EAA	-0.032**	0.073	[-0.06, -0.01]
Material Hardship → Drug Abuse → EAA	-0.021**	0.049	[-0.05, -0.00]

Note: **p<0.01; *p<0.05

Table 16: Statistically significant pathways for material hardship and EAA (Male)

Indirect Pathways	ACME	Prop. Mediated	95%CI
Material Hardship → Cigarettes → EAA	-0.056**	0.107	[-0.11, -0.02]
Material Hardship → Internalising Behaviour → EAA	-0.023*	0.044	[-0.06, -0.00]

Note: **p<0.01; *p<0.05

behaviour, with an ACME of -0.023. 95%CI for this indirect effect ranges from -0.06 to -0.00. Similar to the above, the indirect effect of the mediator operates in the same direction of the association between material hardship and EAA, suggesting that the negative effect of material hardship on EAA are partially carried through by these mediators. No mediating variables were found to be significant for girls, potentially suggesting gender differentiated mechanisms driving the link between ACEs and EAA.

Table 17: Statistically significant pathways for instability and EAA

Indirect Pathways	ACME	Prop. Mediated	95%CI
Instability → BMI → EAA	-0.020**	0.029	[-0.04, -0.00]

Note: **p<0.01; *p<0.05

4.4.3 Instability

When boys and girls are considered together, only 1 mediator was found to partially mediate the relationship between Instability and EAA (Table 17). The ACME of BMI z-score is -0.020, representing about 2.9% of the total effect exerted by instability-related ACEs on EAA. Plausible values of this indirect effect within the 95%CI are between -0.11 and -0.00. The mediation effect was found to be negative in contrast to the (positive) average direct effect, suggesting that behaviours related to adiposity may suppress the deleterious effects of instability on young adulthood EAA.

BMI z-scores similarly mediated the relationship between instability and EAA for boys. Mediation analysis finds the ACME to be about -0.024 (95%CI [-0.06, -0.00]), representing 2.6% of the total effect of instability on EAA (Table 18). Indirect effects were also found to operate in opposite directions, indicating that adiposity-related behaviours too suppresses the effects of instability on EAA. No mediators were found to be significant for girls.

Table 18: Statistically significant pathways for instability and EAA (Male)

Indirect Pathways	ACME	Prop. Mediated	95%CI
Instability → BMI → EAA	-0.024*	0.026	[-0.06, -0.00]

Note: **p<0.01; *p<0.05

Table 19: Statistically significant pathways for deprivation and EAA

Indirect Pathways	ACME	Prop. Mediated	95%CI
Deprivation → Alcohol → EAA	-0.020**	0.050	[-0.04, -0.00]
Deprivation → Externalising Behaviour → EAA	-0.023*	0.056	[-0.05, -0.00]
Deprivation → Internalising Behaviour → EAA	-0.030**	0.073	[-0.06, -0.01]

Note: **p<0.01; *p<0.05

4.4.4 Deprivation

Mediation analysis found three statistically significant mediators across both boys and girls (Table 19). Alcohol consumption, externaling and internalising behaviours exerted partial indirect effects of -0.020, -0023, and -0.03 respectively. Plausible values for alcohol consumption range between 95%CI values of -0.04 and -0.00, which represent about 5% of total effects; ACME of externalising behaviours lie between -0.05 to 0.00 for its 95% CI, which is approximately 5.6% of total effects; and Internalising behaviours have 95%CI of [-0.06, -0.01], which is approximately 7.3% of total effects between deprivation and EAA. Similar to earlier findings, all mediators were negative and operate in opposite directions from its direct effect, thus counteracting the detrimental effect of deprivation-related ACEs on EAA.

Table 20: Statistically significant pathways for deprivation and EAA (Male)

Indirect Pathways	ACME	Prop. Mediated	95%CI
Deprivation → Internalising Behaviour → EAA	-0.057**	0.098	[-0.12, -0.01]

Note: **p<0.01; *p<0.05

Gender stratified analysis finds internalising behaviour to fully mediate the relationship between deprivation and EAA for boys – deprivation direct effects disappear entirely when the mediating effect of internalising behaviour is taken into account. In particular, the ACME is approximately -0.057 (95%CI [-0.12, -0.01]), representing about 9.8% of the total effect of deprivation on EAA (Table 20). Because the mediator reduces the average direct effect of deprivation on EAA to non-significance, it can be said that the detrimental effect of deprivation on EAA is completely mediated through internalising behaviours.

Unlike males, internalising behaviour only partially mediates the relationship between deprivation and EAA for females (Table 21). Deprivation mediates about 4.7% of the total effect, exerting an ACME of about -0.035 (95% CI [-0.08, -0.00]). In contrast to males, internalising behaviours appear to exert a suppressing effect for females, given the opposite directions of the mediated and direct effect of deprivation on EAA. Thus, internalising behaviour appears to alleviate rather than deteriorate one's pace of epigenetic ageing for females.

Table 21: Statistically significant pathways for deprivation and EAA (Female)

Indirect Pathways	ACME	Prop. Mediated	95%CI
Deprivation → Internalising Behaviour → EAA	-0.035*	0.047	[-0.08, -0.00]

Note: **p<0.01; *p<0.05

4.4.5 Child Maltreatment

Of all mediators considered, four mediators were found to exert significant indirect effects on EAA when males and females were considered together (Table 22). Two of these mediators – cigarette use and drug abuse– constitute health risk behaviours, and average direct effects of child maltreatment disappear once these mediation effects have been considered. In other words, the significant effect of maltreatment on EAA is completely negated by cigarette use and drug abuse. Cigarette use exert an ACME of -0.029 (95%CI [-0.05, -0.01]), which is approximately 52% of total effects. ACME of drug abuse is calculated to be -0.028 (95%CI [-0.05, -0.01]), which mediates approximately 50.8% of the total effect. Thus, the opposite directions of these mediation effects suggest that these health risk behaviours suppress the detrimental effects of child maltreatment on EAA.

Contrary to the above, the average direct effect of maltreatment on EAA do not lose significance when externalising and internalising behaviours were treated as mediators. Maltreatment exerts a positive direct effect on EAA that is offset in part by externalising behaviour in the opposite direction by an ACME of -0.027 (95%CI [-0.03, -0.00]). Mediation effects are therefore approximately about 6.2% of the total effect. Internalising behaviour on the other

Table 22: Statistically significant pathways for maltreatment and EAA

Indirect Pathways	ACME	Prop. Mediated	95%CI
Childhood Maltreatment → Cigarettes → EAA	-0.029**	0.521	[-0.05, -0.01]
Childhood Maltreatment → Drug Abuse → EAA	-0.028**	0.508	[-0.05, -0.01]
Childhood Maltreatment → Externalising Behaviour → EAA	-0.027*	0.062	[-0.05, -0.01]
Childhood Maltreatment → Internalising Behaviour → EAA	-0.020**	0.046	[-0.04, -0.01]

Note: **p<0.01; *p<0.05

hand produces an ACME of -0.02 (95%CI [-0.04, -0.01]), which is approximately 4.6% of the total effect. All mediators examined are observed to operate in the opposite direction from direct effects, which suggest pathways that alleviate the detrimental effects of child maltreatment on EAA. No mediators have been found to be statistically significant for gender-specific analyses.

4.4.6 Summary of results

Table 23 summarises the above findings with respect to the pathways connecting ACEs to EAA. When mediation analyses are not stratified by gender, one key observation is that most mediators appeared to demonstrate a negative indirect effect on EAA. This is surprising given the plethora of literature finding these risk factors to contribute to various detrimental health outcomes in adulthood, including an accelerated pace of epigenetic ageing. Yet, in spite of these findings, my results suggest the opposite: that these risk factors appear to attenuate the

Table 23: Summary of mediating effects

Indirect Pathways	β	Prop. Mediated	95%CI
All-inclusive ACE Exposure → Alcohol → EAA	0.006*	0.017	[0.00, 0.01]
All-inclusive ACE Exposure → Externalising Behaviour → EAA	-0.018**	0.054	[-0.033, -0.00]
All-inclusive ACE Exposure → Internalising Behaviour → EAA	-0.020**	0.060	[-0.04, -0.01]
Material Hardship → Alcohol → EAA	-0.011*	0.026	[-0.03, -0.00]
Material Hardship → Cigarettes → EAA	-0.032**	0.073	[-0.06, -0.01]
Material Hardship → Drug Abuse → EAA	-0.021**	0.049	[-0.05, -0.00]
Instability → BMI → EAA	-0.056**	0.029	[-0.11, -0.02]
Deprivation → Alcohol → EAA	-0.020**	0.050	[-0.04, -0.00]
Deprivation → Externalising Behaviour → EAA	-0.023*	0.056	[-0.05, -0.00]
Deprivation → Internalising Behaviour → EAA	-0.030**	0.073	[-0.06, -0.01]
Childhood Maltreatment → Cigarettes → EAA	-0.029**	0.521	[-0.05, -0.01]
Childhood Maltreatment → Drug Abuse → EAA	-0.028**	0.508	[-0.05, -0.01]
Childhood Maltreatment → Externalising Behaviour → EAA	-0.027*	0.062	[-0.05, -0.01]
Childhood Maltreatment → Internalising Behaviour → EAA	-0.020**	0.046	[-0.04, -0.01]

Note: **p<0.01; *p<0.05

harmful effects of ACE exposure on EAA among young adults. More interestingly, average direct effects of some ACE domains were found to be non-significant once particular factors (e.g., smoking, substance abuse, and BMI z-scores) were treated as mediators, suggesting that these factors completely negated the deleterious effects of ACE exposures on their epigenetic age. Such contradictory findings potentially point to differentiated mechanisms across the life course, in which risk behaviours confer protective benefits on EAA during young adulthood, but exert adverse health effects at older ages.

When analyses are stratified by gender, all mediating effects exhibit negative coefficients, which is indicative of a mitigating impact on EAA (Table 24). However, the number of identified

Table 24: Summary of mediating effects by gender

Male				Female			
Indirect Pathways	**ACME**	**Prop. Mediated**	**95%CI**	**Indirect Pathways**	**ACME**	**Prop. Mediated**	**95%CI**
All-inclusive ACE Exposure → Internalising Behaviour → EAA	-0.023**	0.065	[-0.05, -0.01]				
Material Hardship → Cigarettes → EAA	-0.056**	0.107	[-0.11, -0.02]				
Material Hardship → Internalising Behaviour → EAA	-0.023*	0.044	[-0.06, -0.00]				
Instability → BMI → EAA	-0.024*	0.026	[0.06, -0.00]				
Deprivation → Internalising Behaviour → EAA	-0.057**	0.098	[-0.12, -0.01]	Deprivation → Internalising Behaviour → EAA	-0.03*	0.047	[-0.08, -0.00]

Note: **p<0.01; *p<0.05

pathways is notably diminished, with only select mediators demonstrating significant associations between ACEs and EAA. Notably, pathways involving alcohol consumption, drug abuse, and externalising behaviours no longer serve as mediators between the variables of interest, suggesting gender-specific nuances in the mediation process. This observation is reinforced by the finding that females exhibit a notably reduced number of significant mediating pathways compared to males, thus underscoring gender-specific disparities in stress reactivity and coping mechanisms. Such findings highlight the complex interplay of gender-specific responses to ACE exposure and its implications for epigenetic ageing processes. This nuanced understanding contributes to the broader discourse on gender differences in vulnerability to the long term effects of childhood adversity on health outcomes.

5 Discussion

Existing research has so far examined links between ACE exposure and EAA in adulthood, but less attention has been placed on earlier life periods. Because such biological-embedded 'scars' are often transient and may fade over time, it is crucial to re-centre scholarly focus towards the period of adolescence when such biological indicators are most visible. The unique developmental phase and plasticity experienced during adolescence marks a crucial phase when the impact of life stressors on biosocially-mediated outcomes can be most clearly observed. This study therefore contributes to the dearth of literature by examining such adolescent outcomes. My results suggest that ACEs experienced as early as early childhood (age 1 to 3) have a negative impact on one's health outcomes as measured through a newer generation epigenetic clock, specifically that of the GrimAge clock. Similar to studies examining EAA in adulthood, I find that ACE exposures are consistently associated with an accelerated pace of ageing during young adulthood across all-inclusive and most ACE domain-specific analyses.

This is broadly in line with expectations, given extensive literature highlighting how ACE exposure comes to be biologically embedded over time. In particular, studies have found exposures to various kinds of ACEs be associated with shortened telomere length (Lang et al., 2020; Sumner et al., 2019). Adversity in early and middle childhood too, have been shown to induce biological signatures implicated in the stress response system, such as DNA methylation in genes related to psychiatric symptoms and immune function (Martins et al., 2021; Unternaehrer & Meinlschmidt, 2016). Because DNA methylation plays a central role in regulating gene expression, inequalities in childhood environments then translate into disparities in

health outcomes such as depression and obesity in later life (Danese & Tan, 2014; Fleischer et al., 2021; Gerke et al., 2018; Khan et al., 2015). In literature more relevant to my study, recent efforts have also examined the effects of adversity on one's epigenetic age, although sample sizes were small ($n = 400+$) and only first generation epigenetic clocks were used. Sumner et al. (2019) found exposure to maltreatment (e.g., violence) to be associated with accelerated epigenetic ageing as measured by the Horvath clock; while Marini et al. (2020) demonstrated positive associations between sexual/physical abuse, financial hardship, and neighbourhood disadvantage with the Hannum clock. My study thus builds on these findings by examining newer generation epigenetic clocks, which are more predictive of outcomes highly correlated with social influences.

The primary finding in this study pertains more specifically to my first research question: which life course hypothesis best explains the link between ACE exposure and EAA? In answering this question, I adopt a statistical learning approach and found that the relationship between all-inclusive ACE exposure and EAA is best explained by the sensitive period hypothesis, and more specifically during early-middle childhood (ages 3 to 5) for both boys and girls. Only one late childhood sensitive period (age 9) was identified for girls, but was found to be statistically insignificant using selective inference checks. This is broadly in line with literature that finds early-middle childhood to be particularly relevant to biologically-relevant outcomes, such as DNA methylation (Dunn et al., 2019), brain/cognitive development (Knudsen, 2004), and indeed epigenetic ageing itself (Marini et al., 2020).

Building on my first research question, I further examined if the best life course hypothesis

differs according to the *types* or *domains* of ACEs being studied. My results suggest overwhelmingly that the sensitive period hypothesis still dominantly explains the link between ACE exposure and EAA, with very few exceptions. Only one ACE domain was not explained by a sensitive period hypothesis – associations between material hardship and EAA appear to be explained best by a recency hypothesis instead.

In line with my findings, existing studies have demonstrated much support for the sensitive period hypothesis. But current approaches commonly examine such life course hypotheses in isolation, ruling out possible interactions between hypotheses, or the possibility that some hypotheses may lose significance after 'controlling' for hypotheses. The SCLMA approach adopted in this study circumvents this problem by evaluating all theoretical models simultaneously, thus allowing for the interplay of hypotheses. Such an interplay of factors result in a *compound hypothesis*, where the best model is comprised of more than one life course hypothesis.

Of the five ACE categories examined (i.e., all-inclusive ACE; material hardship; instability; deprivation; and maltreatment), a compound hypothesis was chosen as the best model for three ACE categories among boys, and 2 ACE categories among girls. For instance, a combination of the cumulative risk and sensitive period at age 3 was identified in relation to male children's exposure to child maltreatment. Controlling for the age 3 sensitive period however, resulted in the loss of significance of the cumulative risk hypothesis. Put otherwise, the total sum of ACE events experienced (i.e., the cumulative risk) became negligible after accounting for the ACEs encountered when they were 3 years old. This contrasts against earlier studies,

which found support for both hypotheses when they are considered independently (Gerke et al., 2018; Power et al., 2020). As my findings suggest, accounting for multiple life course models simultaneously may lead to different results, and facilitate investigations of how multiple hypotheses collectively influence later life outcomes.

With the exception of child maltreatment, all compound hypotheses identified through the SCLMA procedure consist of multiple sensitive periods for boys. Specifically, sensitive periods at ages 1, 3, and 9 were discerned for the material hardship ACE domain, while ages 5 and 9 were implicated for deprivation. Conversely, for girls, compound hypotheses predominantly revolve around the earlier age ranges of 1-5 for the deprivation ACE domain. In contrast, single hypotheses identified by SCLMA uniformly indicated a sensitive period at age 3. This implies that early childhood represents a notably vulnerable phase for individuals facing adversities during their formative years. This observation aligns with existing literature, which underscores the heightened state of neurological plasticity and receptivity to new experiences during the initial years following birth (Dawson et al., 2000; Susman, 2006). Thus, stress response elicited in response to environmental stressors during this period may potentially be amplified, leading to harmful downstream effects such as an accelerated epigenetic clocks for both boys and girls.

The association between ACE exposure and EAA have been well documented, but lesser known are the mechanisms that drive this association. My third research question investigates this by identifying midstream factors that mediate the relationship between early life adversity and epigenetic ageing. In this investigation, I focus on risk behaviours that have been commonly

found to be related to both ACE exposure and accelerated ageing. The results are surprising – almost all mediators were found to suppress the deleterious effects of ACE exposure on epigenetic ageing among young adults. In other words, risk behaviours commonly associated with accelerated ageing were found instead to offset the harmful effects of ACE exposure on EAA. Gender stratified analyses also find mediators to exert suppressing effects, although most mediators were found to be significant only for males but not females. This suggests that pathways between ACE exposure and EAA may also be differentiated by gender.

Why do risk behaviours commonly associated with accelerated ageing exhibit suppressing effects? One reason could be that engaging in novelty-seeking risk behaviours serve as an outlet of relieving pent up stress, which cushions the deleterious effects of ACE encounters. Earlier studies have provided much evidence of a stress response dampening hypothesis, in which one's emotional and physiological response towards life stressors were found to be attenuated after engaging in novelty-seeking and hedonistic behaviours (Sher & Walitzer, 1986). Alcohol consumption for instance, have been found to be linked with reduced anxiety and cardiovascular responses to life stressors (Sher & Walitzer, 1986); and experimental studies also find post-stressor negative affect to be significantly lower for the alcohol consumption treatment group than the control group (Bresin, 2019), suggesting that such mechanisms may confer protective effects against life stressors. Because risk behaviours such as alcohol or drug abuse are relatively novel for young children, engaging in such explaratory behaviours may be additionally rewarding in fulfilling their need for novelty stimulation. Protective effects of such risk behaviours may however attenuate for older age groups, for whom smoking and alcohol may

be less novel. Such differences in novelty perception may then explain why risk behaviours exert protective effects for young children within my study sample, but not in studies studying older populations.

Alternatively, involvement in risky behaviours may also contribute to enhanced resilience, thereby mitigating the impact of ACEs on epigenetic aging. Specifically, the positive affect elicited by risky behaviours may counterbalance stress levels and emotional strain resulting from ACE events, enabling individuals to cultivate a proactive approach towards managing stress and adversity, thereby bolstering their resilience. Research provides empirical support for this perspective, demonstrating positive associations between participating in risky behaviours and increased psychological resilience, as well as reduced perceived stress (McKay et al., 2018). Furthermore, engaging in novel risk behaviours promotes a departure from familiar and comfort-seeking mindsets, thus facilitating the development of resilience-building capacities (Tops et al., 2013). Much evidence have established the moderating role of resilience on epigenetic ageing. In particular, greater emotional regulation and self-control was found to negate the role of stress on epigenetic ageing (Harvanek et al., 2021); while greater psychological resilience predicted slower DNA methylation age (Zhang et al., 2024). Engaging in such risk behaviours may therefore promote short-term protective benefits against accelerated epigenetic ageing as observed in this study.

Thirdly, children who engage in risk behaviours may render their plights more 'visible', thus attracting heightened attention and subsequently receiving augmented social interventions, including counseling and access to child protection networks. Indeed, empirical studies have

underscored that individuals endowed with access to protective networks and augmented social cohesion exhibit diminished susceptibility to epigenetic aging (Liang & Gomaa, 2023; Martin et al., 2021). This phenomenon may be attributed to the manifold benefits associated with heightened social capital, such as mitigating one's dependence on detrimental family environments, as well as their continued enrollment in educational institutions (Plagens, 2011). Continued educational engagement, in particular, has been posited to cultivate expanded peer support networks and other resources conducive to counteract stress stemming from ACEs within their familial environment. This perspective is consonant with extant empirical findings revealing an inverse correlation between educational attainment and epigenetic ageing (Gomez-Verjan et al., 2021). Such benefits may not apply to older populations for whom social interventions – i.e., child protection networks and schooling – are less readily available and accessible. Engaging in risk behaviours thus present less benefits in adulthood than in younger age groups, leading to penalties that result in sustained stress and accelerated epigenetic ageing. Potentially, this explains why risk factors may result in intensified EAA among adults but exert an opposite effect among younger individuals.

6 Conclusion

6.1 Summary of findings

Numerous existing studies have commonly explored and supported three life course hypotheses —cumulative risk, sensitive period, and recency— in the examination of the relationship

between ACE exposures and various life outcomes. However, lesser known is whether and which of these hypotheses retain significance when other life course models are considered concurrently. In this dissertation, I focus on delineating the interplay between childhood adversity and epigenetic ageing, as well as the relative importance of these three hypotheses in elucidating this relationship. This motivation guides my first two research questions, wherein I investigate: 1) what is the most explanatory life course model regarding the association between ACEs and epigenetic ageing in young adulthood; and 2) if and how these differ by the types of ACEs experienced by the individual.

To address these research questions, I employ a statistical learning approach that concurrently considers all three hypotheses, subsequently identifying the most parsimonious model that best elucidates the relationship between ACEs and epigenetic ageing. The findings from my investigation suggest that a sensitive period hypothesis at age 3 predominantly explains the association between ACE exposure and epigenetic ageing, regardless of gender distinctions or specific types of ACEs. Further analyses reveal that while an age 3 sensitive period hypothesis remains the most explanatory for boys, a compound hypothesis involving ages 3, 5, and 9 sensitive periods is more applicable for girls. However, multivariable regression analysis indicates that the significance of the age 9 sensitive period hypothesis diminishes after adjusting for covariates, suggesting that ACEs experienced at age 9 do not significantly predict variation in epigenetic ageing.

In addressing the second research question, I employ domain-specific analyses focusing on four types of ACEs conceptualized in this study: material hardship, instability, deprivation,

and child maltreatment. These analyses reveal that sensitive periods, particularly at age 3, predominantly explain the relationship between epigenetic ageing and various ACE domains. Notably, while material hardship is best explained by a compound hypothesis comprising the recency and age 1 and 9 sensitive period hypotheses, only the age 1 sensitive period remains significant. Gender-specific analyses further unveil nuances, indicating distinct hypotheses for males (sensitive periods of age 1, 3, 9) and females (recency). For the ACE domain of instability, a sensitive period was identified at age 3 when genders were not differentiated. Subgroup analyses by gender did not change the result; thus exposure to familial instability at age 3 is associated with accelerated epigenetic ageing, although the effects appear stronger for males than females ($\beta_{male} = 0.91; \beta_{female} = 0.45$). For deprivation, findings suggest an age 1 sensitive period when genders are undifferentiated, while gender-specific analyses reveal varied sensitive periods – middle to late childhood for males (ages 5 and 9) and early childhood for females (ages 1 and 3). Similarly, a sensitive period at age 3 is associated with child maltreatment when genders are not differentiated; however, this hypothesis loses significance for boys after controlling for the cumulative risk hypothesis. Thus, being exposed to maltreatment events at age 3 does not significantly predict EAA for boys, once their total number of ACEs experienced (i.e., the cumulative risk hypothesis) have been taken into account. This reinforces the importance of 'controlling' for other hypotheses, an approach that is seldom adopted in earlier research. Girls on the other hand, were found to have an age 3 sensitive period.

After establishing support for the various life course hypotheses, my third research question

turns to examine the pathways that intervene between ACE exposure and epigenetic ageing. All mediators except depression appear to mediate the link between my variables of interest, with alcohol abuse, internalising behaviour, and externalising behaviours appearing most frequently as significant mediators across various ACE domains. Gender-specific analyses, however, reveal some differences in results. Specifically, most mediators appear to have lost significance, with the exception of internalising behaviour, smoking, and adiposity/weight-related behaviours for boys. None of the mediators except internalising behaviour for deprivation were, however, found to be significant for women. This potentially suggests that males and females adopt different coping mechanisms in response to childhood stressors; and such coping mechanisms may exert differential effects on EAA across boys and girls.

Most interestingly, where most of the mediators examined were commonly linked to exacerbated EAA in adulthood in other studies, my findings reveal an unexpected trend where these mediators were found instead to attenuate EAA among young adults. Nearly all mediators (with the exception of one) exhibit negative coefficients, suggesting that such risk behaviors attenuate rather than exacerbate the deleterious impact of ACE exposure on epigenetic age. I suggested several reasons that may explain such a counterintuitive finding. Firstly, engagement in risk behaviors may be perceived as novel and rewarding, fulfilling the need for novelty stimulation. This novelty effect could potentially confer protective effects against stress stemming from ACE exposure. Secondly, involvement in novel activities may evoke positive affect, counterbalancing the stress induced by ACE events and enabling young adults to allocate psycho-emotional resources towards adopting a resilient problem-focused approach in man-

aging stressors. Such resilience may yield long-term benefits by desensitising individuals to the negative effects of future stressors, thereby decelerating epigenetic ageing. Finally, young adults engaging in risk behaviors may garner more visibility than their abstinent counterparts. This heightened visibility can attract greater attention and social resources, providing enhanced access to supportive networks and social infrastructures. Consequently, augmented social capital and networks may enable individuals to be less dependent on unhealthy family environments, thereby mitigating the negative effects precipitated by ACE events within the home environment.

6.2 Implications

A key significance of my findings above is such that mechanisms for epigenetic ageing – and other outcomes – may vary broadly across age groups. Indeed, the risk factors associated with EAA among older individuals may evoke distinct mechanisms compared to younger populations, yielding markedly disparate epigenetic ageing outcomes. As I have demonstrated above, risky behaviours commonly associated with accelerated ageing appeared instead to have diminished the effects of ACE exposure on EAA. Redirecting scholarly attention towards younger age groups therefore holds promise for elucidating pivotal upstream mechanisms with enduring implications for later life outcomes. In the context of life course theory, such mechanisms may represent critical junctures, or 'bifurcation points', shaping individuals' immediate and future trajectories (Bernardi et al., 2019). Mechanisms encompassing stress alleviation, resilience enhancement, and social interventions may impart enduring protective effects on EAA and

associated outcomes when introduced earlier in the life course. Therefore, the implication of these findings is not to advocate for the continuation of risky behaviours among children as a means to mitigate epigenetic ageing. Rather, it underscores the necessity of intensifying efforts to identify mechanisms related to stress alleviation and integrate them into targeted interventions tailored for vulnerable youth populations.

Taking this view, a second implication of my study highlights the relative importance of various life course hypotheses (e.g., cumulative risk; recency; sensitive period) when examining the impact of ACEs on EAA. The bulk of existing life course studies typically examine these hypotheses independent of one another, which increases the chances of discovering 'false positives' even when significant results are obtained. As demonstrated earlier, a single-hypothesis model –as commonly adopted in life course studies– finds accumulative exposure to child maltreatment be a significant predictor of later life EAA among males. Yet such a finding was reduced to non-significance once I control for the number of ACE events experienced during the age 3 sensitive period. This suggests that a nuanced understanding of the interplay between different life course hypotheses is essential for accurately assessing the impact of ACEs on EAA. By considering multiple hypotheses simultaneously, researchers can better disentangle the complexities underlying the relationship between ACE exposure and EAA. Failure to do so may lead to misleading conclusions, which may impair the efficacy of social interventions or policies designed on the basis of such research.

Finally, my study has highlighted how disparities in later life may occur as a result of social experiences being biologically embedded in individuals. Recent advances in sociogenomic

studies have played a pivotal role in understanding how one's genetic disposition – fixed at birth – contributes to the stratification of various social outcomes. My study complements this biosocial perspective by exploring the dimensions of epigenetics, which dynamically changes throughout the life course, unlike genetics, which remain relatively fixed. This dynamic nature of epigenetics implies that the risk factors and inequalities associated with health outcomes are also subject to change, reflecting the ongoing (rather than static) interaction between social experiences and biological processes. By elucidating the interplay between social circumstances and epigenetic mechanisms, my study sheds light on how these dynamic processes contribute to the perpetuation or alleviation of health disparities across the life course. Indeed, epidemiological research has acknowledged the role of such biological processes by largely focusing on the social/health-related *consequences* of epigenetic ageing. While this perspective is undoubtedly valuable, my endeavour has been to expand the discourse by highlighting the reciprocal relationship between social contexts and epigenetic ageing. Rather than the sole examination of how epigenetic ageing influences social outcomes, my study underscores the importance of acknowledging how social experiences, in turn, shape ageing trajectories. By highlighting the intricate interplay between social factors and epigenetic processes, my research seeks to lay the groundwork for exploring biosocial pathways through which early life inequalities contribute to divergent trajectories over the life course.

6.3 Strengths and Limitations

Adopting a SCLMA approach in modelling multiple hypotheses simultaneously have been instructive in uncovering life course perspectives most relevant and strongly associated with accelerated epigenetic ageing. Yet, its greatest strength also serves as its weakness, in that the LARS procedure underlying SCLMA only selects variables that are most strongly correlated with the outcome (i.e., accelerated epigenetic ageing). Hence, life course hypotheses that are weakly correlated with EAA would be omitted from the model selection framework adopted by SCLMA. Adopting a SCLMA approach therefore risks overlooking life course hypotheses that may be nonetheless relevant, but has a weaker association with EAA relative to its other competing hypotheses. This potentially contributes to existing discrepancies between my findings and other studies examining single life course hypotheses in isolation and independent of one another. Despite these shortcomings, utilising the SCLMA procedure has much utility in exploring a wide array of life course hypotheses simultaneously. This allows researchers to identify the most impactful predictors, thereby facilitating targeted interventions to mitigate against the impact of adverse childhood exposure. The ability to model multiple hypotheses concurrently also allows for the exploration of complex interactions and synergistic effects not captured by traditional single-hypothesis approaches. Thus, the SCLMA procedure remains a valuable tool for advancing our understanding of the intricate relationship between life course perspectives and epigenetic aging.

Secondly, the SCLMA approach requires researchers to specify apriori life course models that are hypothesised to explain EAA in adulthood. Requiring researchers to specify their hypothe-

ses upfront contributes to a more structured approach of exploring the relationship between ACE exposure and EAA. This however, also implies that if the 'true' hypothesis is not among those specified by researchers, then the relationship between exposure and outcome, as well as its mechanisms may remain unexplored. Yet, this hypothesis-driven procedure also confers certain advantages, such as providing a clear framework for hypothesis testing and facilitating the interpretation of results within a predetermined theoretical framework. This also facilitates attempts to replicate findings across different contexts, allowing for meaningful generalisations to be made.

Thirdly, the effectiveness of SCLMA's model selection process depends heavily on the accurate specification of the model and the absence of unmeasured confounding. As demonstrated by Zhu et al. (2021), when the model comprises many predictors highly correlated with the true model's predictors, SCLMA may identify a compound life course model consisting of these correlated predictors. While this approach facilitates model identification, it comes at the cost of reduced statistical power, potentially compromising the reliability of the findings. Two strategies have been proposed to mitigate this issue. First, researchers may strive to reduce the number of correlated predictors incorporated into their model, for instance by condensing sensitive periods over longer periods of time. This minimises the likelihood of SCLMA inadvertently selecting predictors that closely resemble the 'true' predictors, thus improving the accuracy of the model selection process. Another recommended approach is to ensure a large sample size in order to bolster statistical power and increase the likelihood of detecting true effects amidst the correlated predictors (Zhu et al., 2021).

Recognising the shortfalls of this SCLMA approach, there is reasonable cause to believe that my study is less affected by such issues. In particular, my descriptive analyses have demonstrated that ACEs across sensitive periods and domains were weakly correlated with one another (Table 4 & Table 5). Furthermore, unlike studies which concurrently examine numerous sensitive periods, I am only examining ACE exposures across 4 waves. This reduces the number of predictor values involved and the amount of correlation between them. Even if my predictors share the correlation problem as outlined by Zhu et al. (2021), my study benefits from a reasonably large sample size ($n = 4897$), which allows SCLMA to identify the relevant life course hypotheses with sufficient power.

6.4 Future Directions

Present research have largely attempted to identify biosocial determinants of accelerated ageing, and investigate the repercussions of accelerated ageing on future health outcomes. Yet, there is also growing interest with respect to interventions aimed at *reversing* the ageing process. Future research could thus delve into exploring protective factors that may attenuate the biological ageing trajectory. Furthermore, given that most research today conducts analyses at the individual level, it would also be useful to explore whether aggregate-level units of analyses –such as social network structures or neighbourhoods– may similarly influence one's pace of epigenetic age. Additionally, it would be useful to explore the dynamics underlying intergenerational transmissions of EAA from parent to child, which would allow researchers to pinpoint both the social and genetic components of epigenetic ageing. This line of in-

quiry holds promise for widening our understanding of the multifaceted influences on ageing processes, and could contribute towards the development of targeted interventions aimed at enhancing healthy ageing.

Furthermore, little research has dedicated efforts to establish causal relationships between epigenetic ageing and relevant outcomes. Yet, a recent genome-wide association study (GWAS) has discovered genome-wide significant loci linked to epigenetic ageing (McCartney et al., 2021). This presents a potential avenue for establishing the causal effects of epigenetic ageing on other outcomes, for instance using Mendelian randomisation (MR) techniques. This approach holds promise for disentangling causal pathways from other spurious factors, facilitating a more comprehensive understanding of epigenetic ageing and its causal impact on health outcomes.

From a methodological standpoint, one present shortcoming of the current SCLMA procedure pertains to its inability to incorporate time-varying covariates. Covariates included in this study, for instance, are limited to variables measured at fixed time points. Yet, it is plausible that certain covariates, such as educational attainment, may vary over time and dynamically affect the relationship between ACEs and EAA. Increased education may, for example, provide access to healthier coping mechanisms or social networks which attenuates the impact of ACEs on EAA. Additionally, the current SCLMA framework is also constrained by its ability to specify a single set of covariates across all specified models. Yet different covariates may hold varying degrees of relevance across different life course models. For instance, covariates associated with housing environments may be more relevant during sensitve periods in early childhood, but diminish in relevance at later stages of one's life as individuals go on to acquire

other social networks. Future research may thus seek to integrate time-varying covariates or hypothesis-specific covariates into the SCLMA framework, which allows for a more flexible modelling process for various life course models. This would enrich our understanding of the intricate interplay between environmental determinants and epigenetic ageing processes, and provide a more nuanced understanding of the mechanisms underlying the relationship between ACE exposure and EAA.

6.5 Data availability and Replication

The FFCWS data can be obtained from the Fragile Families and Child Wellbeing Study website (https://fragilefamilies.princeton.edu/). Detailed information on how to access and utilise the dataset can be found on their official website. The code and files required to replicate this study can be accessed on GitHub (https://github.com/1068202/mphil-thesis).

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Appendix

Variables involved

Table 25: Variables comprising the *GrimAge Clock* measure

Variable	Wave	Survey	Measure	Response
k6me_grim	6	Biomarker	GrimAge (EPIC Array)	Participant's Grim Age
k6mk_grim	6	Biomarker	GrimAge (Illumina 450K Array)	Participant's Grim Age
k6me_age	6	Biomarker	Chronological Age (EPIC Array)	Participant's chronological age
k6mk_age	6	Biomarker	GrimAge (Illumina 450K Array)	Participant's chronological age

Table 26: Variables comprising the *Material Hardship* measure

Variable	Wave	Survey	Measure	Response
cm2povco	2	Mother	Constructed: mother's household income/poverty threshold	Income–Poverty Threshold Ratio
cm3povco	3	Mother	Constructed: mother's household income/poverty threshold	Income–Poverty Threshold Ratio
cm4povco	4	Mother	Constructed: mother's household income/poverty threshold	Income–Poverty Threshold Ratio
cm5povco	5	Mother	Constructed: mother's household income/poverty threshold	Income–Poverty Threshold Ratio

Table 27: Variables comprising the *Early Life Instability* measure

Variable	Wave	Survey	Measure	Response
cm2relf	2	Mother	Mother-father relationship	1 = married; 2 = romantic, cohabiting; 3 = romantic, visiting; 4 = friends; 5 = hardly talk; 6 = never talk; 7 = unknown father
cm3relf	3	Mother	Mother-father relationship	1 = married; 2 = romantic, cohabiting; 3 = romantic, visiting; 4 = friends; 5 = hardly talk; 6 = never talk; 7 = unknown father
cm4relf	4	Mother	Mother-father relationship	1 = married; 2 = romantic, cohabiting; 3 = romantic, visiting; 4 = friends; 5 = hardly talk; 6 = never talk; 7 = unknown father
cm5relf	5	Mother	Mother-father relationship	1 = married; 2 = romantic, cohabiting; 3 = romantic, visiting; 4 = friends; 5 = hardly talk; 6 = never talk; 7 = unknown father

Table 28: Variables comprising the *Childhood Maltreatment* measure; *Wave 5 variables reverse coded

Variable	Wave	Survey	Measure	Response
m2c4	2	Mother	In the past month, has (FATHER) spanked (CHILD) because (he/she) was misbehaving or acting up?	1 = yes; 2 = no
m2c4a	2	Mother	Did he do this (spank child) …	1 = every day; 2 = a few/week; 3 = a few/month; 4 = once or twice
m2b19	2	Mother	In the past month, have you spanked (CHILD) because (he/she) was misbehaving or acting up?	1 = yes; 2 = no

Variable	Wave	Survey	Measure	Response
m2b19a	2	Mother	Did you do this (spank CHILD) …	1 = every day; 2 = a few/week; 3 = a few/month; 4 = once or twice
p3j3, p4g3, p5q1c*	3,4,5	Primary caregiver	How many times in the past year did you shout, yell, or scream at child	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year
p3j4, p4g4, p5q1d*	3,4,5	Primary caregiver	How many times in the past year did you it (him/her) on the bottom with something like a belt, hairbrush, a stick or some other hard object?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year

Variable	Wave	Survey	Measure	Response
p3j6, p4g6, p5q1f*	3,4,5	Primary caregiver	How many times in the past year did you shout, yell, or scream at (CHILD)?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year
p3j7, p4g7, p5q1g*	3,4,5	Primary caregiver	How many times in the past year did you spank (him/her) on the bottom with your bare hand?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year

Variable	Wave	Survey	Measure	Response
p3j8, p4j8, p5q1h*	3,4,5	Primary caregiver	How many times in the past year did you swear or curse at (him/her)?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year
p3j9, p4g9, p5q1i*	3,4,5	Primary caregiver	How many times in the past year did you say you would send child away or would kick child out of the house?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year

Variable	Wave	Survey	Measure	Response
p3j10, p4g10, p5q1j*,	3,4,5	Primary caregiver	How many times in the past year did you threaten to spank or hit (him/her) but did not actually do it?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year
p3j11, p4g11, p5q1k*	3,4,5	Primary caregiver	How many times in the past year did you slap (him/her) on the hand, arm, or leg?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year

Variable	Wave	Survey	Measure	Response
p3j13, p4g13, p5q1m*	3,4,5	Primary caregiver	How many times in the past year did you pinch (him/her)?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year
p3j14, p4g14, p5q1n*	3,4,5	Primary caregiver	How many times in the past year did you call (him/her) dumb or lazy or some other name like that?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year

Table 29: Variables comprising the *Deprivation* measure; *Wave 5 variables reverse coded

Variable	Wave	Survey	Measure	Response
m2b18a	2	Mother	(How often do you) play games like "peek-a-boo" or "gotcha" with (CHILD)?	205 = never; 204 = 1-2 times/month; 203 = several times/month; 202 = several times/week; 201 = every day
m2b18b	2	Mother	(How often do you) sing songs or nursery rhymes to (CHILD)?	205 = never; 204 = 1-2 times/month; 203 = several times/month; 202 = several times/week; 201 = every day
m2b18c	2	Mother	(How often do you) read stories to (CHILD)?	205 = never; 204 = 1-2 times/month; 203 = several times/month; 202 = several times/week; 201 = every day

Variable	Wave	Survey	Measure	Response
m2b18d	2	Mother	(How often do you) tell stories to (CHILD)?	205 = never; 204 = 1-2 times/month; 203 = several times/month; 202 = several times/week; 201 = every day
m2b18e	2	Mother	(How often do you) play inside with toys such as blocks or Legos with (CHILD)?	205 = never; 204 = 1-2 times/month; 203 = several times/month; 202 = several times/week; 201 = every day
m2b18g	2	Mother	(How often do you) pug or show physical affection to (CHILD)?	205 = never; 204 = 1-2 times/month; 203 = several times/month; 202 = several times/week; 201 = every day

Variable	Wave	Survey	Measure	Response
m2h19b	2	Mother	In the past year, did your child go hungry?	205 = never; 204 = 1-2 times/month; 203 = several times/month; 202 = several times/week; 201 = every day
p3j15, p4g15, p5q2a*	3,4,5	Primary caregiver	How many times in the past year did you have to leave your child home alone, even when you thought some adult should be with (him/her)?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year
p3j16, p4g16, p5q2b*	3,4,5	Primary caregiver	How many times in the past year were you not able to show or tell your child that you loved (him/her)?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year

Variable	Wave	Survey	Measure	Response
p3j17, p4g17, p5q2c*	3,4,5	Primary caregiver	How many times in the past year were you not able to make sure (CHILD) got the food (he/she) needed?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year
p3j18, p4g18, p5q2d*	3,4,5	Primary caregiver	How many times in the past year were you not able to make sure your child got to a doctor or hospital when (he/she) needed it?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year
p3j19, p4g19, p5q2e*	3,4,5	Primary caregiver	How many times in the past year were you so drunk or high that you had a problem taking care of your child?	0 = never happened; 1 = once; 2 = twice; 3 = 3-5 times; 4 = 6-10 times; 5 = 11-20 times; 6 = > 20 times; 7 = yes, but not in past year

Table 30: Variables comprising the *Depression* measure; * Reverse coded

Variable	Wave	Survey	Measure	Response
k6d2c*	6	Focal child	I feel I cannot shake off the blues, even with help from my family and my friends	1 = strongly agree; 2 = somewhat agree; 3 = somewhat disagree; 4 = strongly disagree
k6d2n*	6	Focal child	I feel sad	1 = strongly agree; 2 = somewhat agree; 3 = somewhat disagree; 4 = strongly disagree
k6d2s	6	Focal child	I feel happy	1 = strongly agree; 2 = somewhat agree; 3 = somewhat disagree; 4 = strongly disagree
k6d2x*	6	Focal child	I feel life is not worth living	1 = strongly agree; 2 = somewhat agree; 3 = somewhat disagree; 4 = strongly disagree

Variable	Wave	Survey	Measure	Response
k6d2ac*	6	Focal child	I feel depressed	1 = strongly agree; 2 = somewhat agree; 3 = somewhat disagree; 4 = strongly disagree

Table 31: Variables comprising the *Externalising Behaviour* measure

Variable	Wave	Survey	Measure	Response
p6b35	6	Focal Child (Aggressive subscale)	Child is cruel, bullies, or shows meanness to others	1 = not true; 2 = sometimes true; 3= often true
p6b37	6	Focal Child (Aggressive subscale)	Child destroys things belonging to the family or others	1 = not true; 2 = sometimes true; 3= often true
p6b38	6	Focal Child (Aggressive subscale)	Child is disobedient at school	1 = not true; 2 = sometimes true; 3= often true
p6b41	6	Focal Child (Aggressive subscale)	Child gets in many fights	1 = not true; 2 = sometimes true; 3= often true
p6b42	6	Focal Child (Aggressive subscale)	Child physically attacks people	1 = not true; 2 = sometimes true; 3= often true
p6b43	6	Focal Child (Aggressive subscale)	Child is stubborn, sullen, or irritable	1 = not true; 2 = sometimes true; 3= often true

Variable	Wave	Survey	Measure	Response
p6b44	6	Focal Child (Aggressive subscale)	Child has temper tantrums or a hot temper	1 = not true; 2 = sometimes true; 3= often true
p6b45	6	Focal Child (Aggressive subscale)	Child threatens people	1 = not true; 2 = sometimes true; 3= often true
p6b57	6	Focal Child (Aggressive subscale)	Child is unusually loud	1 = not true; 2 = sometimes true; 3= often true
p6b59	6	Focal Child (Aggressive subscale)	Child argues a lot	1 = not true; 2 = sometimes true; 3= often true
p6b49	6	Focal Child (Rule-breaking subscale)	Child doesn't seem to feel guilty after misbehaving	1 = not true; 2 = sometimes true; 3= often true
p6b50	6	Focal Child (Rule-breaking subscale)	Child hangs around with others who get in trouble	1 = not true; 2 = sometimes true; 3= often true

Variable	Wave	Survey	Measure	Response
p6b51	6	Focal Child (Rule-breaking subscale)	Child lies or cheats	1 = not true; 2 = sometimes true; 3= often true
p6b60	6	Focal Child (Rule-breaking subscale)	Child runs away from home	1 = not true; 2 = sometimes true; 3= often true
p6b61	6	Focal Child (Rule-breaking subscale)	Child sets fires	1 = not true; 2 = sometimes true; 3= often true
p6b62	6	Focal Child (Rule-breaking subscale)	Child steals at home	1 = not true; 2 = sometimes true; 3= often true
p6b63	6	Focal Child (Rule-breaking subscale)	Child steals outside the home	1 = not true; 2 = sometimes true; 3= often true

Variable	Wave	Survey	Measure	Response
p6b64	6	Focal Child (Rule-breaking subscale)	Child swears or uses obscene language	1 = not true; 2 = sometimes true; 3= often true
p6b67	6	Focal Child (Rule-breaking subscale)	Child vandalizes	1 = not true; 2 = sometimes true; 3= often true

Table 32: Variables comprising the *Internalising Behaviour* measure

Variable	Wave	Survey	Measure	Response
p6b36	6	Focal Child (anxious/depression subscale)	Child cries a lot	1 = not true; 2 = sometimes true; 3= often true
p6b40	6	Focal Child (anxious/depression subscale)	Child feels worthless or inferior	1 = not true; 2 = sometimes true; 3= often true
p6b52	6	Focal Child (anxious/depression subscale)	Child is nervous, high-strung, or tense	1 = not true; 2 = sometimes true; 3= often true
p6b53	6	Focal Child (anxious/depression subscale)	Child is too fearful or anxious	1 = not true; 2 = sometimes true; 3= often true

Variable	Wave	Survey	Measure	Response
p6b54	6	Focal Child (anxious/depression subscale)	Child feels too guilty	1 = not true; 2 = sometimes true; 3= often true
p6b68	6	Focal Child (anxious/depression subscale)	Child worries	1 = not true; 2 = sometimes true; 3= often true
p6b65	6	Focal Child (withdrawnsubscale)	Child is underactive, slow moving, or lacks energy	1 = not true; 2 = sometimes true; 3= often true
p6b66	6	Focal Child (withdrawnsubscale)	Child is unhappy, sad or depressed	1 = not true; 2 = sometimes true; 3= often true

Elbow Plots

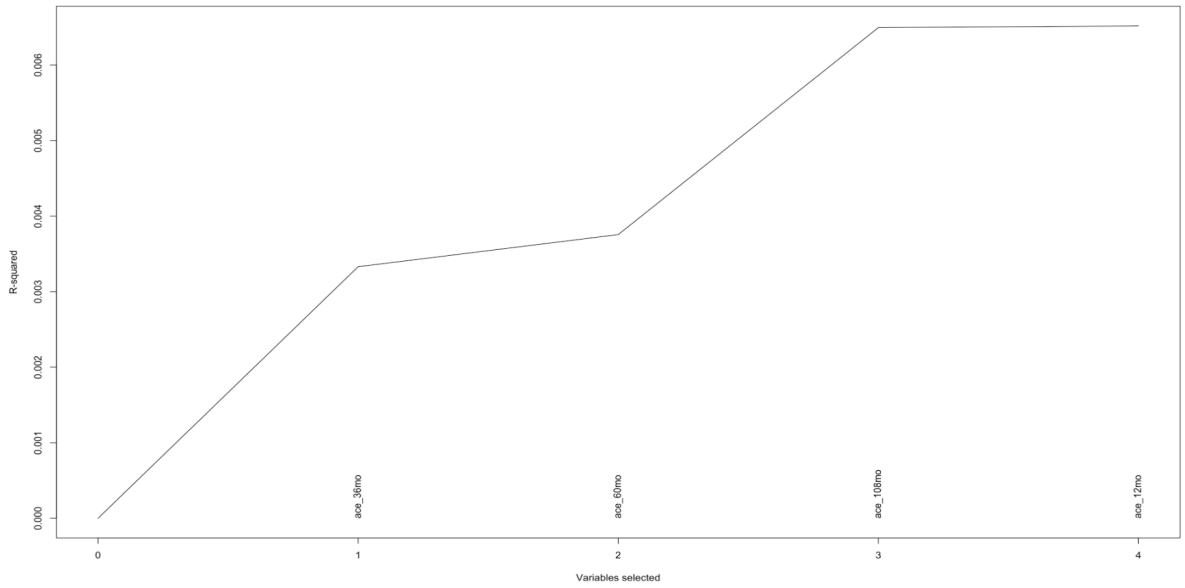

Figure S1: Elbow plot for association between all-inclusive ACE exposure and EAA

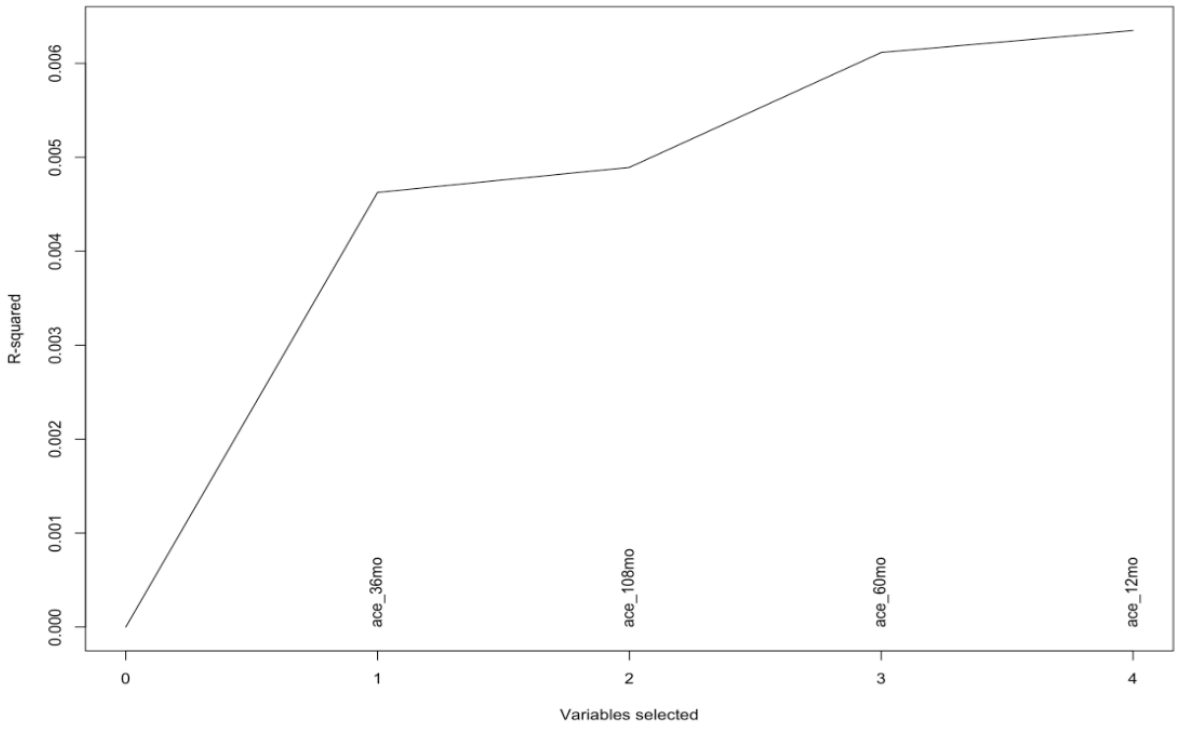

Figure S2: Elbow plot for association between all-inclusive ACE exposure and EAA (Male)

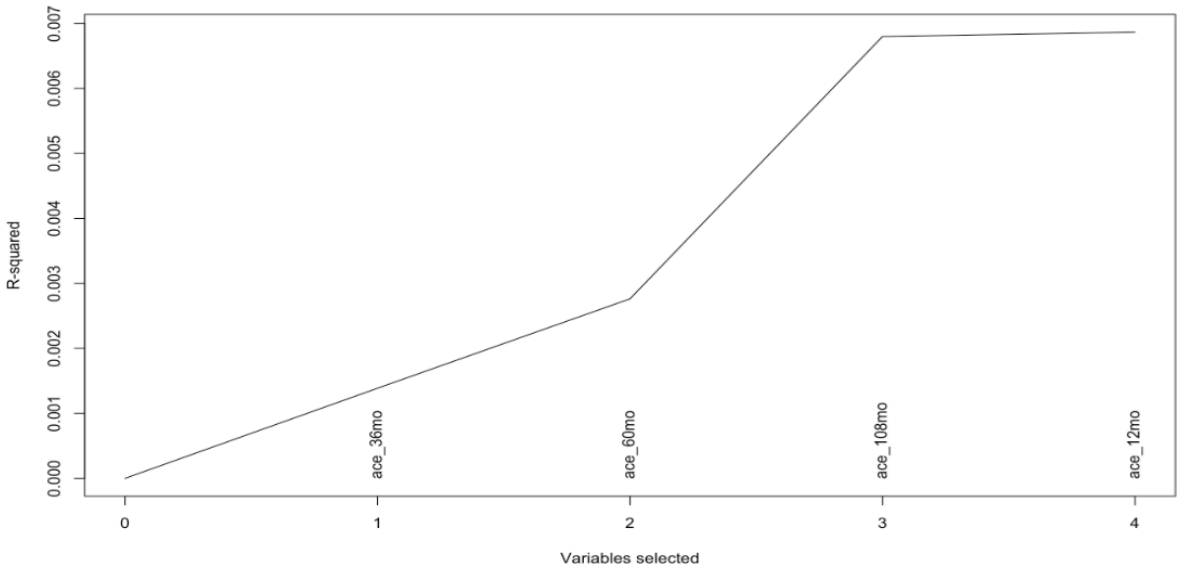

Figure S3: Elbow plot for association between all-inclusive ACE exposure and EAA (Female)

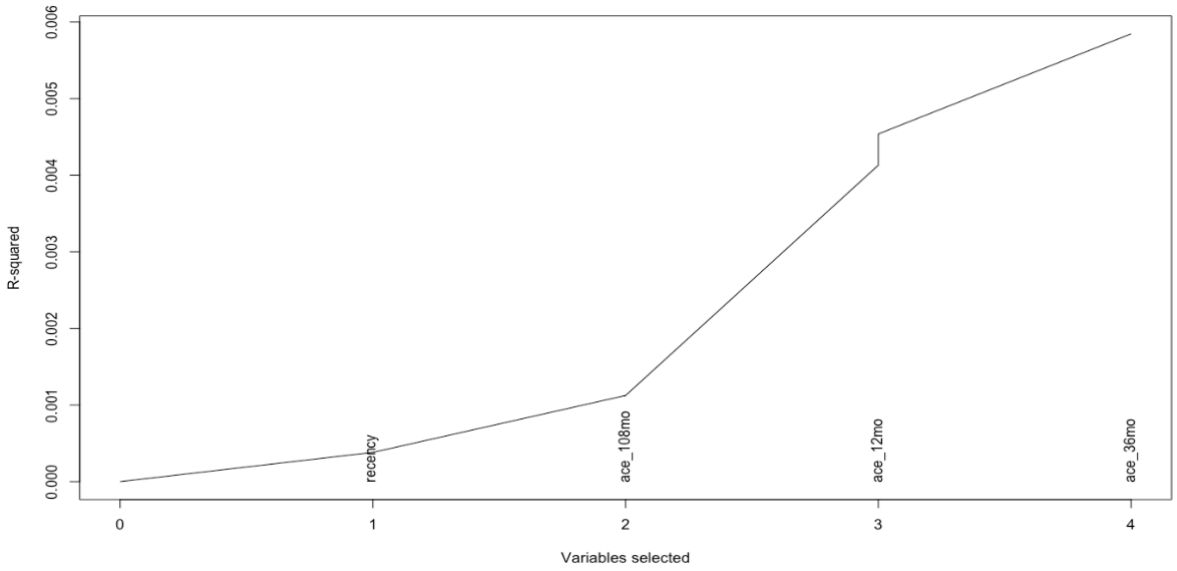

Figure S4: Elbow plot for association between material hardship and EAA

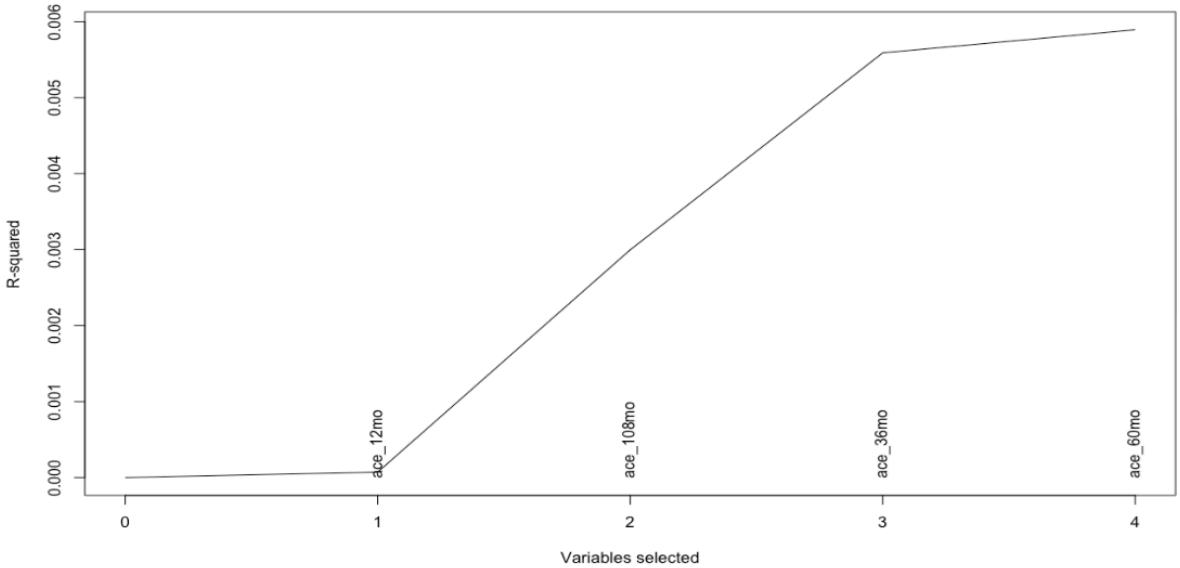

Figure S5: Elbow plot for association between material hardship and EAA (Male)

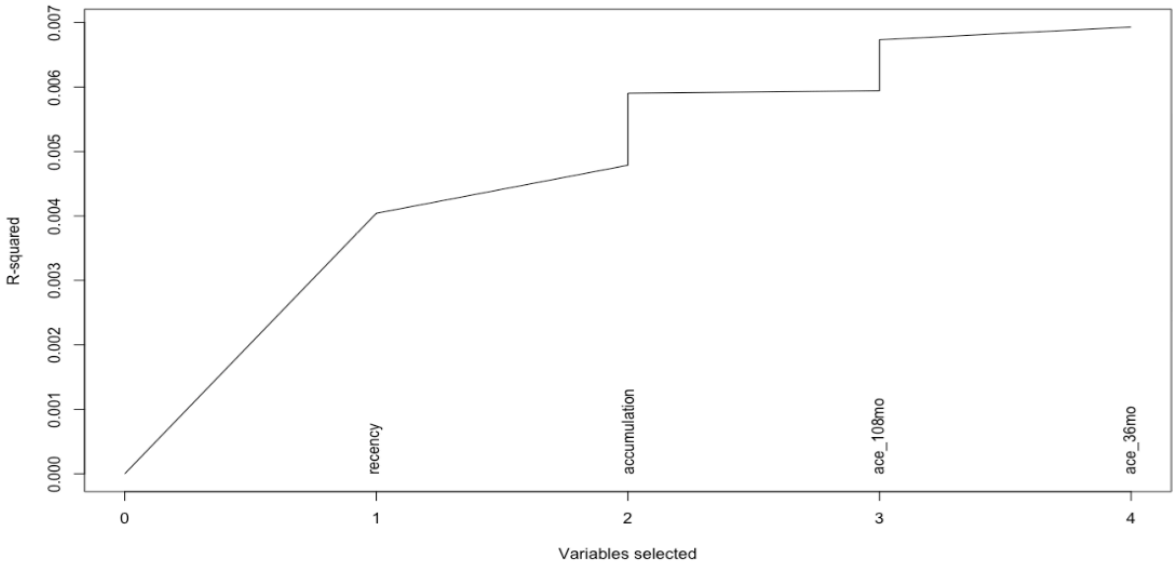

Figure S6: Elbow plot for association between material hardship and EAA (Female)

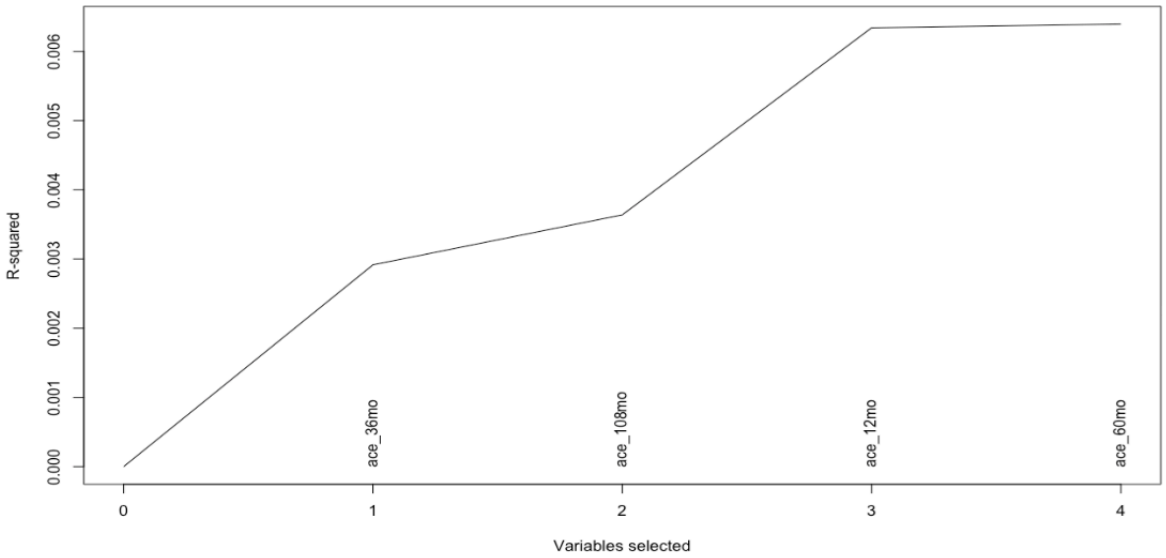

Figure S7: Elbow plot for association between instability and EAA

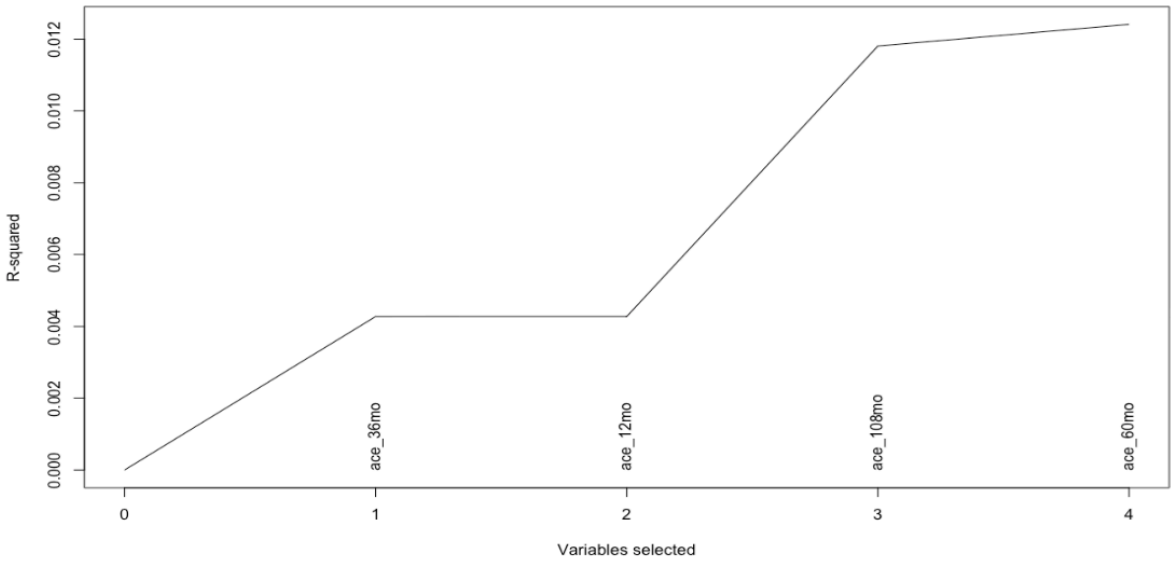

Figure S8: Elbow plot for association between instability and EAA (Male)

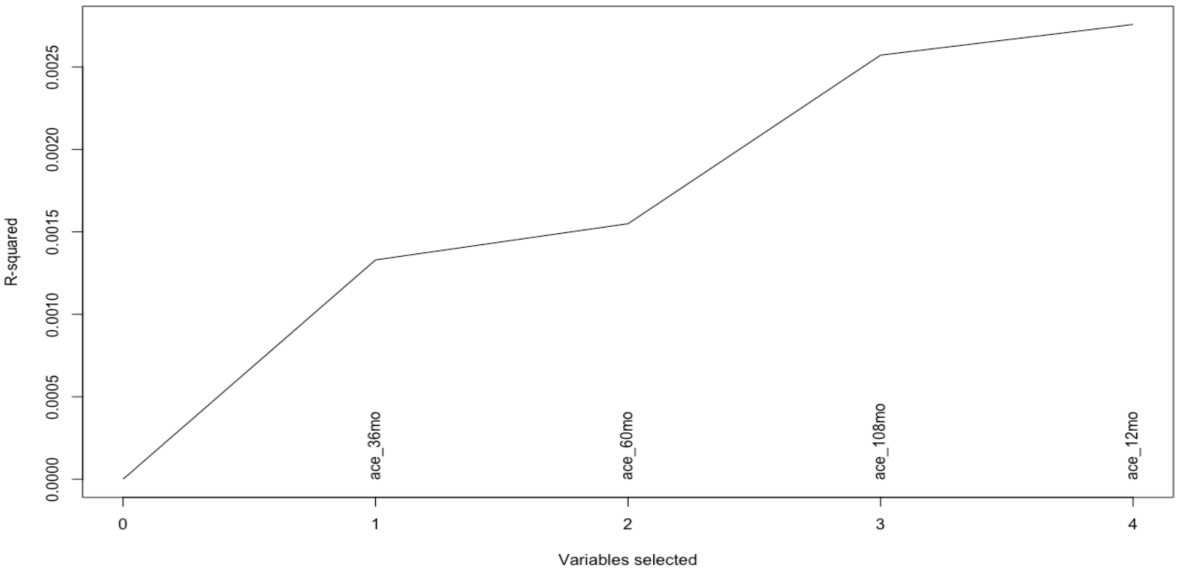

Figure S9: Elbow plot for association between instability and EAA (Female)

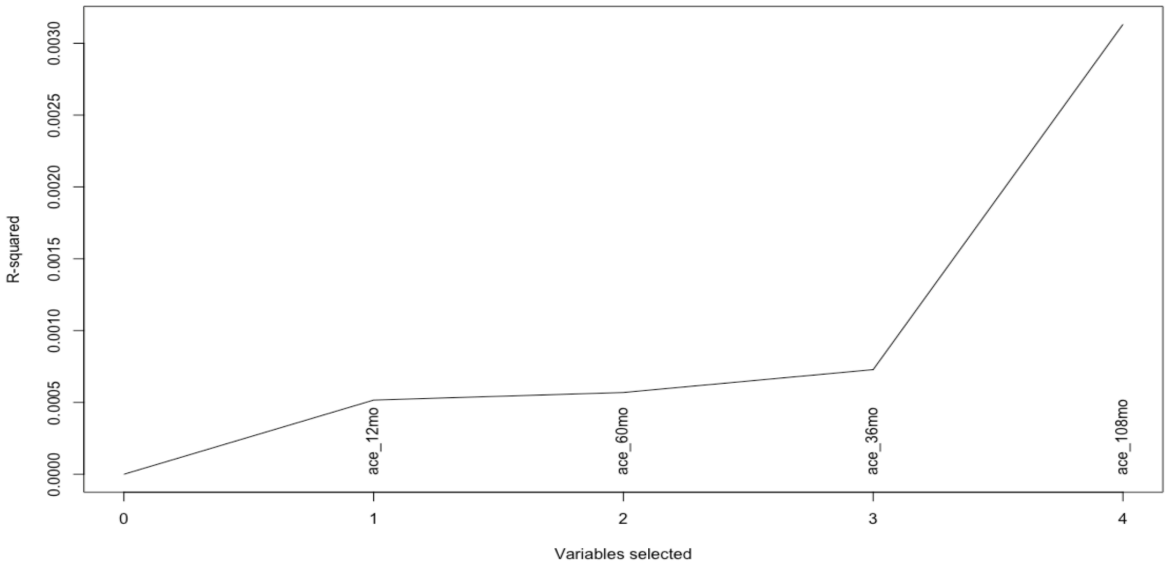

Figure S10: Elbow plot for association between deprivation and EAA

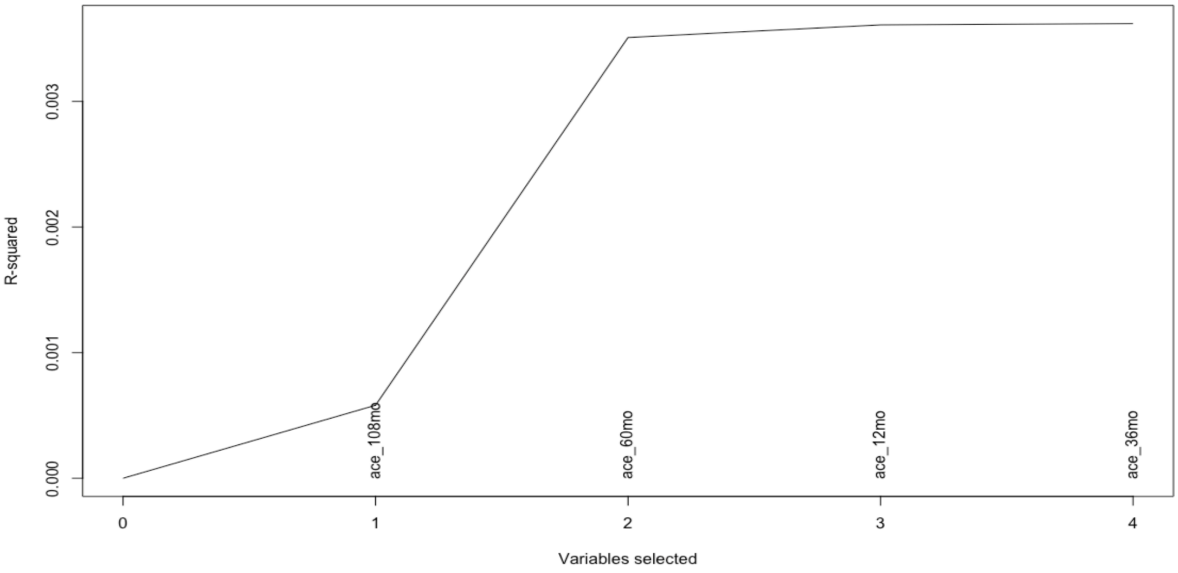

Figure S11: Elbow plot for association between deprivation and EAA (Male)

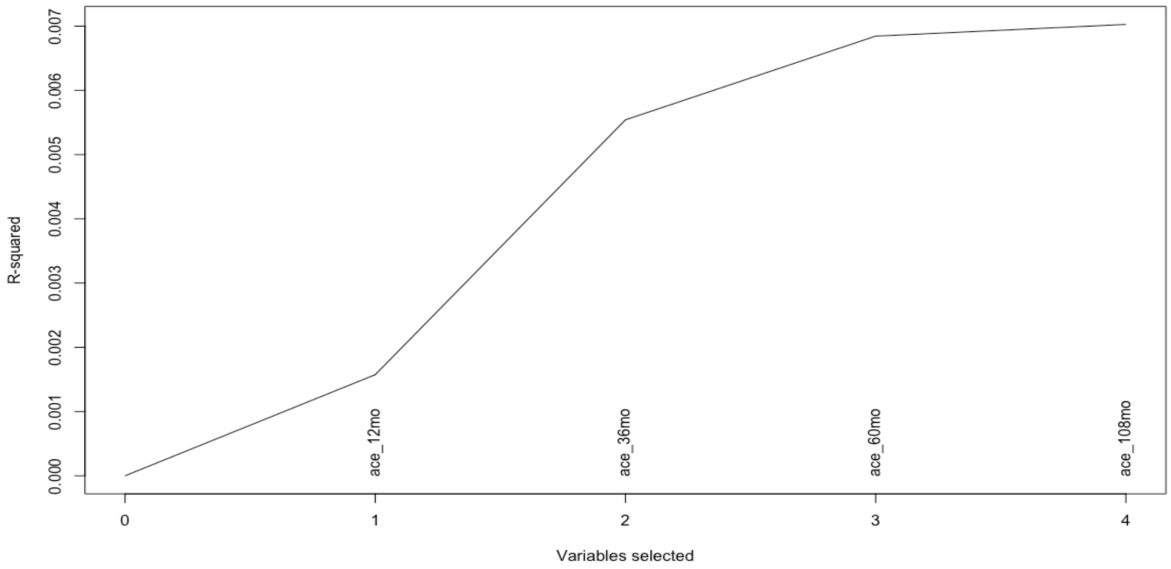

Figure S12: Elbow plot for association between deprivation and EAA (Female)

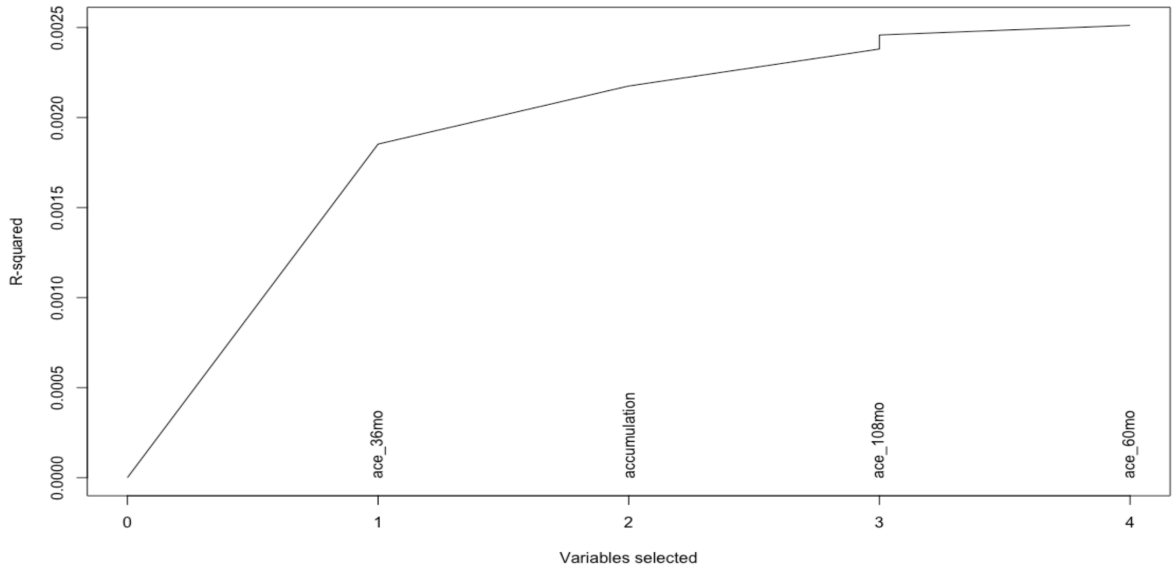

Figure S13: Elbow plot for association between maltreatment and EAA

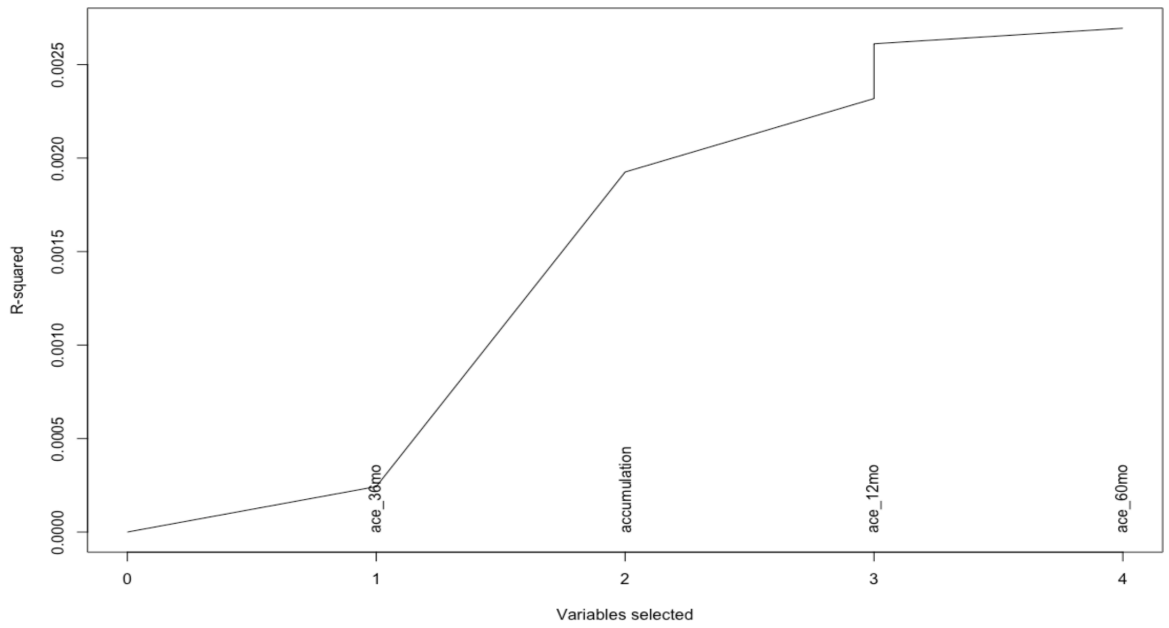

Figure S14: Elbow plot for association with maltreatment and EAA (Male)

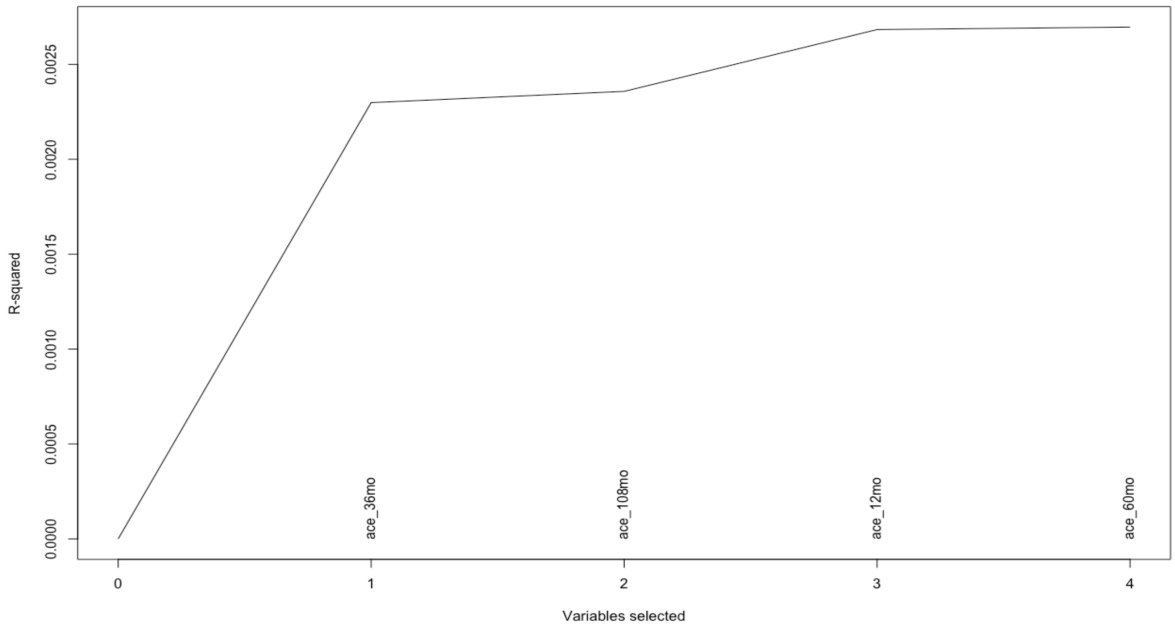

Figure S15: Elbow plot for association between maltreatment and EAA (Female)