Developmental burden of childhood adversity: Insight from longitudinal perspectives

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Preface

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the preface and specified in the text. It is not substantially the same as any work that has already been submitted before for any degree or other qualification except as declared in the preface and specified in the text. This thesis does not exceed the prescribed limit of 60,000 words as specified by the degree committee of the Faculties of Clinical Medicine and Clinical Veterinary Medicine.

The study reported in chapter 2 has been accepted for publication in *Journal of child psychology and psychiatry*.

Nweze, T., Ezenwa, M., Ajaelu, C., & Okoye, C. (2023). Childhood mental health difficulties mediate the long-term association between early-life adversity at age 3 and poorer cognitive functioning at ages 11 and 14. *Journal of child psychology and psychiatry.*

Chapter 3 has been published in *eClinicalMedicine*. Drs Florian Lange and Erin Dunn provided general feedback for my chapter 3 and will appear as:

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Chapter 4 is at the final stage of peer review process and when published will appear as:

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Abstract

Childhood adversity has been implicated in poorer developmental outcomes such as behavioral problems, poorer mental health and cognitive deficits. Studies have also linked adversity to alterations in cortical brain structures. To date however, almost all knowledge of the effects of adversity on outcomes has come from cross-sectional studies or longitudinal studies that used cross-sectional data analysis method. In an attempt to bridge this gap, across three empirical studies, this thesis sets out to implement series of longitudinal data modelling aimed at disentangling the intricacies of the effects of childhood adversity on mental health, cognitive abilities and brain development.

In study 1, I analyzed a large sample (N=13,287) of 5 wave longitudinal data obtained from the Millennium Cohort Study in an attempt to understand how early-life adversity, mental health and cognition affect one another or how the effects unfold over time. To achieve this, I used focused longitudinal mediation model via path model approach. Results showed that early-life adversity was associated with poorer performance in spatial working memory and vocabulary performance. Notably, current and previous mental health mediated a substantial proportion (working memory: 59%; vocabulary: 70%), of these effects. Findings also showed that adversity has an enduring adverse effect on mental health, and that poorer mental health is associated with poorer cognitive performance later on in development. Moreover, the adverse effects of mental health were *cumulative*: poor mental health early on is associated with poorer cognitive scores up to 11 years later, above and beyond contemporaneous mental health. Based on this evidence, I suggested that the academic and cognitive competence of vulnerable children may be enhanced if their early mental health conditions are given deliberate clinical attention.

In a follow-up study 2, I attempted to provide empirical support for dimensional model of adversity which argues that childhood adversity can be classified into subgroups, known as dimensions. For this purpose, I analyzed rich set of adverse childhood experiences obtained from a subset of ALSPAC cohort sample (N = 2,965) using latent class analysis. Findings

showed evidence of five distinct adversity subgroups, namely, low adversity, dysfunctional family, parental deprivation, family poverty and global adversity. To establish a pathway to cognitive functioning among the adversity subgroups, a further analysis using latent class regression revealed that family poverty subgroup performed poorest in working memory and inhibition tasks. A separate analysis revealed that the effects of each individual adversity types on cognitive outcomes were mostly consistent with the observed class performance in which they co-occurred. Regardless, sensitive periods (timing of adversity exposure) explained more variability in these observed effects compared to accumulation hypothesis.

In study 3, I analysed a subset of IMAGEN cohort sample (N = 502) using latent change score model and complete longitudinal mediation model via autoregressive path approach, aimed to understand the long-term interrelations between adverse life events, cortical development and cognitive functioning. Results of latent change score model showed that greater baseline adverse life events predicted a marginal reduction in the right anterior cingulate surface area. In addition, baseline right orbitofrontal cortical thickness predicted a decrease change in adverse life events. I found no evidence of association between adverse life events and volumes of cortical structures or cognitive outcomes. In separate longitudinal analyses, I found no evidence of indirect effects in the two neurocognitive pathways that link adverse life events in adolescence to brain and cognitive outcomes. Although the results of latent change score model appear to support the robust cross-sectional studies which have implicated adverse events in brain alterations, especially in the prefrontal, however, the magnitude of effects observed in this study 3 are smaller than have been reported in the cross-sectional studies, suggesting that potential long-term impact of adverse life events on brain structures may likely be more modest than previously noted.

I end the thesis by articulating the implications of these findings across the 3 empirical studies, indicating the strengths and limitations, and suggesting areas for future directions. Generally, it is my hope that new insight drawn from these longitudinal studies will inform the right policies in the society. Such policies may include but not limited to increase clinical intervention for the vulnerable and most underprivileged children as well greater financial aids to families living in poverty, given recent reports that such aid package can alter the trajectories of developmental outcomes of children in a positive way.

Acknowledgement

First and foremost, I will like to thank the University of Cambridge, Medical Research Council Cognition and Brain Sciences Unit, and Cambridge Trust through Cambridge African scholarship for providing and sustaining the institutional platforms and scholarship scheme needed to undertake this doctoral programme. Growing up in the rural village of Enugu, Nigeria, it was never in my wildest dream that one day, I would walk through the four walls of this elite University. In times of failures, along the course of this training, this was a constant reminder of the limitless possibilities of life.

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I will also want to thank my family and friends as well as my enemies. I want to thank my mother, Elizabeth, whose faith and prayers held me at the impossible moments. I also thank my friends, whose love I will always cherish but more importantly, my enemies, whose hate fed my growth and provided the stepping stones for greater heights.

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1 Chapter 1

General introduction

1.1 Understanding the term childhood adversity

The term childhood adversity (also referred to as adverse childhood experiences, early-life adversity or early-life stress in this thesis) has been defined as 'potentially traumatic events or chronic stressors that occur before the age of 18 and are uncontrollable to the child' (Lewer et al., 2019, p.e487). This implies that victims of childhood adversity usually do not have control over the negative or traumatic events in which they are exposed to, e.g., children living in poverty or violent neighborhood often have little control over their family income or violence in their neighborhood.

A similar definition offered by McLaughlin (2006, pp.363) sees childhood adversity as "experiences that are likely to require significant adaptation by an average child and that represent a deviation from the expectable environment". This later definition uniquely highlights elements of environmental experiences that should be classified as childhood adversity and what should not. First, adverse experiences should be ongoing or chronic events, happening at childhood or adolescence but not at adulthood. Second, the ongoing event in the child's environment should likely result in significant disruption from the child's expectable environment. Taken together, the literature suggests that for experiences to fall under the umbrella of 'adverse childhood experiences', they should be severe (e.g., abuse – physical, sexual and emotional abuses; neglect – deprivation and institutionalization), or chronic (e.g., repeated exposure to violence – parental violence, violent and stressful neighborhood, poverty,

stress) and deviate from the norm of child rearing (e.g., all forms of family dysfunctions and family instability).

1.2 Prevalence of childhood adversity across different studies

Adverse childhood experiences are ubiquitous across almost all societies. In the past decade, numerous studies have attempted to examine the prevalence of childhood adversity in the general populations. One of such studies that examined prevalence of adversity in the United States found that more than 14% and 32% of males and females respectively had childhood histories of sexual abuse (Briere & Elliott, 2003). In the same study, history of physical abuse was more evenly distributed across gender as 22.2% (males) and 19.5% (females) reported being victims of physical abuse. Other worldwide meta-analysis studies have estimated that about 4-20% of children have been sexually violated (Stoltenborgh et al., 2014; Pereda et al., 2009), 5-10% (girls) and 5% (boys) are exposed to penetrative sex and one in every ten children faced neglect or psychological abuse (Andrews et al., 2004; Gilbert et al., 2009). In a similar study that reported gender differences in prevalence of childhood abuse, 23% of females and 36% of males had a history of physical and emotional abuse at childhood (Stoltenborgh et al., 2014). Curiously, it is assumed that cases of physical and sexual abuse are not only being under-reported in high-income countries but even fewer of the reported cases are substantiated by authorities (Gilbert et al., 2009), an indication that child abuse may be more prevalent than noted.

Although the studies described above focused more on sexual and physical abuses, it is pertinent to clarify that the threat posed by adverse childhood experiences is not limited to sexual or physical abuses which dominated early childhood adversity literature but daily childhood stressors commonly experienced by the larger population may also be classified as

adverse childhood experiences, especially when such stressors become chronic. For example, exposure to prolonged period of parental psychopathology may be considered a deviation from expected childhood experiences. (See Table 1.1 for summary of the prevalence of all common types of adversity reported in the literature). One of the most robust study to date that examined multifaceted childhood stressors involved large representative national and regional samples (Kessler et al., 2010). The study sample drawn from over 51, 000 adults from 9 high-income countries, 6 high-middle countries and 6 low/lower-middle income countries measured 12 adversity types that ranged from interpersonal loss, parental maladjustment, and maltreatment. Authors observed that about one-third of the sampled population reported exposure to at least, one type of childhood adversity, suggesting an evenly distributed prevalence rate in both the high, middle and low income countries. Parental death (11.0–14.8%), physical abuse (5.3–10.8%), family violence (4.2–7.8%) and parental mental illness (5.3–6.7%) were the most commonly reported adversity types with more than half of the respondents presenting multiple childhood adversity types.

Table 1.1: Definitions and prevalence of commonly reported types of childhood adversity

Types of Adversity	Definitions	Prevalence across studies
Physical abuse *	This refers to intentional use of force on a child that leads to or has the potential to cause physical injury. Physical abuse can be perpetrated by a child's parents, peers, guardians or anyone else and generally involves acts such as hitting, beating, punching, kicking, etc.	19-22% in a large scale study in the United States (Briere & Elliott, 2003). 8% in a large world-wide cross-sectional study (Kessler et al., 2010). 14-54% cumulative prevalence in global meta-analysis (Stoltenborgh et al., 2014); 12-27% (Moody et al., 2018)
Sexual abuse *	This involves any attempted or completed sexual act/contact or noncontact sexual exploitation of a child by the caregiver. Although mostly perpetrated by guardians and close relatives, it also includes unwanted sexual interactions with strangers or anyone else. This can range from penetrative sex to non-contact sexual exploitation.	4-20% in two global meta-analysis studies (Stoltenborgh et al., 2014; Pereda et al., 2009). 14-32% prevalence of sexual abuse (Kessler et al., 2010) which vary from non-contact sexual exploitation (2-6%), contact sexual abuse (3.13%), penetrative sex (1-6%) and other forms of sex abuse (8-26%; Andrews et al., 2004); 6-20% (Moody et al., 2018).
Psychological/emotional abuse *	Involves interactions that conveys to a child that s/he is worthless, flawed, unloved, unwanted, endangered, or	12.1% (Scher et al., 2004); 33% (Giano, Wheeler, & Hubach, 2020); 4.8%

	valued only in meeting another's needs. Although predominantly perpetrated by caregivers, but can also involve anyone else.	(Taillieu et al., 2016); 6-33% (Moody et al., 2018); 39.5% (Thanh Nguyen, Dunne, & Vu Le, 2010)
Neglect *	Involves failure to meet a child's basic physical, medical, emotional and educational needs. This includes failure to provide food or ensure a child's basic hygiene and safety needs. Institutionalization is one extreme type of adversity that is within the scope of neglect. This involves placing large number of children in residential care usually referred to as orphanage home and outside the care of their families	6.2% (Taillieu); 5.1% (Scher et al., 2004); 4.4% (Kessler et al., 2010); 13-40% (Moody et al., 2018); 29.3% (Thanh Nguyen, Dunne, & Vu Le, 2010) About 3-9 million children are believed to be institutionalised globally with median estimate of 7.52 million children (Desmond et al., 2020).
Parental mental illness	This occurs when a child is raised by one or two parents with diagnosable mental health problems. Commonly reported mental health problems are depression, anxiety, or suicidal thoughts.	28% (Dunn et al., 2018) and 32.3% (Lacey et al., 2020b) cumulative prevalence across childhood in a longitudinal cohort. A smaller rate of 6.2% has been reported in a more diverse sample (Kessler et al., 2010) as well as other cross-sectional studies 7.1% (Calthorpe & Pantell, 2021) and 16.1% (Giano, Wheeler, & Hubach, 2020).
Parental divorce	This involves the termination of a marriage or relationship that has produced a child, leaving such child in the care of one parent only or step parents.	Prevalence rates are 6.6% (Kessler et al., 2010); 22.9% (Calthorpe & Pantell, 2021); 28.2% (Giano, Wheeler, & Hubach, 2020).
Family instability	Aside parental divorce/separation, other forms of parental loss (or unstable parenting) have been examined in childhood adversity studies. This include separation from parents for a period of time, parents getting remarried, frequent caregivers' changes or child placement in care homes.	5.1% (Kessler et al., 2010); 46% (Dunn et al., 2018); 19.8% (Raley et al., 2019).
Parental death (or death in the family)	This involves the death of one or both parents or guardians, as a result of illness, accident, or violence. Death from other very close relatives such as siblings have also been investigated as form of childhood adversity.	An estimated 12.5% of children are believed to have suffered parent death globally (Kessler et al., 2010). Other local estimates of prevalence are 3.3% (Calthorpe & Pantell, 2021); 3% (Hiyoshi et al., 2021);
Domestic violence	This generally occurs in the context of intimate partner violence which involves abuse (physical, emotional or sexual) between two intimate partners or family members. Maternal victimization is the most common form of domestic violence but males can also be victims.	Estimates of prevalence are 6.5% (Kessler et al., 2010); 5.3% (Calthorpe & Pantell, 2021); 17.7% (Giano, Wheeler, & Hubach, 2020); 22-34% life time prevalence (Kieselbach et al., 2021); 4% (Meltzer et al., 2009).
Parental criminal behaviours	Adversities that have been investigated under here range from incarceration of one or both parents to all forms of parental legal troubles.	Estimates of prevalence are 2.9% (Kessler et al., 2010); 6% (Dunn et al., 2018); 7.2% (Calthorpe & Pantell, 2021); 8.2% (Giano, Wheeler, & Hubach, 2020)
Parental alcohol/drug problem	This involves uncontrollable and potential harmful use of alcohol, and illicit drug substance by one or both parents	4% (Kessler et al., 2010); 7.6% (Calthorpe & Pantell, 2021); 26.8% (Giano, Wheeler, & Hubach, 2020)
Neighbourhood stress	This involves all forms of stress associated with living in a particular neighbourhood. The most common form	Prevalence rates vary across countries; 14% (Dunn et al., 2018); 10.8%

	of neighbourhood stress that have been investigated in childhood adversity studies is neighbourhood violence. Other forms include dirt, mugging, noise in the neighbourhood.	(Houtepen et al., 2018); 52% (Vostanis et al., 2001) ; 48% (El-Khodary & Samara, 2020).
Poverty	This is a state of financial deprivation marked by low family income and increased difficulty in meeting the basic human needs such as food, shelter, heat etc. Poverty in childhood adversity studies can sometimes be examined in the general purview of socioeconomic status which include household income, parental education and household employment status.	An estimated 3.4% of the global population are believed to live in poverty (Kessler et al., 2010). Other local estimates are 37% cumulative prevalence (Dunn et al., 2018); 18.8% (Calthorpe & Pantell, 2021); 27-33% (Main & Bradshaw, 2015); 3-27% (Vizard et al., 2019)
Other adversity types	Various forms of childhood adversities not listed above have also been examined. Some of these include bullying by peers/siblings/teachers, child physical illness or serious accident, low child-parent attachment etc.	Estimates of prevalence range from 3.1-9.9 % in physical illness (Kessler et al., 2010; Houtepen et al., 2018) to 25.3-33.4% in bullying (Kshirsagar, Agarwal, & Bavdekar, 2007; Houtepen et al., 2018)
* Definitions adopted from 2008 report of Centres for disease control and prevention.		

In addition to examining the prevalence rates of childhood adversity, more recent studies have attempted to provide insight into possible geographical or sociodemographic factors that may lead to varied prevalence of childhood adversity in the population. For example, rural residency, low income/educational attainment, racial and sexual minority groups have all been associated with higher risk of reporting multiple adverse childhood experiences (Calthorpe & Pantell, 2021; Lewer et al., 2019; Giano, Wheeler, & Hubach, 2020; McLaughlin, Hatzenbuehler et al., 2012). To be specific, a large survey study in the United States that measured multiple childhood adversity by geographical location found that rural residency was associated with 1.29 greater odds of experiencing more than 4 childhood adversity types compared to urban or suburban residency (Calthorpe & Pantell, 2021). This finding was consistent with a comparative study in England which showed that population density (e.g. North East, England) and household income are major drivers of adverse childhood experiences index (Lewer et al., 2019). A similar large scale survey study found widespread childhood adversity prevalence in the general population (57%) with, multiracial

group, sexual minority group, low income or low educational attainment all linked to greater risk of reporting childhood adversity (Giano, Wheeler, & Hubach, 2020). Taken together, studies suggest that aside general population prevalence, some geographical and demographic factors may combine to increase vulnerability to childhood adversity.

1.3 Aims of this thesis

The primary underlying aim of this PhD thesis is to employ longitudinal models to understand the effects of adversity on different developmental outcomes. Most previous studies that have examined the effects of adversity on outcomes have been cross-sectional. Therefore, to extend the knowledge gained from these past cross-sectional studies, I utilised complex statistical approaches and longitudinal design methods to understand how the long-term effects of childhood adversity manifest on mental health, cognition and brain development. In this thesis, I focused on the effects of childhood adversity on mental health, cognition and brain development because they are very important developmental measures that can shape the life outcomes of individuals in their adulthood (Lövdén et al., 2020; Agnafors et al., 2021; Hair et al., 2015). These three variables are also some of the most investigated developmental outcomes by researchers interested in understanding the effects of childhood adversity, and thus, most of the past studies have been mainly cross-sectional. Therefore, a longitudinal investigation into how childhood adversity affects these outcomes – mental health, cognitive and brain development, becomes imperative. In doing this, I leveraged multiple adversity and outcome variables which not only provided informed understanding of the long-term effects of adversity on one developmental outcome (e.g., cognitive functioning) but also probed further for possible nuances in each outcome (e.g., variations in cognitive processes of working memory, language or decision making). Additionally, in this thesis, I tested different

contemporary theoretical models of childhood adversity, including the dimensional models of adversity and the sensitive periods of adversity. Testing these theories not only enabled clearer articulation of the findings derived from the longitudinal examination of the effects of adversity on outcomes, but also enhanced the conclusion I reached.

In the sections below, I highlight previous studies of childhood adversity and its effects on developmental outcomes. I also discuss the dimensional models of adversity, particularly threat vs deprivation hypothesis. I finally end chapter one by extensively juxtaposing the limitations of the past adversity studies in relation to the purpose of this PhD thesis.

1.4 Effects of childhood adversity on developmental outcomes

In the past decade, robust empirical studies have investigated the effects of childhood adversity on different developmental outcomes. The dominant perspective from these collections of studies points to poorer developmental outcomes attributed to early adverse rearing. This has been the basis of deficit model of developmental psychopathology which argues that childhood adversity is associated with impairments or reduced performance in all developmental outcomes (Gilbert et al., 2009). The neurobiological mechanism behind the deficit model has been linked to the abnormal functioning in the hypothalamic-pituitary-adrenal (HPA) pathway (McEwen, 2012; Gunnar & Quevedo, 2007). This is based on the assumption that stress leads to the release of glucocorticoids needed to maintain balance and proper psychophysiological functioning. These glucocorticoids have high concentration in the HPA axis. Based on the principle of allostatic load (McEwen, 2000), chronic stress causes excess release of glucocorticoids leading to an abnormal HPA functioning. This abnormal HPA functioning potentially leads to structural changes in the brain and consequently, disruption in developmental processes (McEwen, 1998; McEwen, 2012). Alternatively, a few other studies

have shown a more dynamic interaction between childhood adversity and developmental outcomes. For example, studies that have simultaneously measured different outcomes have shown that while childhood adversity is associated with poorer developmental outcomes, some individuals do not develop adversely. This variation may sometimes depend on the sample population or the outcomes measured, suggesting possible heterogenous effects of adversity on developmental processes. This assumption has formed the basis of adaptation (hidden talent) or resilience model of childhood adversity (Ellis et al., 2020; Ellis et al., 2017; Frankenhuis, Young, & Ellis, 2020; Frankenhuis & Nettle, 2019).

While many studies have associated childhood adversity with many behavioural problems (Kennedy et al., 2016; Hoover & Kaufman, 2018), the purpose of this section is to solely highlight the developmental outcomes I investigated in my PhD programme, namely, mental health, cognitive abilities and brain development. Thus, in this section, I first highlight studies that showed impairments in these outcomes, on which the foundation of deficit model was assumed. Then, I throw light on other studies that have shown intact, null or complex interaction of developmental outcomes, supporting the assumptions of adaption and resilience model. I end by highlighting the contributions of sensitive periods (timing of exposure) in explaining the effects childhood adversity on developmental processes.

1.4.1 Effects of childhood adversity on mental health

Childhood adversity has been linked to up 30% of all global mental health problems at adulthood (Kessler et al., 2010; Green et al., 2010). For specifics, physical abuse and sexual abuse are believed to respectively account for 5% and 13% of mental illness, after putting into context other adversity types associated with family functioning (Fergusson, Boden, & Horwood, 2008). The common types of mental health problems frequently associated with

childhood adversity include internalizing symptoms (e.g. depression, anxiety; Liu, 2017; Marackova et al., 2016) or externalizing symptoms (e.g. aggression, conduct problems; Thompson, O'Connor, & Farrell, 2021), and suicidal ideation (Björkenstam, Kosidou, & Björkenstam, 2017). The risk of developing these psychopathology has been linked, to a greater extent, to subjective reports of an individual histories of adverse childhood experiences compared to objective-documented evidence of such histories (Danese & Widom, 2020).

Previous works have shown that childhood adversity has been associated with a greater mental health burden in adolescence and early adulthood (Gilbert et al., 2009) as well as earlier onset of mental illness (McLaughlin et al., 2012) which usually persist through adulthood (Green et al., 2010). Numerous cross-sectional studies report that maltreated or stress-exposed children have higher depressive and anxiety symptoms (Dunn et al., 2017; Kim et al., 2013), behavioural problems (Yates et al., 2003), post-traumatic experiences (Tabb et al., 2022) and suicidal ideation (Afifi et al., 2008). These findings have been replicated in a longitudinal study which found that early-life adversity is associated with higher depressive symptoms, suicidality and comorbid anxiety (Klein et al., 2009). While mental health outcomes are therefore clearly linked to early-life adversity, the time frame of their effects and causal interactions are still unclear.

Few longitudinal studies that examined the effects of childhood adversity have provided insight into the prolonged effects of adversity on depression. In one of such studies (Angst et al., 2010), chronic depression was linked to greater childhood adversity while other studies have linked greater childhood adversity to severity of depressive trajectory (Rhebergen et al., 2011) and longer remission course from depression (Fuller-Thomson, Battiston, Gadalla, & Brennenstuhl, 2014). Compelling evidence also points to the contributions of childhood adversity to increased risk of developing post-traumatic stress disorder. Numerous studies, for instance, have shown that post-traumatic stress disorder is linked to physical abuse (Lansford

et al., 2002), sexual abuse (Banyard, Williams, & Siegel, 2001), and neglect (Widom, 1999) in adolescence and adulthood. Risk of suicidal attempts in young people has also been associated with accumulation of multiple adverse childhood experiences (Björkenstam, Kosidou, & Björkenstam, 2017), although links to abuse (Turner et al., 2018), family dysfunction (Clark, Li, & Cropsey, 2016) and domestic violence (Afifi et al., 2008; McLaughlin, O'Carroll, & O'Connor, 2012) have separately been established.

Although the studies highlighted here and many other uncited studies reflect the negative impact of childhood adversity on mental health, a few other studies anchored on *resilience* model equally suggest that not all those exposed to childhood adversity develop psychopathology as some remain mentally healthy. Through the acquisition of protective factors along developmental course, (Fergus & Zimmerman, 2005; Zolkoski & Bullock, 2012; Ho et al., 2019) such as supportive relationships and stable family environment (Fritz et al., 2018; Afifi & MacMillan, 2011), some individuals who experienced childhood adversity may develop effective strategies required to overcome the risk of mental illness associated with their early adverse rearing. Empirical studies have provided support for this assumption. In one such study, parental and family support mediated the effects of community violence on externalizing symptoms, such that those who received adequate family support showed no externalizing behaviours despite witnessing community violence (Hardaway et al., 2016). In another study, adolescents with adequate friends and family support networks showed no depressive symptoms despite an accumulated histories of adverse childhood experiences (Van Harmelen et al., 2016). These taken together suggest that despite the documented evidence of negative impact of childhood adversity on mental health, some individuals manage to maintain good mental health across development through acquisition of resilience factors.

1.4.2 Effects of childhood adversity on cognition

Individuals exposed to childhood adversity are more likely to have poorer cognitive abilities in wide range of domains including attention, decision making, planning, language, memory, emotional processing and executive functions (Guinosso, Johnson, & Riley, 2015; Pechtel & Pizzagalli, 2010). The risk of cognitive impairment has been reported to be dose dependent on the cumulative number of childhood adversity reported by an individual (Brown et al., 2021; Sameroff et al., 1987). Poverty has emerged as one of the most potent predictor of poorer cognitive outcomes across lifespan in high income countries (Nisbett et al., 2012), comparable to cognitive deficits observed among the neglected or institutionalised children (Hildyard & Wolfe, 2002). A body of studies have linked low socioeconomic status to poorer test scores at childhood (Clearfield & Niman, 2012; Dickerson & Popli, 2015; Feinstein, 2003), persisting overtime (Cybele Raver et al., 2013) as well as greater cognitive declines at adulthood (Sheffield & Peek, 2009; Chen & Cao, 2019).

One review study linked poverty to childhood development and wellbeing, particularly in cognitive abilities (Chaudry & Wimer, 2016). Related to this, previous studies have established evidence of causal association between income poverty and cognitive outcomes (Duncan et al., 2011), with improved family income translating to improved child academic and educational outcomes. Given this causal link between poverty and poorer cognitive outcomes, material hardship and family stress have been assumed to be some of the common mechanisms through which poverty exerts its adverse effects on developmental outcomes (Chaudry & Wimer, 2016). For example, scarcity of resources, including lack of educational resources can hamper the basic needs of a child which are essential to the cognitive development of the child. This assumption was supported in previous studies that linked poverty to worse developmental outcomes (Gershoff et al., 2007; Yoo et al., 2009; Zilanawala

& Pilkauskas, 2012). An alternative mechanism through which poverty compromises child's cognitive functioning is family stress (Chaudry & Wimer, 2016). Poverty may heighten parental stress levels and strains relations with family members leading to chaotic homes. This assumption has also been supported by empirical research showing interrelations between family poverty, parental stress and compromised parental relations (McLoyd, 1990).

In addition, chronic poverty may also exert greater adverse effects on cognitive development than short-term low family income. This is because chronic poverty makes individuals less likely to adequately buffer against the effects of material hardship and psychological stress (Chaudry & Wimer, 2016), suggesting that enduring and extreme poverty level may overtime continue to worsen life outcomes (Najman et al., 2018) including cognitive development. For example, one study showed that individuals who are chronically poor were less likely to graduate from high school than their peers who are less persistently poorer (Magnuson, 2014), suggesting the deleterious impact of chronicity of family poverty on educational and cognitive outcomes of a child.

Other adverse childhood experiences such as abuse, family dysfunction, interparental and community violence, parental psychopathology, incarceration or substance use have been implicated in cognitive deficit in various outcomes (Brown et al., 2021; Majer et al., 2010; Pollak et al., 2005). For example, one cross-sectional study showed that individuals who reported four or more adverse childhood experiences had 2.98 higher odds of experiencing subjective decline in adulthood compared to those who reported no adverse childhood experiences (Brown et al., 2021). Another cross-sectional study showed that specific subscales of childhood trauma questionnaire were associated with alterations in cognitive functioning with emotional abuse correlating with poorer spatial working memory performance while physical neglect was associated with spatial working memory and pattern recognition memory (Majer et al., 2010).

While the cognitive deficit associated with childhood adversity is not in doubt, it must be noted that a few studies have observed more complex interactions between environmental experiences and cognitive processes that may have potential nuances on the understanding and interpretations of effects of adversity on cognitive abilities. These cognitive nuances associated with childhood adversity assumed to be *adaptive,* vary based on the population samples (Nweze et al., 2020), measurements and outcomes examined (Fields et al., 2021; Ellwood-Lowe, Whitfield-Gabrieli, & Bunge, 2021) and mediation of protective factors (McFadden & Tamis-Lemonda, 2012; Krishnakumar & Black, 2002).

Previous cross-sectional works have observed certain improved outcomes linked to adaptation among individuals exposed to adversity (Nweze et al., 2020; Fields et al., 2021; Ellis et al., 2020; Frankenhuis et al., 2020; Ellwood-lowe et al., 2021). These variations in findings may be driven partly, by the type of adversity measured and the way it was measured, timing of exposure, or even the cultural context of the sampled population. For instance, studies have shown that individuals exposed to different types of unpredictable childhood stress (e.g., caregiving instability or neighbourhood violence) may have better performance in some cognitive outcomes (e.g., set shifting; working memory) by developing relevant adaptive features needed for environmental survival. At the same time, after exposure to adversity, these same individuals also perform poorer in other outcomes that are not essential to basic survival in such unpredictable environments (e.g., inhibition, Fields et al., 2021; Nweze et al., 2020; Young et al., 2018; Mittal et al., 2015). For example, one study from Nigeria showed that children who are deprived parentally had better performance in working memory (but not inhibition and cognitive flexibility) which is assumed to be an essential gradient of greater academic success and social mobility (Nweze et al., 2020). Other studies have found more complex interactions. One study found that caregiving instability was associated with poorer performance in inhibition and attention but higher performance in cognitive flexibility (Fields

et al., 2021). These findings from the *adaptive* model generally suggest that the effects of childhood adversity on cognitive functioning are not uniform, as some cognitive domains remain intact despite the deficits observed in other cognitive domains following period of childhood adversity.

Important mediators such as nurturing home environment and parenting behaviours have been noted to attenuate the effects of adverse childhood experiences on cognitive functioning (McFadden & Tamis-Lemonda, 2012; Krishnakumar & Black, 2002). Together, these studies support the consensus that childhood adversity generally impairs cognitive processes while acknowledging potential variations in cognitive competence that may emerge overtime.

1.4.3 Effects of childhood adversity on brain development

The last outcome that I will highlight in this chapter is brain development and how its developmental process may be derailed by impact of childhood adversity. Typical maturation of the human brain is partly dependent on the right environmental experiences (Bick & Nelson, 2015), of which early childhood experiences such as responsive caregiving is essential (Tottenham, 2014). Studies have shown that violations of these expected childhood experiences, including neglect, institutionalisation, abuse etc., are associated with alterations in the integrity of the brain structures. Across different studies, global volumetric attenuations in different cortical regions linked to abuse (De Brito et al., 2012; Hanson et al., 2010; De Bellis et al., 2002) or child institutionalization (McLaughlin et al., 2014; Hanson et al., 2013; Sheridan et al., 2012; Mehta et al., 2009) have been reported. Mixed findings have been reported in studies examining the link between childhood adversity and changes in the brain subcortical, with some studies reporting changes in amygdala and hippocampus (Luby,

Tillman, & Barch, 2019; Hanson et al., 2015; Edmiston et al., 2011), but another study suggesting that these changes may not be apparent until adulthood (Woon & Hedges, 2008) given documented reports of null results at childhood (De Bellis et al., 1999).

On the other hand, frontoparietal structures have shown greater sensitivity to adverse childhood experiences (McLaughlin, Weissman, & Bitrán, 2019) given a body of studies that have found reductions in these regional cortical structures after period of neglect (Herzberg et al., 2018; Hodel et al., 2015; McLaughlin et al., 2014) or abuse (Edmiston et al., 2011; Hanson et al., 2010). For example, child deprivation e.g., institutionalization or poverty (Sheridan & McLaughlin, 2014) as well as mild and uncontrollable stress (Arnsten, 2009; Lupien et al., 2009) have been linked to alterations in the frontoparietal regions, including facets of the prefrontal regions. The effects of childhood adversity on the frontoparietal regions are present at adolescence (Arnsten, 2009; Lupien et al., 2009), with child abuse (Gold et al., 2016; Kelly et al., 2013; Thomaes et al., 2010) or child institutionalization (Mackes et al., 2020; Hodel et al., 2015; McLaughlin et al., 2014) being related to structural brain alterations in various prefrontal and parietal regions. Other studies that examined the association between cortical structures and mild childhood stressors found alterations in the anterior cingulate cortex (Baker et al., 2012; Cohen et al., 2006). Given that these cortical structures, especially prefrontal cortex subregions, continue to develop during adolescence (Tamnes et al., 2017), it may make these regions more susceptible to brain attenuations induced by stress compared with other brain areas.

Although the general assumption is that childhood adversity (of any type) is bad for the developing brain, stress acceleration hypothesis (Callaghan & Tottenham, 2015) believed to have short term adaptive benefits has equally gained some attention. This hypothesis is based on the assumption that early exposure to adversity leads to premature development of the

amygdala-frontal circuitry that plays an important role in the regulation of emotional behaviours, leading to the acquisition of adult-like fear learning. This premature development, while meeting the short-term needs of emotional regulation in presence of adversity (e.g. absence of a responsive caregiver) may lead to decreased plasticity in this circuitry and emotional dysregulation at adulthood (Callaghan & Tottenham, 2015). Empirical studies have provided support for this model, with one study showing that early maternal deprivation was associated with early emergence of amygdala-prefrontal connectivity which corresponded to less anxiety in the deprived children (Gee et al., 2013).

It is important to note that only few studies examining the effects of childhood adversity on brain development have simultaneously examined the multiple morphometric measures of the brain i.e. volumetric, surface area and cortical thickness of the brain. I know of few recent studies that examined all three morphometric measures in whole brain analysis (Mackes et al., 2020) or regions of interest analysis (Rinne-Albers et al., 2020), and another study that examined at least, two brain morphometrics in the cortical regions analysis (e.g. Gehred et al., 2021) while several other studies have measured either one of brain volume, surface area or cortical thickness. Therefore, this thesis will attempt to enrich the literature by examining all three morphometric measures of brain assessments (i.e., volume, surface area and cortical thickness). A simultaneous investigation of all three outcomes will enable me to disentangle the effects of stress on relatively established brain volumes, compared to the more fine-grained surface area and cortical thickness. In other words, I ask if adversity has equal or disproportionate effects on brain volume, surface area and cortical thickness.

1.4.4 Role of timing of childhood adversity exposure on developmental outcomes

There has been a renewed interest on the importance of timing of adversity exposure on developmental processes. Known as sensitive period of development, it seeks to examine the specific developmental time course that exposure to adverse environmental experiences will likely have the greatest costs to developmental outcomes. Early studies that examined this question relied mostly on institutionalised children who were adopted into more enriching homes as early as 12-24 months, with evidence pointing to the importance of an early secure attachment figure on children's emotional and cognitive processes (Smyke et al., 2010). However, recent studies have now attempted to statistically draw a more robust inference by comparing sensitive periods of development with other competing theoretical perspectives (Gabard-Durnam & McLaughlin, 2019). Some of the theoretical models that have been compared with sensitive period are the *accumulation* hypothesis in which the effects of adversity on outcomes increase as the number of adversity increases; and recency hypothesis in which recent occurrences have greater effects on outcomes than earlier occurrences. Studies across numerous outcomes have shown that adversity exposure at very early sensitive period (before age 3) accounts, to a greater extent, the effects of adversity observed on mental health problems (Dunn et al., 2017), emotional dysregulation (Dunn et al., 2018) or DNA Methylation (Dunn et al., 2018) compared to accumulation and recency hypotheses, suggesting the importance of adequate environmental experiences at early stage of development. Together, studies of sensitive periods of childhood adversity suggest that the observed variations in developmental outcomes may partly be explained by the timing of the particular adversity exposure measured.

1.5 Dimensional models of adversity

In Table 1.1, I highlighted the individual types of childhood adversity that have been robustly investigated and reported in the literature. The interesting phenomenon is that most of these adversity types tend to co-occur in individuals presenting multiple exposures, i.e. the most unfortunate or underprivileged individuals can sometimes report exposure to multiple adversity types. For example, a world-wide study observed that 2.9% of the global population reported being exposed to at least, 5 types of adversity (Kessler et al., 2010). This proportion of percentage exposure to adversity further rises to 4.1% and 8.5% if individuals reporting a minimum of 4 and 3 adversity types respectively, are taken into account. A recent large scale cross-sectional study in the United States found similar results, with 5.3% of the population reporting being exposed to, at least, 4 types of adversity (Calthorpe & Pantell, 2021).

However, most empirical studies of childhood adversity often examine only one type of adversity (specificity approach) which has limitation because of the co-occurring pattern of adversity. An alternative cumulative risk approach on the other hand involves tallying all adversity reported by an individual, yet this approach is problematic because each adversity type has distinct effects on outcomes. This has led some researchers into articulating an alternative dimensional approach (McLaughlin et al., 2021) that takes into account, the limitations of specificity and cumulative risk approaches. Dimensional model generally assumes that adverse childhood experiences can be classified into central and distinct dimensions (e.g., threat vs deprivation or environmental harshness vs unpredictability) or dimensions on a continuum, depending on the types of adversity examined. This approach could enable a more robust understanding of the specific mechanism through which the effects of adversity on developmental processes manifest. Although papers on theoretical opinions dominated the literature at the early stage of conceptualization of dimensional model, recent works have attempted to test this dimensional model of adversity with analysis methods such as clustering analysis (latent class analysis), or networks analysis. While the dimension of

environmental *harshness vs unpredictability* is popular in the evolutional perspective (Ellis et al., 2009), in this section, I discuss *threat vs deprivation* which is the most robust theoretical dimension of childhood adversity in the developmental psychology. I end the section by throwing light on a few studies that have empirically tested this dimensional model.

Threat vs Deprivation: This involves two dimensions that distinguish the influences of adversity on the emotional, cognitive and social processes. First conceptualized by (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014; McLaughlin & Sheridan, 2016, see also Humphreys & Zeanah, 2014), the model distinguishes experiences of *deprivations* involving absence of environmental inputs from experiences of *threat* involving presence of unexpected environmental inputs. Proponents argued that different adversity types (e.g. physical abuse, sexual abuse, domestic violence, institutionalization, neglect) have distinct underlying effects on neurodevelopmental processes, such that dimension of *threat* reflects experiences that present harm/threat of harm of varying degrees (e.g. physical abuse, sexual abuse, domestic violence) and *deprivation* (e.g. neglect, institutionalisation, poverty) reflects absence of expected social and cognitive stimulations or other complex environmental inputs. This is because childhood development marked by low psychosocial or cognitive stimulations will yield neurobehavioral structures designed to deal with the absence of age-appropriate developmental experiences that would likely differ from structures shaped by presence of chronic threatening inputs. But rather than suggest that threat and deprivation are the only inherent dimensions that can be captured across multiple adversity types (Sheridan & McLaughlin, 2014), proponents of this model are more concerned with identifying the mechanism by which dimensions of adversity affect neurodevelopmental processes as well as the mechanism that drives the observed effects (Sheridan & McLaughlin, 2014; McLaughlin & Sheridan, 2016).

The dimensional model was recently criticised for being fuzzy and having the underlying assumption of specificity approach (Smith & Pollak, 2020) given that the early conceptualisation of *threat vs deprivation* dimensions involved studies that mostly focused on the effects of individual types of adversity that lacked clear distinction. However, an important clarification was made that the purpose of dimensional approach, as an alternative to specificity and cumulative risk approaches, is to measure various childhood environmental experiences along a continuum of severity/types and identify those that share common features as a dimension, so that any study examining a single type of adversity, without consideration for other types of adversity would not be considered a dimensional model (McLaughlin et al., 2021).

Empirical works have begun to measure the underlying dimensions of childhood adversity across multiple range of adverse childhood experiences. For example, using latent class analysis, a form of cluster analysis, Lacey et al (2020a) identified 5 classes of adversity across numerous adversity types consisting of participants with low adverse childhood experiences (ACEs; 56%), parental separation and maternal mental illness (18%), parental mental illness, separation and conviction (15%), abuse and mothers mental illness (6%) and poly ACEs (6%). A follow-up study (Lacey et al., 2020b) found similar clusters including low ACEs (81.1%), maternal mental illness (10.3 %), maternal mental illness and physical abuse (6.3 %) and interparental violence, parental mental illness and emotional abuse (2.4 %). In a separate population cohort study, (Ho et al., 2020) found three clusters of adverse childhood experiences made up of low ACEs (76.0%), household violence (20.6%), and household dysfunction (3.4%). Using information on child maltreatment, another study found three clusters, namely, low risk maltreatment children, children at risk of neglect only and finally those at high risk of maltreatment and abuse (Denholm et al., 2013).

1.6 Limitations of the past studies versus purpose of the current projects

In the previous sections, I highlighted numerous studies that examined the effects of childhood adversity on developmental outcomes. However, my observation is that some gaps that can unravel important insights into the mechanism that drives the effects of childhood adversity, still exist. Prime in this gap is the cross-sectional nature of most previous studies on childhood adversity. Childhood adversity is known to occur across period of early lifespan development, and could last all through childhood development (especially if one is not lifted from adversity by some form of intervention). The effects of childhood adversity may also manifest shortly after exposure or later on, potentially lasting for a long time. Given the pattern of childhood exposure which can occur at any time across childhood development and the subsequent implication of this exposure on outcomes, it therefore becomes imperative that field move beyond cross-sectional studies of adversity towards longitudinal perspectives which are better designed to answer questions on the short and long-term effects of adversity occurring at different timepoints. I note here the merits of cross-sectional studies of adversity – in terms of capturing vital exploratory information such as prevalence of adversity at a particular time or investigating the effects of adversity on outcomes at a particular time. I also recognise that several studies have gone beyond cross-sectional model by attempting to collect longitudinal data on children's adverse experiences, so that more accurate information on the later effects of childhood adversity on outcomes can be established. Yet, very few of the longitudinal studies have attempted to longitudinally model adversity across multiple timepoints to understand its variability and change overtime on developmental outcomes. Such longitudinal modelling is imperative if researchers are to reach robust causal conclusion on the effects of childhood adversity on outcomes. Another limitation of cross-sectional approach is that it relies on retrospective reports of childhood adversity. Given previous studies which have noted

limited validity (Tofthagen, 2012) or weaker effects (Gehred et al., 2021) in retrospective reports, longitudinal studies usually designed prospectively, offer an important remedy to this drawback of retrospective studies. In addition, the longitudinal modelling helps to critically tease apart the importance of timing of childhood adversity on outcomes, in a way that cross-sectional studies cannot. Therefore, the prime purpose of my PhD programme is to use different longitudinal modelling to understand the intricate effects of childhood adversity on mental health, cognitive abilities and brain cortical structures across childhood and adolescence.

Another limitation of childhood adversity studies is the use of participants who have been exposed to extreme types of adverse childhood experiences. Earliest studies on childhood adversity primarily focused on individuals who have been abused, physically or sexually, as well as extremely maltreated individuals. Later studies in this category included a unique set of samples who were institutionalised, mainly in their early life. Given ethical constraints in designing experimental studies of childhood adversity, the use of institutionalised children provided an opportunity to study the effects of severe neglect and deprivation on outcomes, in a pseudo experimental condition. In addition to this unique sample of institutionalised children, these other severe types of adversity (i.e., abuse, maltreatment) provided an early opportunity to understand the negative impact of adversity on outcomes. However, most of these samples also present psychopathological symptoms at the time of assessment. Thus, it is difficult to differentiate the effects of developmental outcomes attributable to either adversity or psychopathology. In my PhD projects, in addition to examining some of these extreme types of adversity, I also investigate the effects of the moderate adversity types prevalent in the general population. Studies of childhood adversity drawn from population samples have grown in recent years and offer valuable insight into the dynamic relationship between adverse family and environmental childhood experiences on developmental outcomes. Another benefit of these population samples, in the context of my projects, is that it allows me to simultaneously

investigate multiple types of adverse childhood experiences which will enable me test contemporary theoretical models of childhood adversity - for example, the dimensional model highlighted above – to see if the different adversity types can be classified by subtypes based on clustering of responses. Through the established adversity subgroups, I can further attempt to map a pathway to cognitive functioning, to see if the cognitive processes of one subgroup differ from another.

Closely related to the limitation highlighted above is that some of the past studies (especially those examining the severe types of adversity) relied on small sample sizes and measured few outcomes. Thus, in addition to maximizing the large sample benefits of population cohorts, I also simultaneously assess multiple developmental outcomes and through longitudinal mediation models, attempt to establish any existing interrelation between adversity and two or more developmental outcomes. Understanding the neuro(behavioural) pathways through which the effects of adversity unfolds across different timepoints on different developmental outcomes are essentially crucial towards appreciating the effects of adversity on such outcomes.

1.7 Summary of research questions and structure of this thesis

Across my programme, I conducted three empirical research projects, which constituted chapters 2-4 of this thesis. Each chapter examined pertinent research questions of how adversity affects developmental outcomes. In chapter 2, I used focused longitudinal mediation model to examine how the effects of early-life adversity on mental health unfold over 5 assessment timepoints, spanning an 11 year time period. More importantly, I examined if participants' mental health across the assessment timepoints mediates (cumulatively or separately), the association between early-life adversity and cognitive functioning across

childhood development. In chapter 3, I empirically tested the dimensional model of childhood adversity using latent class analysis which can cluster participants based on their response patterns. Crucially, if latent class analysis showed evidence of sub-groups in the data, further analysis was conducted to establish a pathway to cognitive functioning among the subgroups using latent class regression analysis. I finally tested the effects of individual types of childhood adversity on multiple cognitive outcomes, with the primary aim of examining the sensitive periods of adversity (and the competing accumulation model) to determine the developmental time when exposure to childhood adversity will have the greatest impact on multiple cognitive outcomes. In chapter 4, I present the last empirical research of my thesis that used brain and cognitive variables, as well as measures of adverse life events. This project chapter used latent change score model to test the long-term effects of adverse life events on all three brain morphometrics (volume, surface area and cortical thickness). The long-term effects of adverse life events on cognitive processes of working memory and decision making were also examined using the same change score model. I ended the chapter by presenting results of complete longitudinal mediation model that examined two potential neurocognitive pathways through which the effects of adverse life events manifests on cortical brain structures and cognitive functioning. Finally, in chapter 5, I articulate the general conclusion of the results of all the empirical chapters and highlight the strength and limitations of these empirical projects as well as research areas for future works.

2 Chapter 2

It doesn't end there: Mental health difficulties across ages 3-14 mediate the long-term association between early-life adversity and cognitive abilities

2.1 Introduction

Although early-life adversity can result in adaptive developmental changes (Nweze et al., 2020; Ellis et al., 2020; Frankenhuis et al., 2020; Frankenhuis and Nettle, 2020; Ellwood-Lowe et al., 2020; Howard et al., 2019), the understanding that early-life adversity has adverse consequences on a wide range of developmental outcomes has been a core tenet of child psychiatry for decades (Chandan et al., 2019; Humphreys et al., 2015; Golm et al., 2020). While many researchers and practitioners appreciate that the effects of early-life adversity are most likely heterogenous and dynamic over the long-term (Ioannidis et al., 2020), there has however been little empirical work that incorporates the necessary breadth of outcomes, time frames and appropriate statistical and theoretical frameworks necessary to probe such complex effects. To truly understand and effectively intervene in the trajectories of early-life adversity effects, such heterogeneity needs to be effectively mapped. The current study addresses these shortcomings using large-scale panel data, and theoretically informed longitudinal mediation analyses, elucidating the nuanced and age-sensitive associations of early-life adversity on

mental health and cognitive functioning. Here, I defined early-life adversity as experiences before age 3 that deviate from the expected childhood environment, but which can also occur before the age of 18 (McLaughlin, 2016).

Previous works from prospective longitudinal studies have shown that exposure to early-life adversity is associated with poorer performance in a wide range of cognitive functions (Golm et al., 2020; Hawkins et al., 2021; Colvert et al., 2008; Bos et al., 2009; Castle et al., 2010). Similarly, early-life adversity has been associated with a greater mental health burden in adolescence and early adulthood (Gilbert et al., 2009) as well as earlier onset of mental illness (McLaughlin et al., 2012). Numerous cross-sectional studies report that maltreated or stress-exposed children have higher depressive and anxiety symptoms (Harpur, Polek & van Harmelen, 2015; Humphreys et al., 2020), behavioral problems (Yates et al., 2003), post-traumatic experiences (Brewin, Andrews & Valentine, 2000) and suicidal ideation (Afifi et al., 2008). While these outcomes are therefore clearly linked to early-life adversity, the time frame of their effects are still unclear. It is further unknown specifically when and how early-life adversity affects these outcomes of interest, limiting the ability to understand the underlying trajectories that lead to poorer outcomes.

It is likely that the associations between early-life adversity, cognitive functioning and mental health arise, at least in part, due to developmental interactions. For example, one longitudinal study that used latent growth curve model and growth mixture model found bi-directional interactions between mental health and cognitive abilities across childhood development (Fuhrmann et al., 2021). Relatedly, other meta-analyses studies also support unidirectional association between mental health and cognition across childhood development (Irie et al., 2019; Rock et al., 2013), suggesting potential direct relations between the two domains. However, the exact dynamics of this relationship is yet unknown; a lack of studies that have modelled multiple assessment waves of cognitive and mental health outcomes

following early-life adversity has precluded a more in-depth understanding of these dynamics. I aim to understand these interrelations with a targeted longitudinal modelling strategy focused on mediation analysis. Doing so, I can demonstrate to what extent childhood mental health mediates the association between early-life adversity and cognitive functioning.

To perform such analyses and investigate the longitudinal associations of early-life adversity on mental health and cognitive functioning, the current study uses five assessment waves of the Millennium Cohort Study (Connelly & Platt, 2014), a prospective cohort study of 18, 818 children born in United Kingdom between 2000 to 2002. Using a multiple mediation model, this work addresses three core questions. Firstly, whether early-life adversity has solely proximal (at the time of exposure), or also distal effects on mental health over longer time frames. Secondly, whether poorer childhood mental health is associated with decreased cognitive performance in early adolescence and if so, whether these effects are cumulative, above and beyond contemporaneous mental health. Lastly, whether early-life adversity affects later cognitive functioning through childhood mental health.

Leveraging the unique longitudinal data of the Millennium Cohort Study (Connelly & Platt, 2014), this study therefore disentangles the short-term effects of early-life adversity and mental health from the potential long-term, cumulative consequences of early-life adversity and poor mental health on cognition in childhood through a multivariate model comparison framework. By addressing these fundamental questions with tailored longitudinal modelling methodology, multiple cognitive outcomes and a range of time frames, I am able to sketch developmental patterns and trajectories of impairment and adaptation following early-life adversity across childhood and adolescence.

2.2 Methods

2.2.1 Participants

As part of this study, I analyzed data from the Millennium Cohort Study (Connelly & Platt, 2014), an ongoing longitudinal cohort study of children born between September 1, 2000 and January 11, 2002 in the United Kingdom. Using government records, stratified random sampling was used to recruit children born in England, Wales, Scotland and Northern Ireland to ensure adequate representation of the four countries and the diverse ethnicities of United Kingdom (Connelly & Platt, 2014). For the present study I used five waves of data collected at 3, 5, 7, 11 and 14 years from participants who either provided data at age 11 (N = 13,287, Male = 6,712, Female = 6,575, Mean age = 10.68, SD = 0.48) and/or at age 14 (N = 11,726, Male = 5,884, Female = 5,842; Mean age = 13.77, SD = 0.45).

2.2.2 Measures

Adversity: Parents of MCS cohort members completed a comprehensive survey of adverse childhood experiences (ACEs) when their child was three years old. This was the age in which the most comprehensive set of ACEs were measured in the MCS. In this study, I operationalized adversity in line with the Adverse Childhood Experiences framework (Dunn et al., 2018; 2019; Kessler et al., 2010; McLaughlin, 2006), including in the analyses the following binary measures (yes/no response options): number of carers in the household (one or two carers), parental separation (main parent lived apart from child since 9 months of age), homelessness, parental violence (evidence of use of force in the relationship by both partners),

longstanding illness in the family (child illness, parental illness). I further included additional adverse childhood experiences measured at this wave: a 4-item parental conflict questionnaire, a 6-item parental mental health questionnaire (Kessler et al., 2002) and a 4-item harsh discipline questionnaire. Scores of these additional questionnaires were summed separately. Lastly, I also included a measure of parental poverty via family income split into 6 levels (range: £0-3300pa to £55000+pa). All the adversity variables above were coded such that higher values represent greater adverse experiences; they were further rescaled to a standard normal distribution. To reduce the dimensionality of these adversity variables into a single summary metric, they were subsequently entered into a Principal Component Analysis (PCA) to extract a global measure of adversity – the first dimension in the PCA. PCA was preferred over factor analysis because I was interested in maximizing the variance in these adversity variables rather than the underlying latent factors that represent the variables. Thus, the PCA involved the ACEs lumping approach (Smith and Pollak, 2020) for the all adversity variables that contributed sufficient variance to the first component that I named the global adversity. The adversity scores for the first component also have good internal consistency with Cronbach's alpha of 0.77.

As can be seen in Table 2.1, with the exception of child illness, mother's illness, child separation from parents and parental harsh discipline, all variables showed moderate to high loadings on the first component. I didn't remove the variables that loaded relatively low than others because they cumulatively contributed to our global adversity metric. That is, for all the adversity variables entered into the model, PCA essentially extracted their maximum variances across dimensions. This is because theoretically, I believe the adversity variables here do not share an underlying factor thus, I combined them to reflect a formative construct of global adversity using the PCA approach. Thus, while "child illness, "parent illness (mother)", "child separation from parent" and "parental harsh disciple" may have loaded low on the first

dimension, they contributed non-negligible variances to our global adversity construct (dim 1) while loading more highly in the second dimension which was not of much interest in the present study. In PCA approach, the first component has the maximum variance extracted from the data and this is followed by the second and third dimensions respectively which have lower levels of the remaining variances. It is thus common to see one or two variables load better on the subsequent dimensions but the first dimension will always have good representations of variances in the (adversity) variables.

Table 2.1: Factor loadings of the adverse childhood experiences (age 3), global mental health (age 11) and global mental health (age 14)							
adverse childhood experiences (age 3)				**Global mental health (age 11)**		**Global mental health (age 14)**	
ACEs Measures	DIM 1	DIM 2	DIM 3	Mental health measures	DIM 1	Mental health measures	Dim 1
Number of carers in household	0.727	-0.384	0.060	Subjective Wellbeing	0.786	Subjective wellbeing	0.799
Family Poverty	0.556	-0.219	0.168	Self-esteem	0.793	Self-esteem	0.811
Mother's depression	0.481	0.558	-0.137	Depressive symptoms	0.738	Mood and feelings	0.858
Partners' depression	0.485	0.152	0.066			Self-harm	0.670
Child separation from parent	0.125	0.112	0.195				
Child illness	0.105	0.270	0.518				
Parent (1) illness	0.187	0.473	0.453				
Parent (2) illness	0.240	0.013	0.526				
Parent (1) violence	0.713	-0.134	-0.102				
Parent (2) violence	0.654	-0.243	-0.076				
Homelessness	0.283	0.023	-0.020				
Parental harsh discipline	0.110	0.521	-0.410				
Parent (1) conflict	0.642	0.292	-0.275				
Parent (2) conflict	0.756	-0.096	-0.055				
Note: ACEs = Adverse childhood experiences; DIM = Dimension; Parent 1 = Mother; Parent 2 = Father							

Mental health: Participant mental health was measured at ages 3, 5, 7, 11 and 14 using a 25-item parent-completed Strengths and Difficulties Questionnaire (SDQ; Goodman et al., 2000). The SDQ includes five questions each for five domains (scored 0-2): 'emotional symptoms', 'peer problems', 'conduct problems', 'pro-social behavior' and 'hyperactivity domains'. The scores for all domains were summed (except the prosocial behaviour which was excluded because it is a non-difficulty domain) to create a total difficulties score reflecting difficulties in both externalizing and internalizing behaviours with higher scores reflecting higher difficulties and poorer mental health (Goodman & Goodman, 2009). The Strengths and Difficulties Questionnaire has been shown to exhibit measurement invariance across ages 3-14 in the Millennium Cohort Study, making it a valuable longitudinal measure of mental health (Murray et al., 2021).

While it should be noted that the Strengths and Difficulties Questionnaire was the primary mental health measure of interest, in a later sensitivity analysis, I reanalysed the data with a broader set of global mental health measures available provided at ages 11 and 14, to supplement the Strengths and Difficulties Questionnaire available at ages 3, 5 and 7. This sensitivity analysis would enable me to test whether the effects of adversity on mental difficulties assessing internalizing and externalizing symptoms differed from a broader set of mental health measuring wellbeing, self-esteem and mood. In this sensitivity analysis, specifically, I included the 5-item Rosenberg self-esteem questionnaire (age 11 and 14), a 6-item subjective wellbeing questionnaire (age 11 and 14), a 6-item depressive symptoms questionnaire (age 11), a 13-item mood and feeling questionnaire (age 14) and a single-item self-harm question (age 14). All questionnaires were reverse coded where necessary so that higher values represent poorer mental health. Similar to the procedure for the adversity variables described above, PCA was preferred over factor analysis because I was interested in maximizing the variance in these broader mental health measures because they were all highly

correlated with each other. At age 11, the sum scores for each of the self-esteem, subjective wellbeing, depressive symptoms questionnaires were entered into a Principal Component Analysis to extract a global mental health score. Similarly, the sum scores for each of the self-esteem, subjective wellbeing, self-harm, mood and feeling questionnaires at age 14 were entered into Principal Component Analysis to extract a global mental health score for this wave. Results showed that one global component of mental health was sufficient to explain mental health at both assessment waves (See Table 2.1).

Cognitive tasks: During interviewers visits to the different participating households, participants' cognitive abilities were examined at age 11 using CANTAB (Robbins et al., 1994) Spatial Working Memory and Cambridge Gambling tasks and at age 14 using CANTAB Cambridge Gambling Task and the Applied Psychology Unit vocabulary test (Levy and Goldstein, 1984). In the current study, I analysed the Spatial Working Memory task (assessing short-term memory) and the vocabulary task (measuring crystallized ability) because both cognitive domains have shown to be excellent predictors of learning and academic achievement across different grade levels (Fanari et al., 2019; Postlethwaite, 2011). Previous studies have established good psychometric properties in both cognitive tasks (Levy and Goldstein, 1984; Karlsen et al., 2022). In the Working Memory task used at age 11, participants searched for a blue token in a number of colored boxes on a screen. Using elimination strategy, participants were expected to find one blue token in each of the colored boxes. Repeatedly touching a box that have been found to contain a token is a within-trial error, and repeatedly touching an empty box is a between-trial error. There is a progressive increase in task difficulty from 3 to 8 boxes presented on the screen. Both within and between trial errors were summed to create the dependent measure, where higher values indicated more errors, thus poorer Working Memory ability.

The CANTAB vocabulary task was filled out by participants at age 14. Participants were presented with 20 target words and then asked to choose the most relevant synonym from five options. The total number of correct responses was summed to create the dependent measure, where higher values indicate higher vocabulary.

2.2.3 Statistical analyses

All analyses for this study were conducted in R (Team, 2019) and Rstudio (version 3.6.2). As it was essential to have complete data in the first stage of the analysis, i.e. prior to Principal Component Analysis, I used multiple imputation for all missing adversity and mental health variables using the Mice R package (Buuren & Groothuis-Oudshoorn, 2011). I then went on to conduct a Principal Component Analysis for the adversity and mental health variables where I extracted the components scores for each individuals for both the adversity and global mental health data. To further accommodate missingness during the main mediation analysis, I applied Full Information Maximum Likelihood which has been shown to have desirable properties and yield unbiased estimates if data is missing at random (Enders, 2001).

The main analyses primarily rely on two sequential mediation models, which were modelled as structural equation models (SEMs; Iacobucci et al., 2007). Both models use global adversity at age 3 as the independent variable, mental health scores from all waves as the mediating variables and the cognitive outcomes as the dependent variable. The first model (N = 13,287), shown in Figure 2.1, spans 4 waves and used total errors in Working Memory task at age 11 as the cognitive outcome variable. In model 2 (N = 11, 726), shown in Figure 2.2, 5 waves were analyzed and vocabulary at age 14 was used as the cognitive outcome variable. For each mediation analysis, I included all individuals who provided data for the relevant

outcome variable (Working Memory and vocabulary respectively). To test the specific research questions, I implemented a model comparison approach (Rodgers, 2010) and used contrast-coding to compare distinct hypotheses about the developmental effects of adversity on mental health and ultimately cognitive performance. To facilitate comparisons of effect magnitudes across waves, all variables were scaled to a standard normal distribution.

To provide an additional test of each specific research questions, I introduced constrained and unconstrained parameters in SEM. The constrained and unconstrained models were compared using likelihood ratio tests to determine whether the more complex model (where all effects are freely estimated) outperformed simpler models more than would be expected by chance. To this effect, I examined the first research question regarding the long-term effects of adversity on mental health by fitting a model where I introduced equality constraints on all pathways between adversity and mental health (path a1-a4 or a1-a5; see Figure 2.1 & Figure 2.2) and compared it to an unconstrained model. In doing so, I test whether early-life adversity has solely proximal or also distal effects on mental health across ages 3-14. To rule out a purely self-propagating process, I additionally tested an alternative hypothesis to this question, where an early impact of adversity on mental health is maintained by autoregressive effect, by reparametrizing the model accordingly: By constraining direct effects of adversity on later mental health to 0, with mental health at age 3 affecting age 5 and so on. To address the second research question about whether mental health affects cognition, I fit another model where all pathways from mental health to cognitive performance (b1-b4 or b1-b5) were constrained to equality (see Figure 2.1 & Figure 2.2) and compared it to an unconstrained model. To examine the third research question, whether the effects of mental health on cognition were cumulative and not only present at the same wave, I fit another model where *only* the b4 or b5 pathway of current mental health at age 11 or 14 was freely estimated, and the others were constrained to 0. This allowed me to examine whether only the

contemporaneous mental health state (i.e. mental health state at the time of cognitive assessment) influenced cognition or whether previous mental health measures all contributed in explaining cognitive performance.

Given the large sample size, I report traditional significance tests at a more conservative threshold ($\alpha = 0.005$; Benjamin et al., 2018) and report effect size measures throughout.

The scripts supporting my analyses can be found at osf.io/428sh.

2.3 Results

To examine the mediating effect of mental health on the association between early-life adversity and cognitive performance, I fit a simultaneous mediation model as shown in Figure 2.1 & Figure 2.2. This model tests the hypothesis that global adversity at age 3 affects mental health contemporaneously (age 3) and at later ages (5, 7, 11 and 14), as well as affecting cognitive performance (working memory at age 11 and vocabulary at age 14). I hypothesized that adversity is associated with cognitive performance, and that this effect will be mediated (i.e., partially attenuated) by differences in mental health in the intervening years.

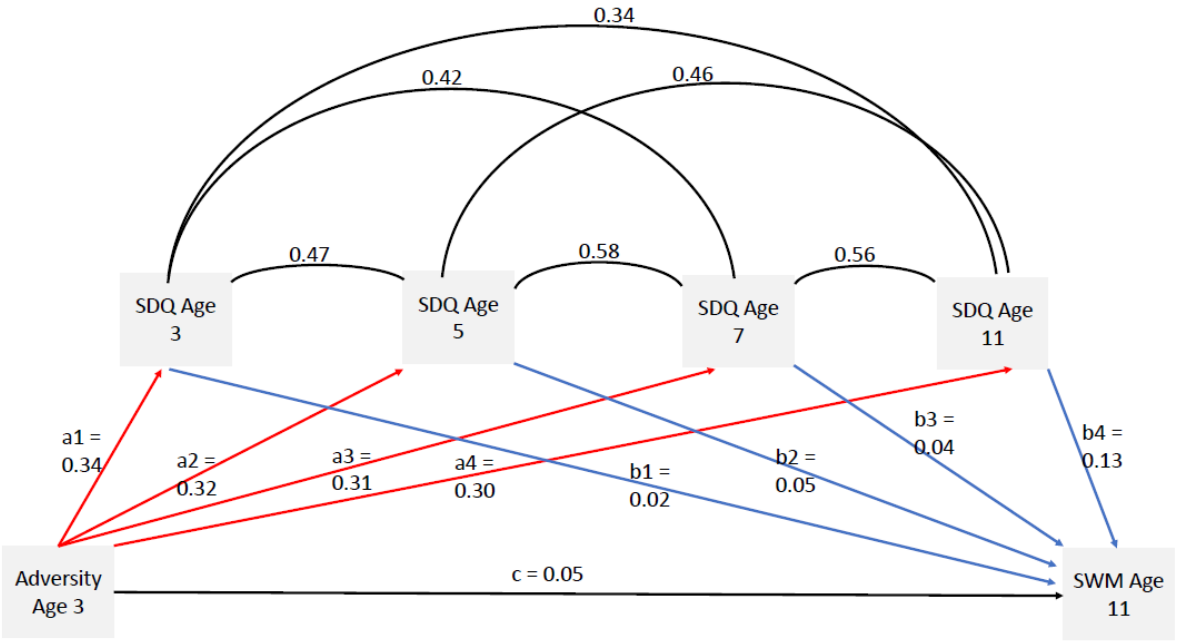


Figure 2.1: Showing the multiple mediation paths of the associations between global adversity at age 3, mental health at age 3, 5, 7 and 11 and spatial working memory at age 11. Note: SWM = Spatial working memory; SDQ: Strength and Difficult Questionnaire.

2.3.1 Working memory performance

First, I fit the full model predicting early-life adversity, mental health and performance in working memory as displayed in Figure 2.1. Parameter estimates (Table 2.2) revealed a significant total association between global adversity and working memory ($\beta = 0.123$, $p < 0.001$). This association was considerably attenuated after taking into account the indirect associations through mental health at ages 3, 5, 7 and 11 (i.e. residual direct effect; $\beta = 0.051$, $p < 0.001$). In other words, the mediation pathways accounted for over 59% of the total effect. Examining these effects in more detail (see Figure 2.1 & Figure 2.3) showed that there were significant indirect associations between adversity and working memory through mental health at age 11 ($\beta = 0.038$, $p < 0.001$), age 7 ($\beta = 0.012$, $p = 0.004$) and age 5 ($\beta = 0.016$, $p < 0.001$), but no mediation at age 3 ($\beta = 0.006$, $p = 0.127$). Using a dummy contrast coding approach, I found that the indirect pathway from adversity to mental health at age 11 was significantly stronger than those at all previous timepoints (all $p<0.001$). In contrast, the other three indirect effects did not differ in magnitude (likelihood ratio tests: all $p>0.005$). This showed that global adversity predicted poorer mental health at all timepoints, but that the subsequent effect on working memory performance was strongest for most recent measures of mental health. Most strikingly, although the most recent mental health measures had the strongest effect, individual differences in mental health earlier in life contributed unique variance beyond the contemporaneous effect, showing the importance of good mental health in early childhood for the emergence of cognitive abilities. This supports my hypothesis that early-life adversity is associated with poorer cognitive outcomes, at least in part by having a lasting impact on mental health, which subsequently leads to poorer cognitively functioning later on.

Table 2.2				
Direct, indirect and contrast effects of Adversity and mental health measures across different ages on spatial working memory performance, N =13,287				
Direct effects	**β**	**t-value**	**p-value**	**95%CI**
GA->SWM	0.051	5.304	< 0.001	0.032, 0.070
Indirect effects	**β**	**t-value**	**p-value**	**95%CI**
GA->MH11->SWM	0.038	10.535	< 0.001	0.031, 0.045
GA->MH7->SWM	0.012	2.872	0.004	0.004, 0.021
GA->MH5->SWM	0.016	3.800	< 0.001	0.008, 0.024
GA->MH3->SWM	0.006	1.525	0.127	-0.002, 0.013
Total Adversity MH Effect	0.123	13.670	< 0.001	0.106, 0.141
Contrast Effects	**β**	**t-value**	**p-value**	**95%CI**
GA->MH11->SWM > GA->MH7->SWM	0.026	3.937	< 0.001	0.013, 0.039
GA->MH11->SWM > GA->MH5->SWM	0.022	3.821	< 0.001	0.011, 0.034
GA->MH11->SWM > GA->MH3->SWM	0.032	5.934	< 0.001	0.022, 0.043
GA->MH7->SWM > GA->MH5->SWM	-0.004	-0.510	0.610	-0.017, 0.010
GA->MH7->SWM > GA->MH3->SWM	0.006	1.035	0.301	-0.006, 0.018
GA->MH5->SWM > GA->MH5->SWM	0.010	1.535	0.125	-0.003, 0.023
Direct, indirect and contrast effects of Adversity and mental health measures across different ages on vocabulary skills, N = 11,726.				
Direct effects	**β**	**t-value**	**p-value**	**95%CI**
GA->VOCAB	-0.033	-3.362	0.001	-0.053, -0.014
Indirect effects	**β**	**t-value**	**p-value**	**95%CI**
GA->MH14->VOCAB	-0.029	-7.964	< 0.001	-0.036, -0.022
GA->MH11->VOCAB	-0.007	-1.712	0.087	-0.015, 0.001
GA->MH7->VOCAB	-0.010	-2.335	0.020	-0.018, -0.002
GA->MH5->VOCAB	-0.014	-3.391	0.001	-0.022, -0.006
GA->MH3->VOCAB	-0.018	-4.647	< 0.001	-0.026, -0.010
Total Adversity MH effects	-0.111	-12.025	< 0.001	-0.129, -0.093
Contrast Effects	**β**	**t-values**	**p-value**	**95%CI**
GA->MH14->VOCAB > GA->MH11->VOCAB	-0.021	-3.287	0.001	-0.034, -0.009
GA->MH14->VOCAB > GA->MH7->VOCAB	-0.019	-3.201	0.001	-0.030, -0.007
GA->MH14->VOCAB > GA->MH5->VOCAB	-0.014	-2.521	0.012	-0.026, -0.003
GA->MH14->VOCAB > GA->MH3->VOCAB	-0.010	-1.977	0.048	-0.021, -0.000
GA->MH11->VOCAB > GA->MH7->VOCAB	0.003	0.389	0.697	-0.011, 0.016
GA->MH11->VOCAB > GA->MH5->VOCAB	0.007	1.116	0.264	-0.005, 0.019
GA->MH11->VOCAB > GA->MH3->VOCAB	0.011	1.840	0.066	-0.001, 0.023
GA->MH7->VOCAB > GA->MH5->VOCAB	0.004	0.648	0.517	-0.009, 0.018
GA->MH7->VOCAB > GA->MH3->VOCAB	0.008	1.353	0.176	-0.004, 0.020
GA->MH5->VOCAB > GA->MH3->VOCAB	0.004	0.598	0.550	-0.009, 0.017

Note: GA = Global adversity; MH = Mental health (Age 14, 11, 7, 5, 3); SWM = spatial working memory; V OCAB = vocabulary; CIs = 95% confidence intervals; β = standardized estimates.

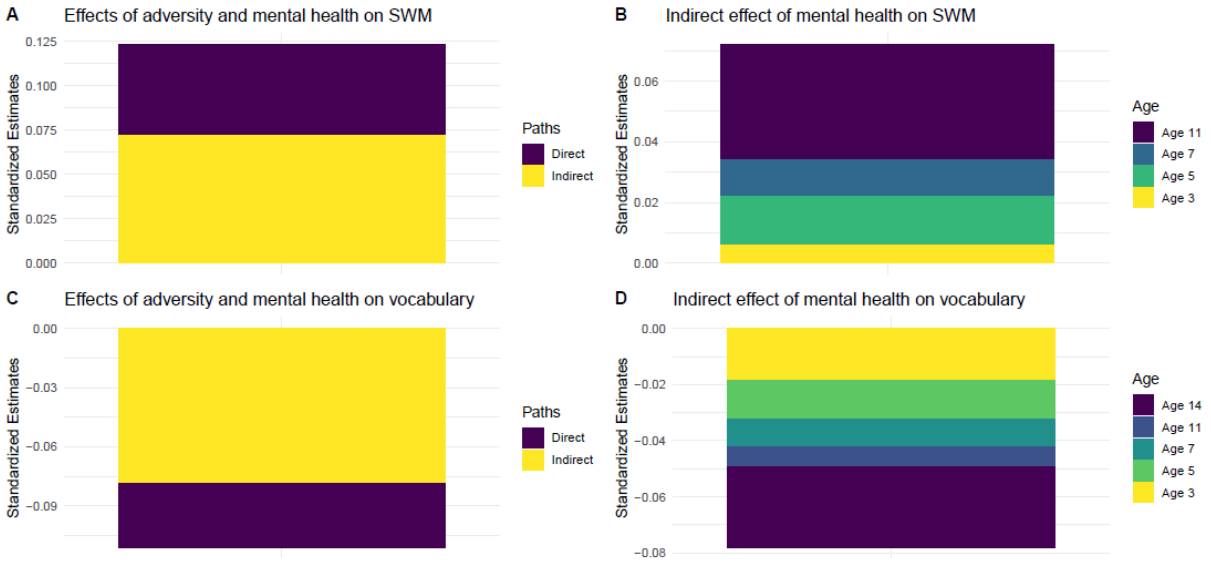


Figure 2.3: Showing total, direct and indirect associations of global adversity, mental health on cognitive tasks. **Panel A:** indirect associations of mental health across ages 3-11 accounted for 59% of total effects; **Panel B:** age contributions of mental health measures to poor performance in working memory, **Panel C:** direct and indirect paths to vocabulary ability (indirect associations of mental health across ages 3-14 explained 70% of the variance in poor vocabulary); **Panel D:** age contributions of mental health across ages 3-14 on vocabulary.

2.3.2 Effects of adversity on mental health and cognition

To provide additional test of the first research question on the effects of adversity on mental health, I next examined whether the effect of global adversity was solely proximal, i.e. affecting mental health early on in life or rather had longer term direct effects. To do so, I compared a model where *all* pathways from adversity to mental health were constrained to equality. This model had a poorer fit $\Delta\chi^2(3) = 17.744$, $p < 0.001$, suggesting that the effects of adversity on mental health were not equal over time. Inspection of the parameters showed that more

adversity was associated with poorer mental health at each time point, but slightly more strongly so for early mental health at age 3 (β=0.337) than for later mental health at age 11 (β=0.296). As can be seen in Figure 2.1, poor mental health outcomes were stable across waves with high correlations, suggesting that poor mental health early on is likely to be partly maintained. To examine whether this could explain the distal effects of adversity (i.e. through self-maintenance of early poor mental health), I tested an alternative hypothesis, where an early impact of early-life adversity on mental health is maintained by autoregressive effect, I reparametrized the model accordingly, with mental health at age 3 affecting age 5 and so on. Estimating this model showed that constraining direct effects of adversity on later mental health to 0 considerably worsened fit $\Delta\chi^2(3) = 578.88$, $p < 0.001$. The direct effects of adversity on later mental health above and beyond the autoregressive component were considerable for all ages (all $\beta>0.09$), demonstrating that early-life adversity is associated with long term consequences on mental health above and beyond self-maintenance.

Table 2.3

Structural invariance of long-term effects of adversity and mental health across spatial working memory and vocabulary outcomes

	Overall model indices				Model comparison	
Models	**χ2**	**df**	**AIC**	**BIC**	**Δχ2**	**Δdf**
Across spatial working memory at age 11						
Differential effects of global adversity on mental health across 4 data waves						
Unconstrained	**0.000**	**0**	**190320**	**190523**		
Constrained 1	17.744	3	190332	190512	17.744***	3
Differential effects of mental health across 4 data waves on spatial working memory						
Unconstrained	**0.000**	**0**	**190320**	**190523**		
Constrained 2	47.278	3	190362	190541	47.278***	3
Cumulative effects of mental health across 4 data waves on spatial working memory						
Unconstrained	**0.000**	**0**	**190320**	**190523**		
Constrained 3	62.078	3	190376	190556	62.078***	3
Vocabulary skills at age 14						
Differential effects of global adversity on mental health across 5 data waves						
Unconstrained	**0.000**	**0**	**193483**	**193741**		
Constrained 1	24.073	4	193499	193728	24.073***	4
Differential effects of mental health across 5 data waves on vocabulary						
Unconstrained	**0.000**	**0**	**193483**	**193741**		
Constrained 2	18.013	4	193493	193722	18.013**	4
Additive effects of mental health across 5 data waves on vocabulary						
Unconstrained	**0.000**	**0**	**193483**	**193741**		
Constrained 3	118.91	4	193594	193823	118.91***	4

χ2 = Chi square; df = degree of freedom; AIC = Akaike's Information Criteria; BIC = Bayesian Information Criteria; Δχ2 = Change in chi square; Δdf = change in degree of freedom
Note: The smaller the values, the better the model (bolded)

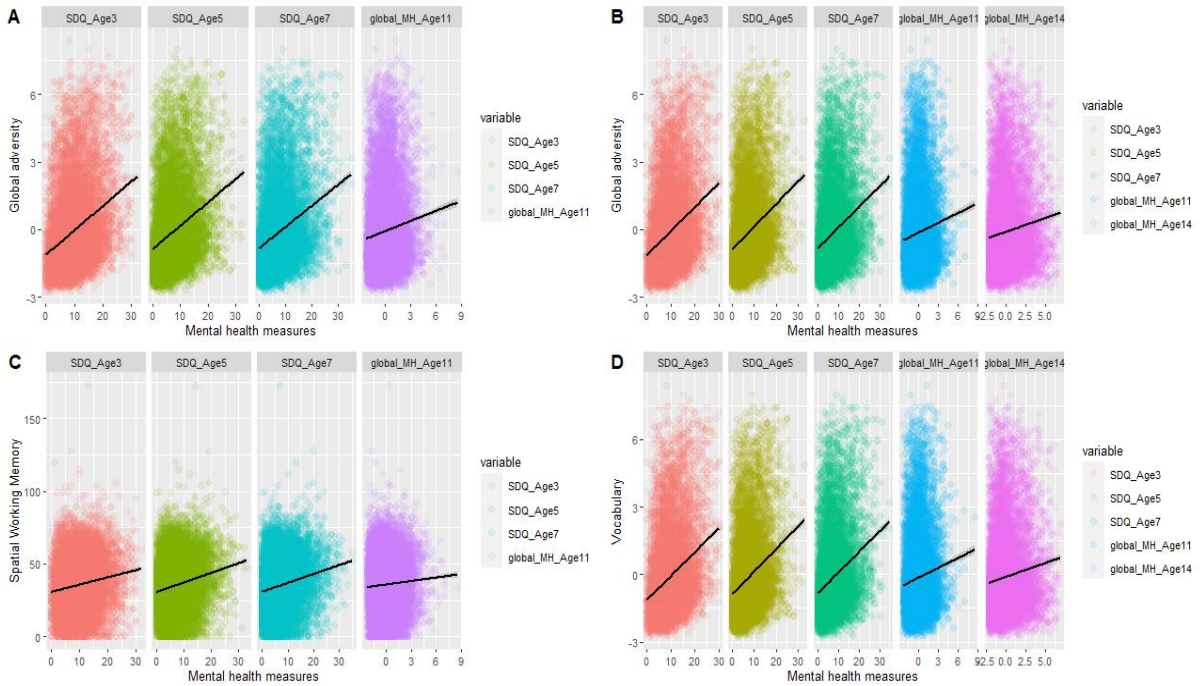


Figure 2.4: Regression plots showing differential association between global adversity and mental health across different waves and differential relationship between mental health measures and cognitive outcomes. **Panel A**: Relationship between global adversity and mental health age 3, age 5, age 7 and age 11 (all significant at p<0.001). **Panel B**: Relationship between global adversity and mental health age 3, age 5, age 7, age 11 and age 14 (all significant at p<0.001). **Panel C**: Relationship between mental health at age 3 (p= 0.127), age 5 (p<0.001), age 7 (0.004) and age 11 (p<0.001) on spatial working memory. **Panel D**: Relationship between mental health at age 3 (p<0.001), age 5 (p=0.001), age 7 (p= 0.019), age 11 (p= 0.087) and age 14 (p<0.001) on vocabulary.

To examine the relative strength of the effects of mental health at each age on Working Memory performance, I analysed a model where the effects of mental health on Working Memory were constrained to equality (Table 2.3). This fit significantly worse also, $\Delta\chi2(3) = 47.278$, $p < 0.001$, suggesting differences in the effects of timing of mental health measures on Working Memory performance, with contemporaneous mental health at age 11 having the strongest effects ($\beta=0.129$) but weaker, non-negligible effects of earlier mental health status (age 3, $\beta=0.017$; age 5, $\beta=0.050$; age 7, $\beta=0.040$; see also Figure 2.4). Additionally, I tested a cumulative effects, model (See Table 2.3), where *only* the *b* pathway from mental health at age 11 was freely estimated, and the others were constrained to 0. This model fit considerably worse $\Delta\chi^2(3)= 62.078$, $p < 0.001$. In other words, in addition to strong contemporaneous effects between mental health and Working Memory at age 11 ($\beta=0.129$), earlier mental health difficulties have additional effects on Working Memory performance (e.g. $\beta=0.050$ for mental health at age 5).

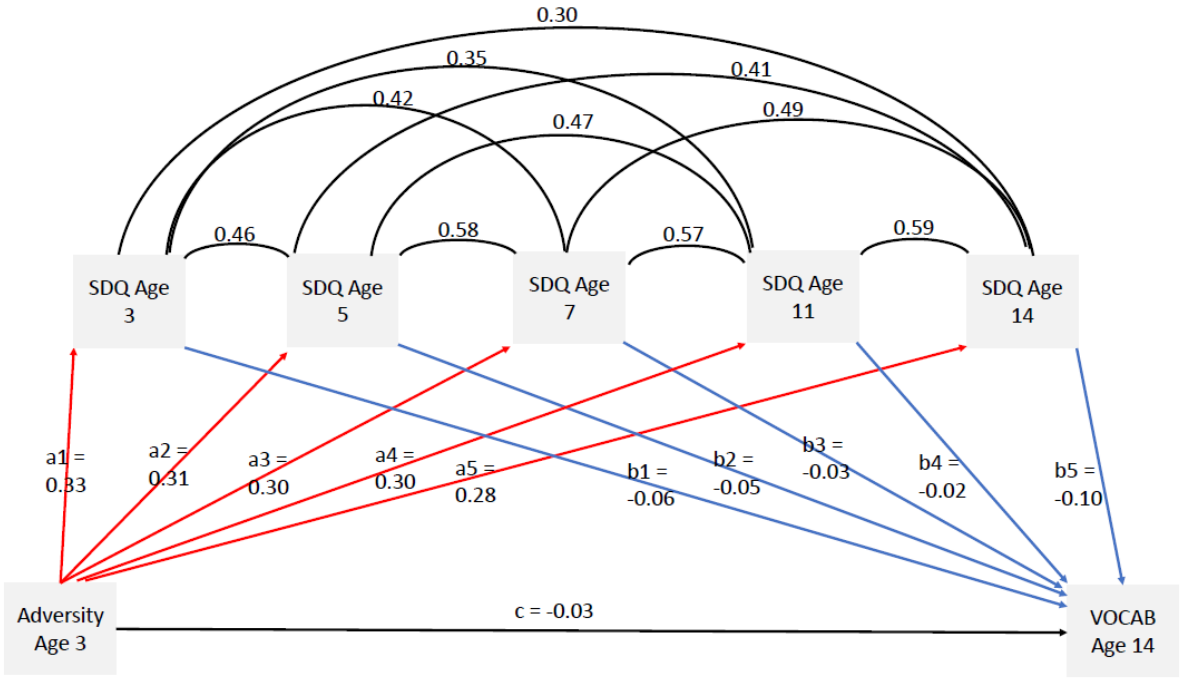


Figure 2.2: A multiple mediation analysis showing direct and indirect paths of the associations between global adversity at age 3, multiple mediators at age 3, 5, 7, 11 and 14 and word activity at age 14. Note: VOCAB = Vocabulary; SDQ: Strength and Difficult Questionnaire.

2.3.3 Vocabulary performance

To examine whether the mediating effect of childhood mental health on early-life aversity and cognitive functioning was specific to a more executive, cognitive task of Working Memory or also generalize to a knowledge based measure, I next look at vocabulary outcome. Following the same analysis approach as for Working Memory, I fit a second full multiple mediation model of performance in vocabulary task at age 14 with corresponding additional wave of mental health measure at age 14 (Figure 2.2).

Parameter estimates shown in Table 2.2 revealed a significant total association between adversity and vocabulary performance (β = -0.111, $p < 0.001$), such that greater early-life adversity was associated with a smaller vocabulary over a decade later. Similar to the first model for Working Memory performance described above, the residual direct effect between

adversity and vocabulary performance (β = -0.033, p = 0.001) was partially attenuated after taking into account the total indirect effects of mental health across ages 3-14. In other words, indirect associations through mental health across ages 3-14 accounted for the large portion of the total effects (70%). Specifically, I observed a significant indirect association between early-life adversity and vocabulary performance through mental health at age 14 (β = -0.029, p < 0.001), age 5 (β = -0.014, p = 0.001), and age 3 (β = -0.018, p < 0.001) but not ages 11 and 7 (all p>0.005). In other words, in contrast to the findings for Working Memory, poorer mental health at the age 3 and 5 had the strongest indirect associations after contemporary mental health at age 14. See Table 2.2 for full details.

To test whether the effect of mental health on vocabulary performance was equal for all ages, an equality constrained model for *b* paths examining the specific effects of mental health timing on vocabulary fitted significantly worse, $\Delta\chi^2(4) = 18.013$, p = 0.001. This indicated specificity in the effects of timing of mental health measures on vocabulary performance, with the largest effect of contemporaneous mental health (b5: β = -0.104 for age 14) but robust effects at early ages (e.g. b1: β = -0.055 for age 3). Next, I examined the cumulative effects of mental health on vocabulary ability by fitting a model where only mental health at age 14 was freely estimated and the others were constrained to 0 (See Table 2.3). Similar to working memory, the model fit significantly worse $\Delta\chi^2(4) = 118.91$, p < 0.001, suggesting that the effect of mental health on vocabulary is long lasting, above and beyond current mental health state. Taken together, these findings show that early-life adversity at age 3 predicted poorer mental health outcomes, both contemporaneously (age 3) and at later ages (5, 7, 11 and 14) which subsequently predicted poorer cognitive functioning in both SWM and vocabulary tasks at late childhood.

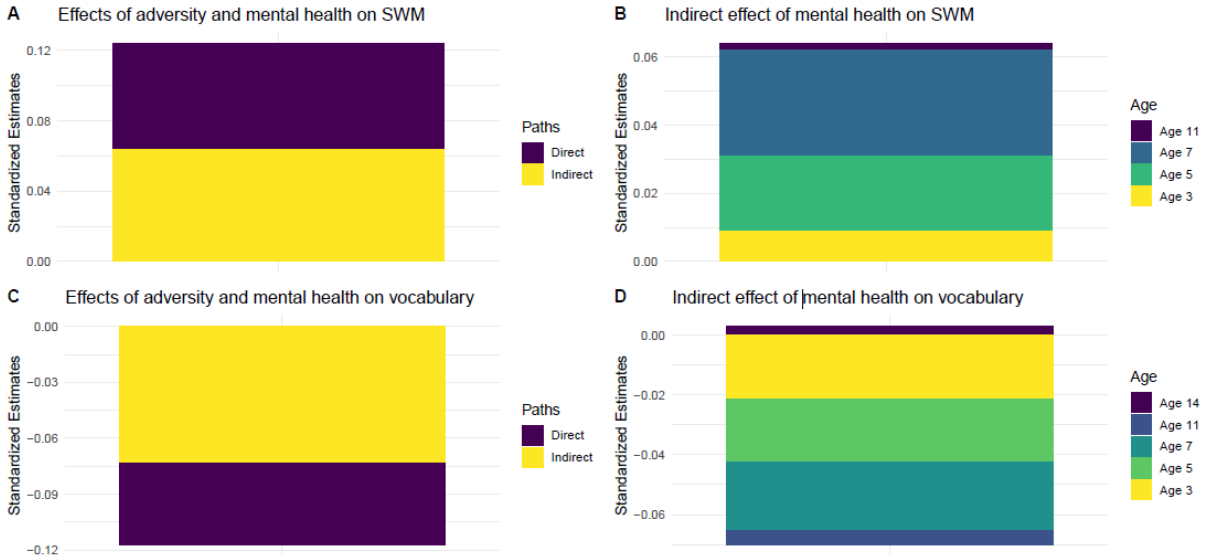


Figure 2.5: (Sensitivity analysis using global mental health measures at ages 11 and 14; and SDQ at ages 3, 5, and 7). Figure show total, residual direct and indirect associations of global adversity, mental health on cognitive tasks. **Panel A**: residual direct (adversity) and indirect (mental health) paths to performance in spatial working memory; **Panel B:** age contributions of mental health measures to poor performance in working memory (contemporary global mental health measure at age 11 only accounted for minimal 3% of total indirect effects compared to 53% in the primary analysis); **Panel C:** residual direct (adversity) and indirect (mental health) paths to performance in vocabulary task; **Panel D:** age contributions of mental health measures to poor performance in vocabulary (combined contemporary global mental health measures at ages 11 and 14 only accounted for minimal 11% of total indirect effects compared to 46% in the primary analysis).

2.3.4 Sensitivity analysis

I reanalysed the data with a broader set of global mental health measures available only at ages 11 and 14, to examine if global mental health measures (mood, self-esteem and wellbeing) have similar effects on cognition as Strengths and Difficulties Questionnaire available at ages 3, 5 and 7. Results of the first model examining performance on working memory showed significant indirect associations between adversity and working memory through mental health at age 7 ($\beta = 0.031$, $p < 0.001$) and age 5 ($\beta = 0.022$, $p < 0.001$) but not contemporary mental health at age 11 ($\beta = 0.002$, $p = 0.093$), or at age 3 ($\beta = 0.009$, $p = 0.030$). Indirect effects of contemporary mental health at age 11 accounted for a very small portion (3%) of the total indirect effects of mental health compared to a larger effect (53%) in primary analysis (see

Figure 2.5 & Table 2.4). In addition, results of the model examining vocabulary performance showed significant indirect associations between adversity and vocabulary through mental health at age 11 (β = -0.005, p < 0.001), 7 (β = -0.023, p < 0.001), 5 (β = -0.021, p < 0.001), and 3 (β = -0.021, p < 0.001), but not the contemporary global mental health at age 14 (β = 0.003, p = 0.023). The combined global mental health measures at ages 11 and 14 only accounted for non-significant 11% of total indirect effects of mental health on vocabulary performance compared to 46% in the primary analysis (see Figures 2.3 & 2.5 for comparison). The results of these sensitivity analyses differ from the primary analyses where the contemporary SDQ measures at age 11 and 14 had the strongest indirect associations on working memory and vocabulary. For the results of all associations and contrast effects as well as the descriptive and intercorrelation of all study variables, see the supplementary materials.

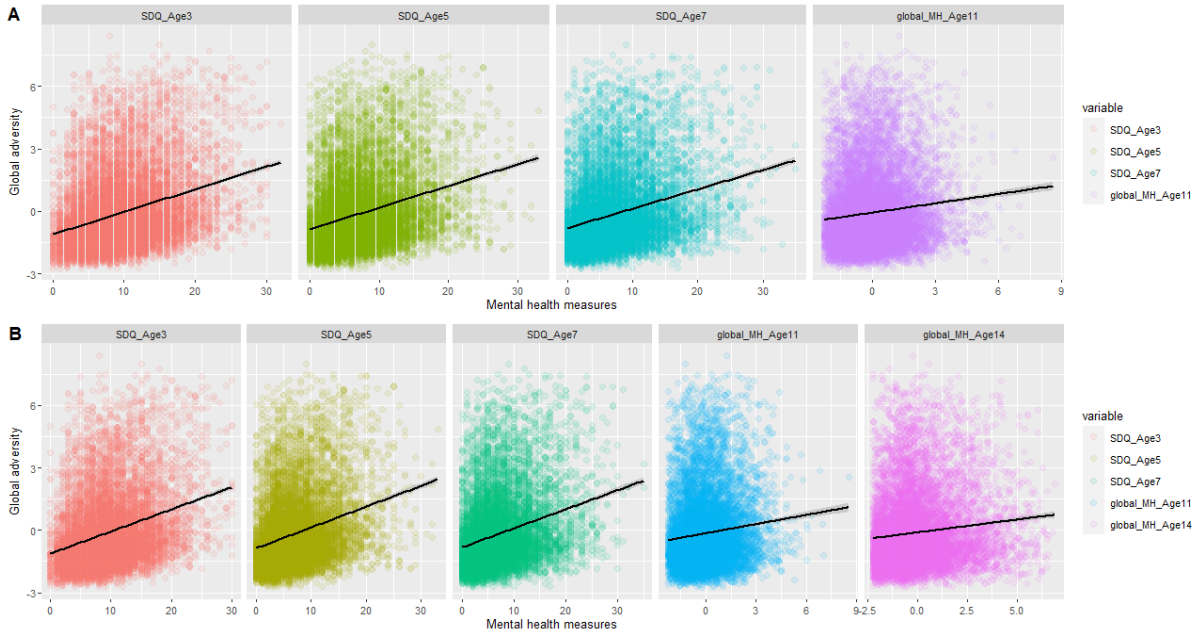


Figure 2.6: (Sensitivity analysis using global mental health measures at ages 11 and 14; and SDQ at ages 3, 5, and 7). Regression plots show differential effects of global adversity on mental health across different waves of mental health data. **Panel A** – model 1: effects of global adversity on mental health at age 3, 5, 7, and 11. **Panel B** – model 2: effects of global adversity on mental health at age 3, 5, 7, 11, and 14. Note: mental health at age 11 and 14 was captured with more robust mental health questionnaires.

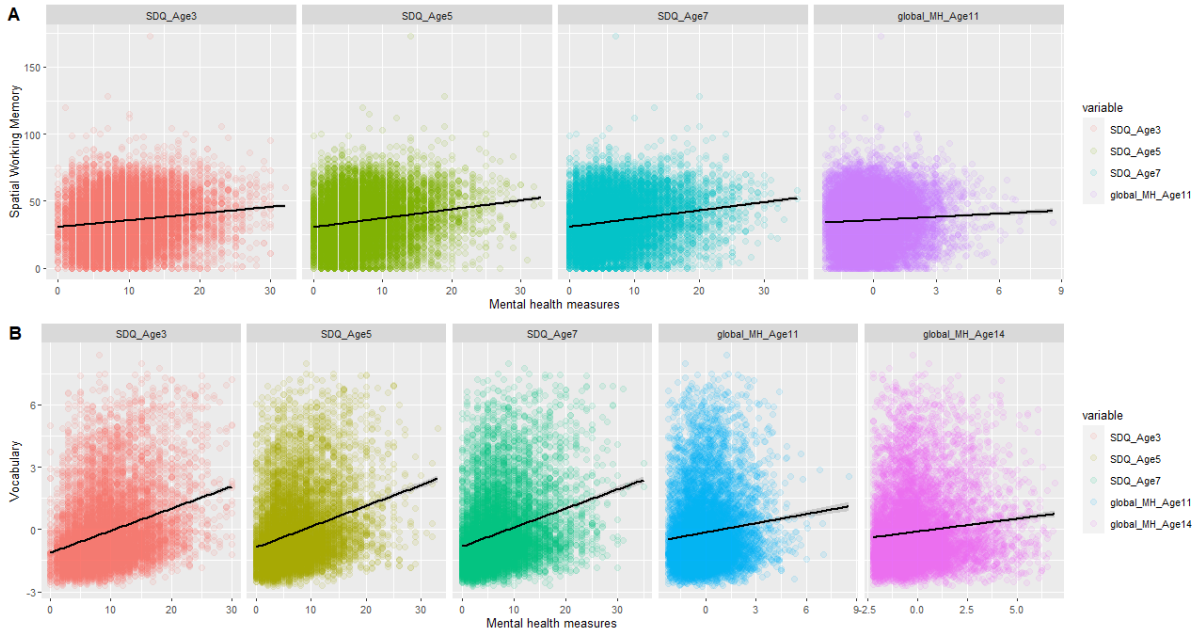


Figure 2.7: (Sensitivity analysis using global mental health measures at ages 11 and 14; and SDQ at ages 3, 5, and 7). Regression plots show differential associations of mental health across different waves on cognitive abilities. **Panel A** – model 1: associations of mental health at age 3, 5, 7, and 11 on spatial working memory. **Panel B** – model 2: associations of mental health at age 3, 5, 7, 11, and 14 on vocabulary. Note: mental health at age 11 and 14 was captured with more global mental health questionnaires.

Table 2.4

Direct, indirect and contrast effects of Adversity and mental health measures across different ages on spatial working memory performance, N =13287

Residual direct effects	**β**	**t-value**	**p-value**	**95%CI**
GA->SWM	0.060	6.276	< 0.001	0.041, 0.079
Indirect effects	**β**	**t-value**	**p-value**	**95%CI**
GA->MH11->SWM	0.002	1.678	0.093	-0.000, 0.004
GA->MH7->SWM	0.031	7.748	< 0.001	0.023, 0.039
GA->MH5->SWM	0.022	5.250	< 0.001	0.014, 0.030
GA->MH3->SWM	0.009	2.165	0.030	0.001, 0.016
Total Adversity MH Effects	0.124	14.045	< 0.001	0.106, 0.141
Contrast Effects	**β**	**t-value**	**p-value**	**95%CI**
GA->MH11->SWM > GA->MH7->SWM	-0.030	-6.926	< 0.001	-0.038, -0.021
GA->MH11->SWM > GA->MH5->SWM	-0.021	-4.715	< 0.001	-0.029, -0.012
GA->MH11->SWM > GA->MH3->SWM	-0.007	-1.704	0.088	-0.015, 0.001
GA->MH7->SWM > GA->MH5->SWM	0.009	1.293	0.196	-0.005, 0.023
GA->MH7->SWM > GA->MH3->SWM	0.023	3.676	< 0.001	0.011, 0.035
GA->MH5->SWM > GA->MH5->SWM	0.014	2.051	0.040	0.001, 0.027

Direct, indirect and contrast effects of Adversity and mental health measures across different ages on vocabulary skills, N = 11726.				
Residual direct effects	**β**	**t-value**	**p-value**	**95%CI**
GA->VOCAB	-0.044	-4.449	< 0.001	-0.064, -0.025
Indirect effects	**β**	**t-value**	**p-value**	**95%CI**
GA->MH14->VOCAB	0.003	2.277	0.023	0.000, 0.005
GA->MH11->VOCAB	-0.005	-3.926	< 0.001	-0.007, -0.002
GA->MH7->VOCAB	-0.023	-5.834	< 0.001	-0.030, -0.015
GA->MH5->VOCAB	-0.021	-4.984	< 0.001	-0.029, -0.013
GA->MH3->VOCAB	-0.021	-5.390	< 0.001	-0.029, -0.013
Total Adversity MH effects	-0.111	-11.936	< 0.001	-0.129, -0.092
Contrast Effects	**β**	**t-value**	**p-value**	**95%CI**
GA->MH14->VOCAB > GA->MH11->VOCAB	0.007	3.868	< 0.001	0.004, 0.011
GA->MH14->VOCAB > GA->MH7->VOCAB	0.025	6.278	< 0.001	0.017, 0.033
GA->MH14->VOCAB > GA->MH5->VOCAB	0.023	5.402	< 0.001	0.015, 0.032
GA->MH14->VOCAB > GA->MH3->VOCAB	0.024	5.798	< 0.001	0.016, 0.032
GA->MH11->VOCAB > GA->MH7->VOCAB	0.018	4.319	< 0.001	0.010, 0.026
GA->MH11->VOCAB > GA->MH5->VOCAB	0.016	3.701	< 0.001	0.008, 0.024
GA->MH11->VOCAB > GA->MH3->VOCAB	0.016	4.018	< 0.001	0.008, 0.024
GA->MH7->VOCAB > GA->MH5->VOCAB	-0.002	-0.289	0.773	-0.015, 0.011
GA->MH7->VOCAB > GA->MH3->VOCAB	-0.002	-0.250	0.803	-0.013, 0.010
GA->MH5->VOCAB > GA->MH3->VOCAB	0.000	0.071	0.943	-0.012, 0.013
Note: GA = Global adversity; MH = Mental health (Age 14, 11, 7, 5, 3); SWM = spatial working memory; V OCAB = vocabulary; CIs = 95% confidence intervals; β = standardized estimates.				

2.4 Discussion

This study examined the long-term consequences of early-life adversity on mental health and cognitive abilities using five longitudinal assessment waves from a large (N=13,287) population cohort. I found that global adversity at age 3 was strongly associated with poorer mental health across all ages (3-14 years), and that this could not be explained solely by stability of poor early mental health. Similarly, global adversity predicted poorer Working Memory (age 11) and vocabulary (age 14). The effect of global adversity on cognition was partially mediated by poorer mental health during development. These findings suggest that early-life adversity may affect cognitive outcomes at much later ages through its consequences on mental health in early and middle childhood.

To begin with, I found that early-life adversity at age 3 strongly predicted poorer mental health across ages 3-14, with the associations strongest in early childhood, compared to later in development. This highlights a gradual but small dissipation of the negative effects of early-life adversity on mental health across childhood. One possible explanation for this finding centers on the timing of exposure to adverse childhood experiences. Recent empirical and theoretical work on sensitive periods for early-life adversity (exposure to stress before or during age 3: Dunn et al., 2019; Gabard-Durnam & McLaughlin, 2019; Takesian & Hensch, 2013) suggest an enduring developmental effect associated with early-life adversity. Using the Avon Longitudinal Study of Parents and Children, another British population cohort sample, Dunn et al. (2019) found that developmental timing (adversity before age 3) but not accumulation (number of times exposed) or recency (recent exposures) predicted DNA methylation linked to psychiatric risks. This developmental time period, characterized by rapid neuronal changes, may be particularly sensitive to environmental stressors, after which it would require a more substantial exposure to stress to have similar impact on the neural system (Gabard-Durnam &

McLaughlin, 2019). Therefore, these findings are compatible with the hypothesis that exposure to adverse childhood experiences at this developmentally sensitive time shapes the long-term adverse mental health outcomes in this sample.

An additional but complementary explanation for the enduring adverse mental health outcomes observed in this sample maybe a result of increased vulnerability associated with the onset of mental health difficulties. Although there is some empirical evidence for the "scarring" hypothesis (enduring psychological changes after the onset of depression that increases future risks), numerous studies have observed that poor mental health at baseline predicted adverse mental health at follow-up (O'Grady, Tennen, & Armeli, 2010; Rohde, Lewinsohn, Seeley, 1990; Zeiss & Lewinsohn, 1988; Bos et al., 2018). Given that the associations between early-life adversity (age 3) and mental health (ages 3-14) were weaker at late childhood and adolescence than in early childhood, it is plausible that the sensitive time of the exposure to adversity marked a greater vulnerability to mental health difficulties with a gradual remission overtime.

Secondly, findings also show that adverse mental health predicted poorer cognitive abilities in working memory and vocabulary tasks. This was consistent with previous studies that found an association between early childhood mental health and adolescent cognitive ability (Delia et al., 2021; Rock et al., 2013). More importantly however, further longitudinal modelling revealed that the relationship between mental health and cognition was not just contemporaneous but had long-term cumulative consequences: Poorer mental health at all previous timepoints together contributed to poorer cognitive abilities later on. Although the indirect association of mental health on cognition was strongest for the contemporary measures at age 11 and 14 in the two analyses, previous mental health outcomes contributed substantially to the cognitive impairments observed in these samples. A distinct pattern was observed here for vocabulary performance. Early childhood mental health at ages 3 and 5 accounted for as

much variance in vocabulary as contemporary mental health. Contrary to the performance in working memory task where the indirect association of contemporary mental health at age 11 was significantly greater than all previous timepoints (ages 3, 5 and 7), contrast effects showed that the indirect association of contemporary mental health at age 14 only was only significantly greater than intermittent timepoints of ages 11 and 7 in their contributions to poorer vocabulary but did not differ with early childhood mental health at ages 3 and 5. These findings suggest that the development of vocabulary maybe more sensitive to poor mental health and negative experiences at an early age than working memory. This is in line with evidence for early sensitive periods for word acquisition and language development (Kuhl, 2004).

Follow-up analyses in this study showed that the contemporary mental health measures at age 11 and 14 using global mental health questionnaires (measuring wellbeing, mood, self-esteem and others), rather than the Strengths and Difficulties Questionnaire used in the main analysis, explained little or no variance in poor cognitive performance in both working memory and vocabulary tasks. This discrepancy may be due to differences in the underlying mechanisms through which SDQ and the global mental health measures affect cognition. For example, specific SDQ sub-domains (e.g. hyperactivity symptoms, conduct problems) may be more associated with poorer cognition through inattention and distractibility during either the acquisition of information (vocabulary) or the performance of demanding tasks (working memory), compared to the global mental health which generally measures overall wellbeing, mood and self-esteem. Thus, it is plausible that poor mental health wellbeing, mood and self-esteem, although adverse, may not contribute significantly to impaired learning and memory. In other words, individuals may report poor wellbeing, mood and self-esteem, but not show poor cognition. In contrast, mental health difficulties captured by Strengths and Difficulties

Questionnaire measures may be associated with a significant disruption to both daily behavioural and cognitive functioning.

2.4.1 Limitations of the study

Although this study has several strengths, including a large sample size, unique longitudinal modelling, multiple timepoints and diverse cognitive and mental health outcomes, findings should be interpreted in light of the following potential limitations. First, while the Strengths and Difficulties Questionnaires from age 3-14 were completed by parents, data on the global mental health measures was self-reported by participants. Thus, differences in results may reflect differences in the appraisal of mental health by parents and participants. Second, global mental health measures were only available at age 11 and 14 in the MCS study. Future studies using global mental health measures throughout childhood and adolescence are needed to clearly tease apart the potential differential negative association of mental health difficulties and mental health wellbeing, mood and self-esteem. An additional limitation to generalizability is differential sampling and attrition in the MCS study (Connelly & Platt, 2014), especially as a function of ethnicity, partially limiting the generalizability of these findings. Last, while I focused on adversity at the crucial early childhood stage, having rich adversity data throughout the lifespan would allow me to rule out alternative causal pathways.

2.4.2 Conclusion

These findings are compatible with the hypothesis that early-life adversity shows strong associations with cognitive performance (working memory and vocabulary) in late childhood,

at least in part through the adverse effects on mental health in the intervening years (ages 3-14). These findings have important implications for clinicians, parents and educators: addressing the behavioural and psychological difficulties in early childhood may help foster cognitive and academic resilience after early-life adversity.

3 Chapter 3

Cognitive variations following exposure to childhood adversity: Evidence from a pre-registered, longitudinal study.

3.1 Introduction

Previous studies have shown that childhood adversity is associated with poorer developmental outcomes (Chandan et al., 2019; Golm et al., 2020). A few other studies have observed substantial better outcomes linked to adaptation among individuals exposed to adversity (Fields et al., 2021; Ellis et al., 2020; Frankenhuis et al., 2020; Frankenhuis and Nettle, 2020; Nweze et al., 2020). These variations in findings may be driven partly, by the type of adversity measured and the way it was measured, timing of exposure or even the cultural context of the sampled population. Thus, this study leverages a large scale longitudinal, multi-measure adversity data to examine the differential and time-sensitive effects of childhood adversity on cognitive functioning at adulthood.

As a good predictor of many life outcomes at adulthood (Lövdén et al., 2020), cognitive functioning is one developmental outcome that has been linked to childhood adversity. Principally, several studies have found that adversity globally impairs cognitive functioning, with individuals exposed to adversity considerably showing worse performance in tests

measuring general executive functioning such as inhibition (Pollak et al., 2010; McDermott et al., 2012), working memory (Hanson et al., 2013; Hostinar et al., 2012), shifting (McDermott et al., 2012) and affective processing (Cicchetti and Toth, 2005; Perlman et al., 2008). However, these findings are not perfectly uniform, as some projects have noted individuals exposed to specific types of adversity have improved performance in specific cognitive domains likely to be adaptive for their survival and matched to their environments, including memory (Nweze et al., 2020; Young et al., 2018, Goodman et al., 2019), shifting (Mittal et al., 2015), as well as enhanced ability in detecting negative threatening emotional expressions (Dunn et al., 2016; Pollak & Sinha, 2002; Pollak et al., 2009; Gibb et al., 2009). These findings taken together, suggest that the effects of adversity on cognitive functioning may be quite heterogenous in nature.

Yet, despite the compelling evidence from these empirical studies, important gaps remain. First, most studies of childhood adversity have used either specificity or cumulative risk score approaches when operationalizing adversity. In specificity approach, the effects of specific types of childhood adversity are examined while cumulative risk score involves tallying up all the adversities reported by an individual to create a risk score. As noted by McLaughlin et al., 2021; McLaughlin and Sheridan, 2016, these two approaches have limitations. This is because childhood adversity mostly co-occurs (Hunt et al., 2017; Thompson et al., 2020) with varying effects; this fact is ignored by specificity and risk score approaches ignored. Second, many of the past studies have often relied on cross-sectional and non-population-based sample data, making it difficult to examine the effect of timing of adversity exposure on cognitive outcomes. Relatedly, because of a paucity of longitudinal studies, there is limited insight on the developmental timeframes in which children cognitive abilities are most vulnerable to adversity exposure. While theoretical models of sensitive periods (time-dependent effect of adversity) and accumulation (greater effect of adversity as a result of

greater number of occurrences) have been proposed, and tested on a limited set of developmental outcomes (Marini et al., 2020; Dunn et al., 2019; 2018), these models have not been adequately examined on key cognitive outcomes e.g., executive function tasks. To the best of my knowledge, only Dunn et al., 2018, elaborately tested these models on recognition of facial emotion.

In the current study, I attempted to address these limitations by examining a rich measurements of adverse childhood experiences using a combination of specificity approaches and dimensional model of adversity (McLaughlin et al., 2021; McLaughlin and Sheridan, 2016). Specifically, latent class analysis was used to classify participants into adversity subgroups based on their response patterns of adversity exposure. The value of using dimensional model (e.g., latent class) lies in its ability to expose the dominant pattern of childhood adversity exposure. Rarely do individuals exposed to one adversity type not also report, at least, another type of adversity. Studying adversity using specificity approach is suitable for investigating a single adversity type in isolation. That is, when individuals in a population are reporting only a single type of adversity. In practice, this is not robust as some other adversity types are left out. Studying multiple adversity types separately will help but not completely solve this problem. Thus, latent class analysis is one technique that could provide insight into the pattern of responses among those reporting multiple adversity types, so that closely related adversities cluster together. In addition to examining the subgroups of adversity, the study also probes the specific effects of individual types of adversity. By using both specificity and dimensional approaches, I can compare the effects of individual adversity types in relation to the clusters or classes in which they co-occurred, as well as disentangle the specific mechanism through which adversity generally affects cognitive functioning. Second, guided by the theoretical models of sensitive periods and accumulation, I examine the timing effects of adversity exposure on cognitive functioning. To achieve this, I used structured life

course modelling approach (SLCMA; Smith et al., 2021; Marini et al., 2020; Dunn et al., 2018; Dunn et al., 2019) to examine the time of exposure in which adversity is likely to have the greatest effect on cognitive functioning. By using SLCMA, the study can also directly compare the two theoretical models and determine whether sensitive periods or accumulation model best explains the observed variability between childhood exposure and cognitive functioning. Sensitive period hypothesis assumes that for every observed effect of childhood adversity on cognitive outcomes, a greater portion of the variance will be explained by a particular time of the adversity exposure. This particular time of (adversity) exposure in our study could be between 8 months to 8.7 years when exposure to adversity was reported. Accumulation hypothesis on the other hand argues that it is the number of times an individual was exposed to adversity across these exposure timepoints that would explain the most variance in the observed effects between adversity exposure and cognitive outcomes. It is important to note that latent classes cannot be used to examine SLCMA as there are typical assumptions that must be met before analysis of SLCMA can take place. e.g., use of dichotomized manifest variables. These manifest variables must be measured across multiple timepoints from which SLCMA model can examine which specific timepoint (sensitive period) or accumulation model had the greatest explanatory power for the observed effect. Full methodological and statistical description of SCLMA has been detailed elsewhere (Smith et al., 2021). Previous studies that have tested these theoretical models on other health outcomes have shown that sensitive period models explained more of the observed effects than the accumulation models (Marini et al., 2020; Dunn et al., 2019). Therefore, it is crucial to see if these findings can be replicated on cognitive outcomes. Replicating these findings on cognitive outcomes will lead to a holistic appreciation of the impact of timing of adversity exposure on broader range of outcomes and specifically, provide a more informed knowledge to better support children who may be at high risk during these important developmental stages.

Thus, using the Avon longitudinal study of parents and children (ALSPAC), a population cohort study (Wolke et al., 2009), the following research questions were specifically addressed;

1. Can adverse childhood experiences be classified into distinct classes or profiles?
2. Do distinct adversity classes have differential effects on different facets of cognitive functioning in later life?
3. What are the independent effects of each adverse childhood experiences on cognitive outcomes, taking into account the timing of exposure and the theoretical models of sensitive periods and accumulation?

The current study benefits from a large longitudinal panel data, as well as multiple adversity and cognitive measures which will not only provide an informed understanding of the nuanced effects of adversity but also help demystify the effect of timing of adversity exposure on cognitive outcomes. More importantly, it will enable a direct comparison between previously used measurement models (specificity vs dimensional approaches) as well disentangle between two popular but largely untested theoretical models (sensitive periods vs accumulation) to provide a better insight into whether specific timing of adversity exposure or greater number of adversity occurrences best explains the observed variability between childhood adversity and cognitive functioning. Given previous studies (McLaughlin et al., 2021; McLaughlin and Sheridan, 2016), I hypothesize the existence of, at least, four adversity classes that include the dimensions of threat, deprivation, low adversity and global or pervasive adversity. I also hypothesize that adversity will have differential effects on different facets of cognitive functioning (e.g., impair inhibition and positive emotions but improve working memory and recognition of negative emotions) and these effects will vary according to different adversity subgroups.

3.2 Methods

3.2.1 Participants

Data came from the Avon longitudinal study of parents and children (ALSPAC; Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019), a multi-wave population cohort study that prospectively sampled mothers living in the Avon county, United Kingdom. A pre-birth cohort of 14,541 pregnant women residing in Avon with the expected delivery between 1 April 1991 to 31st December 1992 accepted to participate in the study designed to investigate the influence of environmental risk factors on the health and development of children. Data from mailed questionnaires and clinic visits were routinely obtained at regular intervals, of which 75% of participants completed at least one follow up. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The data dictionary of the ALSPAC study website has full details of all the data that are available at every assessment wave (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

The final analytic sample in this study consists of 2,965 participants (Male = 1,125; Female = 1,840) whose mothers responded to a set of childhood adversity measures between 8 months to 8.7 years and who at age 24 visited the clinic and completed three cognitive measures of stop signal task (inhibition), N-back task (working memory) and emotional recognition task.

3.2.2 Measures

Childhood adversity: 11 types of childhood adversity that have been extensively examined in the ALSPAC cohort (Dunn et al., 2018; 2019; Anderson et al., 2018; Soares et al., 2017; Lawn et al., 2018; Bowen & Nowicki, 2007; Jensen et al., 2015) were used in the study. They include the following;

1. *Physical abuse:* Assessed at 7 timepoints (1.6 years, 2.6 years, 3.6 years, 4.9 years, 5.9 years, 6.9 years, 8.7 years), mothers responded to whether their child has been physically hurt by anyone. Exposure to physical abuse at any of the assessment wave was coded 1, otherwise 0.

2. *Sexual abuse:* Mothers responded to whether their child has been abused by anyone at any time from 1.6 years to age 8.5 years. Assessments were taken at 7 timepoints (1.6 years, 2.6 years, 3.6 years, 4.9 years, 5.9 years, 6.9 years, 8.7 years), with exposure coded 1 and non-exposure coded 0.

3. *Inconsistent caregiving:* When participants were aged 1.6 years, 2.6 years, 3.6 years, 4.9 years, 5.9 years, 6.9 years, 8.7 years (7 timepoints), mothers were asked if the main career of their child has changed since time of last assessment. A positive response was coded 1 at each assessment timepoint and taken as an indicator of inconsistent caregiving.

4. *Family instability:* Family instability was measured by questions asking mothers if their child was (a) taken into care (b) separated from the mother > one week (c) separated from the father > one week (d) acquired a new parent. These questions were obtained at 7 timepoints (1.6 years, 2.6 years, 3.6 years, 4.9 years, 5.9 years, 6.9 years, 8.7 years).

Exposure to any of these events at any assessment point was coded 1 and taken as an indicator of family instability.

5. *Caregivers' abuse:* Parental physical or emotional abuse was assessed at 6 timepoints (8 months, 1.9 years, 2.9 years, 3.11 years, 5.1 years, 6.1 years) and respondents were asked (a) you were physically cruel to your children (b) your partner was physically cruel to your children (c) you were emotionally cruel to your children (d) your partner was emotionally cruel to your children. Exposure to any of these questions at any assessment timepoint was coded 1 to indicate exposure to caregivers' abuse, otherwise coded 0 to indicate non-exposure.

6. *Maternal psychopathology:* Maternal psychopathology was assessed with three different indices: 1. Crown-Crisp Experimental Index (CCE1; Crown & Crisp, 1979) which has both anxiety and depression subscales; 2. Edinburgh Postnatal Depression Scale (EPDS; Cox, Holden, & Sagovsky, 1987). These two questionnaires were administered at 3 timepoints (8 months, 1.9 years, 2.9 years). The third measure of maternal psychopathology was a question on suicide attempts obtained at 6 timepoints (8 months, 1.9 years, 2.9 years, 3.11 years, 5.1 years, 6.1 years). Following the threshold established in previous ALSPAC studies (Dunn et al., 2018), participants were coded to be exposed to maternal psychopathology at any assessment point if the mother reports any of (a) CCEI anxiety subscale score greater than 10 (b) CCEI depression subscale score greater than 9 (c) EPDS score greater than 12 (d) suicidal attempt since last assessment time.

7. *Maternal victimization*: Mothers were asked if their partner was physically or emotionally cruel to them. A positive response to either question was coded 1 and taken as indicator of exposure to maternal victimization. These questions were obtained at 6

timepoints when participants were aged 8 months, 1.9 years, 2.9 years, 3.11 years, 5.1 years, 6.1 years.

8. *Parental legal problems*: Mothers were asked if they had been in trouble with the law or if their partner had been in trouble with the law at different 6 timepoints (when the child was aged 8 months, 1.9 years, 2.9 years, 3.11 years, 5.1 years, 6.1 years). A positive response to either of the questions at any timepoint was coded 1 and served as indicator of exposure to parental legal problem.

9. *Parental separation or divorce:* Mothers were asked if they had either separated or divorced from their partners at any of the 6 timepoints: 8 months, 1.9 years, 2.9 years, 3.11 years, 5.1 years, 6.1 years. A positive response to either question at any assessment timepoint was coded 1 and taken as indicator of exposure to parental separation.

10. *Financial distress:* When participants were aged 8 months, 1.9 years, 2.9 years, 5.1 years, 7.1 years (5 timepoints), mothers were asked on a scale of 1- 4 (1 = not difficult; 2 = slightly difficult; 3 = fairly difficult; 4 = very difficult), the degree to which they find it difficult to afford (a) food (b) cloth (c) heat (d) rent (e) items for child. In line with the threshold established by Dunn et al., 2018, participants were coded 1 if at any timepoint, their mothers reported slight difficulty in affording at least three or more of child's items.

11. *Neighbourhood stress*: When participants were aged 1.9 years and 2.9 years, mothers were asked to indicate on a scale of 0-2 (0 = no problem; 1 = minor; 2 = serious problem) the following problems in their homes (a) noise from other homes (b) noise from the street (c) rubbish dumped (d) vandalism (e) burglaries (f) mugging (g) disturbance from the youths. A total score 8 and above (corresponding to 95th percentile) was coded 1 and served as indicator of exposure to neighbourhood stress.

These adversity measures described above were obtained from questionnaires mailed to mothers when participants were between 8 months to 8.7 years. Each adversity type was assessed between 2 to 8 timepoints. Exposure to each adversity type at each timepoint was initially coded 1, or 0 if no exposure was reported to have occurred at the assessment timepoint. To examine exposure to adversity across childhood, each adversity type was recoded across all timepoints, rather than at each timepoint. That is, each adversity type was coded 1, if participant was reported to have been exposed at any of the assessment timepoint, otherwise participant with no exposure at any of the assessment timepoints was coded 0. Additionally, to examine the theoretical models of sensitive periods and accumulation, the adversity data was remodelled accordingly. Sensitive periods hypothesis assumes that childhood adversity has developmental time-dependent effects on outcomes. Thus, for each type of adversity assessed, exposure to adversity types was modelled at each assessment timepoints (1 = exposed; 0 = non-exposed) to determine the effects of adversity timing ranging from 8 months to 8.7 years. Accumulation on the other hand, involved the summed number of exposure to each adversity type reported across all the assessment timepoints.

Cognitive measures: At age 24, participants in the study attended a clinic session and completed three computerized cognitive battery, namely stop signal task (Logan et al., 1984), N-back task (Kirchner, 1958) and emotion recognition task (Penton-Voak et al., 2012). These cognitive data were collected and managed by REDCap electronic data capture tools (Harris et al., 2009). By using multiple cognitive measures, I can examine whether the effect of adversity is limited to a more executive driven mechanism (e.g. N-back and stop signal task) or also extends to general affective processing (emotion recognition task). Prior to the main assessment, participants completed practice trials to familiarize themselves with the cognitive tasks described below:

Stop signal task: This is a measure of inhibition which assesses the ability to withhold prepotent responses. The task consists of two trial blocks. In the first block of the initial "go" trials, participants were shown a fixation cross at the centre of the screen, followed by the letter "X" or "O". They were asked to press the left arrow of their keyboard whenever the letter "X" appears or the right arrow when "O" appears. In the second trial block, the procedure is the same as the first, except that the "stop signal" is introduced in 25% of the trials. This involves a random loud audio bleeps following the presentation of the letter "X" or "O". Participants were asked to withhold their responses whenever they hear the bleep. An estimate of stop signal reaction time (SSRT) was derived as the primary dependent outcome with higher scores indicating poorer inhibitory control (See Logan, 1984). However, participants scores were reverse coded, so that higher values indicate better performance.

N-back Task: Widely used as a measure of working memory, participants in this study completed the N-back task that requires them to monitor a series of stimuli (consisting of letters and numbers) presented on the screen and respond by pressing 1 on the keyboard whenever a stimulus presented match the one presented in two trials earlier or press 2 whenever the stimulus is different. The task consists of 48 experimental trials with 8 targets of matching trials. The derived discriminability (d') score was the primary dependent outcome with higher scores indicating higher net accuracy and better working memory ability.

Emotional recognition task. Here, participants were asked, across 96 trials, to correctly identify a given displayed emotion from possible 6 basic emotions of happiness, sadness, surprise, anger, fear and disgust. On each trial, a facial image is shown on the screen for 200ms and participants were asked to select from the 6 options, the emotion that best describes the

displayed face. Each emotion type was presented for 16 times and varied in intensity i.e. low and high intensities. The primary dependent outcome in this task is the sum of correctly identified emotions in the total trials. The scores for each emotion sub-types were also obtained. Higher scores indicate better performance and greater ability to identity emotions in facial expressions.

3.2.3 Missing data

In the ALSPAC study and as previously reported, participants from disadvantaged households were more likely to skip follow-ups (Wolke et al., 2009), thus to deal with this issue, I used multiple imputation available in the MICE package in R (Buuren & Groothuis-Oudshoorn, 2011) to account for missing adversity data. Cognitive data was not imputed as only participants with complete cognitive data were selected in the final analytic sample.

3.2.4 Analyses

To address the three research questions, five statistical analyses were carried out, namely, latent class analysis, latent class regression, zero-order correlation, multivariate regression and structured life-course modelling approach (SLCMA). All analyses were carried out in R (Team, 2019) and R studio version 3.6.3.

First, I used latent class analysis to answer the first research question of whether childhood adversity can be classified into discrete classes or subgroups. Latent class analysis is a multivariate technique which can classify response patterns across categorical data into

classes or clusters, using probability profile across each possible response. Participants (N=2,965) binarized scores (ever exposed = 1 vs never exposed = 0) of childhood adversity exposure were initially entered into poLCA package (Linzer & Lewis, 2011). To determine the best *N* class that explains the data, initial exploratory models for class 1 to class 8 models were carried out. Class 5 model was preferred because it yielded comparatively better estimates of BIC and entropy after 50 repetitions at 5000 iterations per model (see Table 3.1 and Figure 3.1).

Second, to test the second research question of whether the adversity classes can predict differential cognitive performance, participants scores in the cognitive tasks were added as covariates in the latent class analysis. This is known as latent class regression in which the probability of class membership is predicted by scores of SSRT, N-back task and total emotion correctly identified.

Third, to examine the independent effect of each 11 adversity types on cognitive outcomes, taking into account the theoretical models of sensitive periods and accumulation, a zero-order correlation analysis was first conducted before fitting a multivariate regression model. I conducted zero-order correlation and multivariate regression analyses to establish evidence of associations between the 11 adversity types and cognitive outcomes before I used SLCMA to test whether sensitive periods or accumulation hypothesis better explain these associations. To test zero-order correlation and multivariate regression, the binarized scores of 11 childhood adversity types were entered as predictors and the scores of all cognitive outcomes including scores of the 6 sub-types of emotion, as the outcomes. Lastly, to account for the effect of timing in explaining the observed association between each adversity type and cognitive outcomes, a structured life course modelling approach (SLCMA) was modelled. By fitting SLCMA, I can compare the two competing theoretical models of sensitive periods (before age 3 = Very early childhood, 3-5 = Early childhood, 6-8 = middle childhood) and

accumulation to determine which of them best explain the observed association between each adversity type and all cognitive outcomes. As noted in past literature, SLCMA uses least angle regression (LAR) and covariate test to identify the single model (or potentially more than one combination models) that has the highest parsimonious explanation for the observed outcome variation. In this analysis, the binarized scores for each 11 adversity types at all assessment timepoints were modelled as the predictors and all the cognitive scores, as the outcomes. LAR was then able to identify for each adversity type, the assessment timepoint (or the theoretical model) with the strongest association with the cognitive outcome, thus able to identify whether sensitive periods or accumulation model best explained variation in each cognitive outcomes.

For all analyses, a nominal significance threshold of $\alpha = .05$ was applied, but given the sample size and study design, focus on descriptions of result wherever appropriate.

Table 3.1

Exploratory latent class analysis involving 1-8 class models to determine the optimal class solution

	BIC	Entropy
Model 1	29661.23	NAN
Model 2	27487.36	0.7887366
Model 3	27391.71	0.7550159
Model 4	27346.83	0.8235624
Model 5	**27304.43**	**0.822617**
Model 6	27356.97	0.8527311
Model 7	27414.43	0.8473717
Model 8	27471.22	0.8645015

BIC = Bayesian information criterion. Note: A combination of fit indices were used to determine the optimal class model with the class solution with lowest BIC value and relatively higher entropy score preferred.

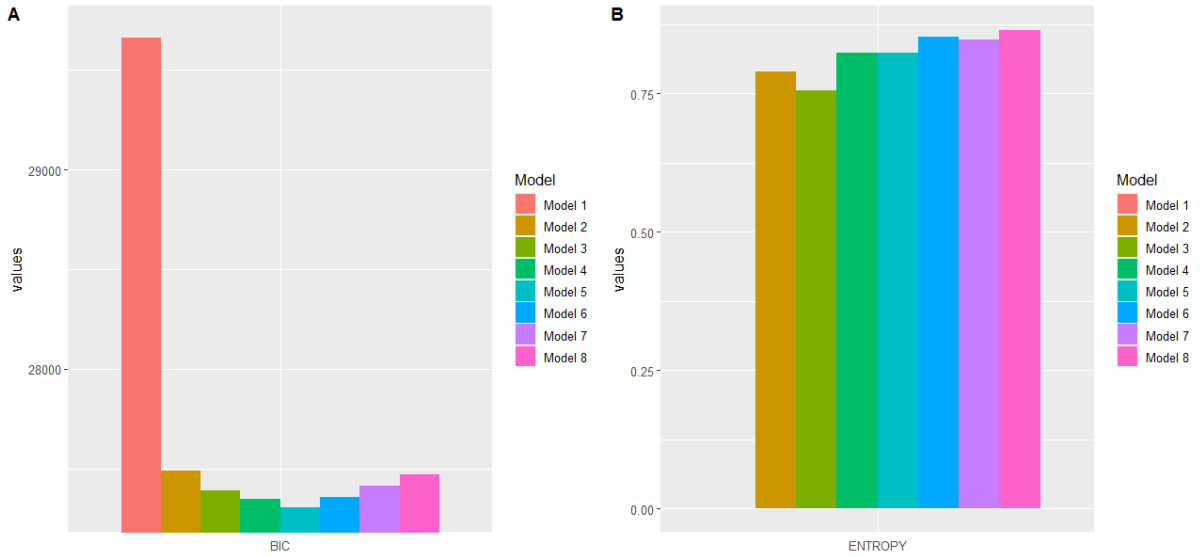


Figure 3.1: Shows the fit indices of the exploratory latent class analysis for model 1- model 8. Panel A = BIC scores. Panel B. Entropy scores. Class 5 solution was preferred because it yielded lowest BIC value with relatively high entropy score.

3.2.5 Deviations from pre-registration

The research questions and analytic strategies (e.g. latent class analysis, latent regression, multivariate regression and zero-order correlational analysis) were specified in a pre-registration document here https://osf.io/5dxqm/. However, the analytic strategies employed in this study deviated from the pre-registration in three major ways. First, aside the main statistical analyses specified in the pre-registration, an additional structured life-course modelling approach (SLCMA) was performed to account for the effects of timing of adversity exposure. This additional analysis enabled a clearer understanding of the theoretical importance of timing of adversity exposure and addressed the question of whether sensitive periods or accumulation model best explained the observed association between childhood adversity and cognitive functioning. Second, contrary to the pre-registered strategy of summing the adversity exposure across all assessment timepoints for each adversity type, adversity exposure was rather

binarized (exposed = 1; not exposed = 0) in line with previous ASLAPAC studies (Dunn et al., 2016, 2018, 2019). This binarized format is more statistically compatible with latent class analysis as the continuous variable format of the cumulative approach specified in the pre-registration would have saturated the model and made it more difficult to interpret. Lastly, it was specified in the pre-registration that all available sample would be used in the analyses. This is relatively vague and would have involved 4 different subsamples i.e. participants who had data on adversity measures between 8 months to 8.7 years, as well as different samples of respondents who completed either stop signal task, n-back task and emotion recognition task at age 24. Rather, the final analytic sample consists of 2,965 participants whose mothers responded to a set of adversity measures at 8 months (the first timepoint) and who at age 24, completed all three cognitive tasks used in the study.

3.2.6 Data availability

To access the supporting data for this study, please contact ALSPAC team http://www.bristol.ac.uk/alspac/researchers/access/. However, the R scripts for the analyses are available on request https://osf.io/5dxqm/

Table 3.2

Number and (percentage) of exposure to childhood adversity across childhood and at different assessment timepoints in the study sample.

	Childhood (8months – 8.7 years)	8 months	1.3 – 1.9 years	2-6 - 2.9 years	3.6 – 3.11 years	4.9 years	5.1 – 5.9 years	6.1 – 7.1 years	8.7 years
Physical abuse	470 (15.9%)	-	72 (2.4%)	93 (3.1%)	96 (3.2%)	137 (4.6%)	96 (3.2%)	80 (2.7%)	116 (3.9%)
Sexual abuse	29 (.9%)	-	0 (0%)	1 (.03%)	5 (.17%)	7 (.2%)	13 (.4%)	8 (.2%)	5 (.1%)
Inconsistent caregiving	736 (24.8%)	-	236 (8%)	235 (7.9%)	213 (7.2%)	203 (6.8%)	110 (3.7)%	79 (2.7%)	70 (2.4%)
Family instability	1487 (50.2%)	-	368 (12.4%)	649 (21.9%)	609 (20.5%)	433 (14.6%)	372 (12.5%)	286 (9.6%)	293 (9.8%)
Caregivers abuse	426 (14.4%)	78 (2.6%)	93 (3.1%)	94 (3.2%)	120 (4%)	-	173 (5.8%)	192 (6.5%)	-
Maternal psychopathology	661 (22.3%)	229 (7.7%)	310 (10.5%)	431 (14.5%)	8 (.2%)	-	9 (.3%)	12 (.4%)	-
Maternal victimization	721 (24.3%)	205 (6.9%)	226 (7.6%)	315 (10.6%)	236 (8%)	-	283 (9.5%)	245 (8.3%)	-
Parental legal problems	248 (8.4%)	24 (.81%)	47 (1.6%)	60 (2%)	83 (2.8%)		76 (2.6%)	55 (1.9%)	-
Parental separation/divorce	497 (16.8%)	82 (2.8%)	116 (3.9%)	168 (5.7%)	156 (5.3%)		190 (6.4%)	178 (6%)	-
Financial distress	676 (22.8%)	316 (10.7%)	300 (10.1%)	318 (10.7)	-	-	199 (6.7%)	149 (5%)	-
Neighbourhood stress	527 (17.8%)	361 (12.2%)	353 (11.9%)	-	-	-	-	-	-

Note: Exposed = 1; Not exposed = 2. Values in the table represent the proportion of participants exposed to different adversity types across childhood and at different assessment timepoints. Participants are coded to be exposed to adversity across childhood (8 months – 8.7 years) if exposure at any of the assessment timepoints was reported.

Table 3.3

Pearson correlation coefficients between the adversity variables in the study sample.

Variables	1	2	3	4	5	6	7	8	9	10	11
1. Physical abuse	-										
2. Sexual abuse	.14 ***	-									
3. Inconsistent caregiving	.09***	.02	-								
4. Family instability	.12***	.07***	.12***	-							
5. Caregivers abuse	.23***	.14***	.09***	.17***	-						
6. Maternal psychopathology	.16***	.09***	.04*	.12***	.24***	-					
7. Maternal victimization	.16***	.10***	.10***	.21***	.44***	.23***	-				
8. Parental legal problems	.16***	.13***	.06***	.14***	.23***	.15***	.24***	-			
9. Parental separation/divorce	.11***	.13***	.05**	.29***	.26***	.18***	.42***	.30***	-		
10. Financial distress	.10***	.09***	.00	.12***	.19***	.24***	.21***	.20***	.30***	-	
11. Neighbourhood stress	.14***	.08***	.00	.10***	.15***	.16***	.16***	-16***	.14***	.26***	-

Note: N = 2965; *** = significant at p<0.001; ** = significant at p<0.01; * = significant at p<0.05.

3.3 Results

3.3.1 Descriptive results

Descriptive results displayed in Table 3.2 show the proportion (number and percentage) of participants exposure to different adversity types across assessment timepoints as well as Pearson correlations between different adversity types (Table 3.3). I present below the results of tests of my research questions.

3.3.2 Can childhood adversity be classified into distinct classes?

To answer the first research question of whether childhood adversity can be classified into discrete classes, participants (N=2,965) scores of all 11 adversity types were entered into latent class analysis. The adversity measures were binarized to indicate exposure to each 11 adversity types across childhood (1 = ever exposed, 0 = never exposed). An initial exploratory analysis involving class 1-8 models was conducted to determine the optimal class solution. Class 5 model emerged the most optimal and interpretable class solution with better fit indices (lowest BIC score and relatively high entropy value). See Table 3.1 and Figure 3.1. Next, I inspected the population shares and the prevalence of exposure to each adversity measure, for each 5 latent classes as well as any unique profiles or characterizations that define the classes.

Table 3.4					
An estimated class-conditional response probability for 5 adversity classes.					
Adversity types	Class 1 (Low adversity)	Class 2 (Dysfunctional family)	Class 3 (Parental deprivation)	Class 4 (Family Poverty)	Class 5 (Global adversity)
Physical abuse	8.99	37.86	17.27	17.91	68.06
Sexual abuse	0.14	0.82	1.27	1.20	17.42
Inconsistent caregiving	21.92	39.15	30.94	8.67	49.01
Family instability	39.89	59.28	91.78	57.66	95.61
Caregivers' abuse	1.47	53.14	33.10	14.36	85.14
Maternal psychopathology	10.78	47.68	34.19	52.39	69.37
Maternal victimization	6.86	61.72	76.90	28.84	89.87
Parental legal problems	2.90	8.90	22.29	12.04	71.89
Parental separation/divorce	3.38	0.00	100	31.41	89.73
Financial distress	10.26	21.92	38.11	97.02	84.71
Neighbourhood stress	9.86	25.04	17.55	60.14	65.28
Note: Values (%) represent the percentage probability that participants in each adversity classes respond to being exposed to the different adversity measures.					

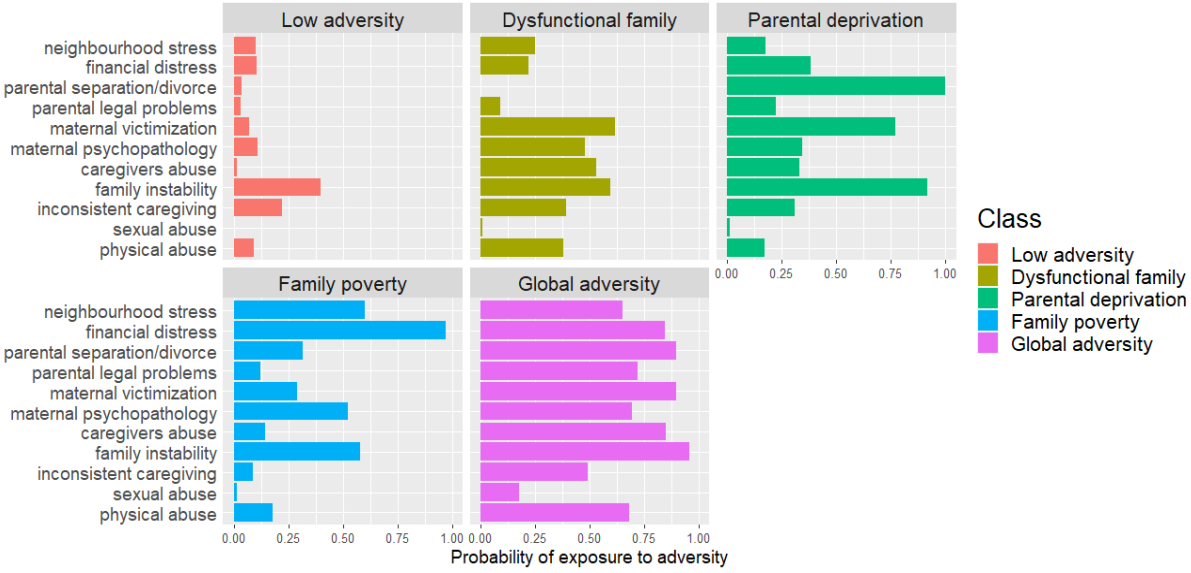


Figure 3.2: Latent class analysis showing the five adversity classes and the corresponding class-conditional response probability for all the adversity measures.

Class 1 (Figure 3.2, top left), referred to as "*low adversity*", consists of 71.6% of the population. Members in this class have very low probability of being exposed to any of the 11

adversity measures with only less than 11% probability of exposure in all adversity measures except inconsistent caregiving (21%) and family instability (39%). Class 2 (Figure 3.2, top centre), made up of 9.58% of all participants is referred to as "dysfunctional family" because members have medium to high probability of exposure to one or more adversity measures characterized by dysfunctional family rearing. Specifically, members in this class reported relatively high probability of exposure to family instability (59%), caregivers' abuse (53%), maternal psychopathology (47%), maternal victimization (61%) and inconsistent caregiving (39%). Class 3 (Figure 3.2, top right) consists of 9.65% of the population. I refer to this class as "*parental deprivation*" because members uniformly responded to being exposed to parental divorce or separation (100%) as well as extremely high probability of exposure to family instability (91%) made up of the following variable questions: child separated from mother or father; child taken into care; child acquired new parent. I called class 4 (Figure 3.2, bottom left) "*family poverty"* because participants responded extremely high to exposure to adversity measures designed to capture various degrees of socioeconomic disparities and financial deprivation. Consisting of 6.07% of the total samples, members in this class have 97% and 60% probability of exposure to financial distress and neighbourhood stress respectively. Lastly, Class 5 (Figure 3.2, bottom right) is referred to as "*global adversity*" because members in this class (3.1%) have very high probability of being exposed to all the adversity measures in this study. Probability of exposure to adversity measures in this class range from 17% (sexual abuse) to 95% (family instability). See Table 3.4 for all the class-conditional response probability for the adversity exposures in the 5 adversity classes. Taken together, these findings provide additional strong empirical evidence of classes or dimensions of adversity which have been theoretically classified in previous literature.

3.3.3 Do adversity classes predict differential cognitive performance?

To address the second research question of whether discrete adversity classes predict differential cognitive performance, I modelled a latent class regression.

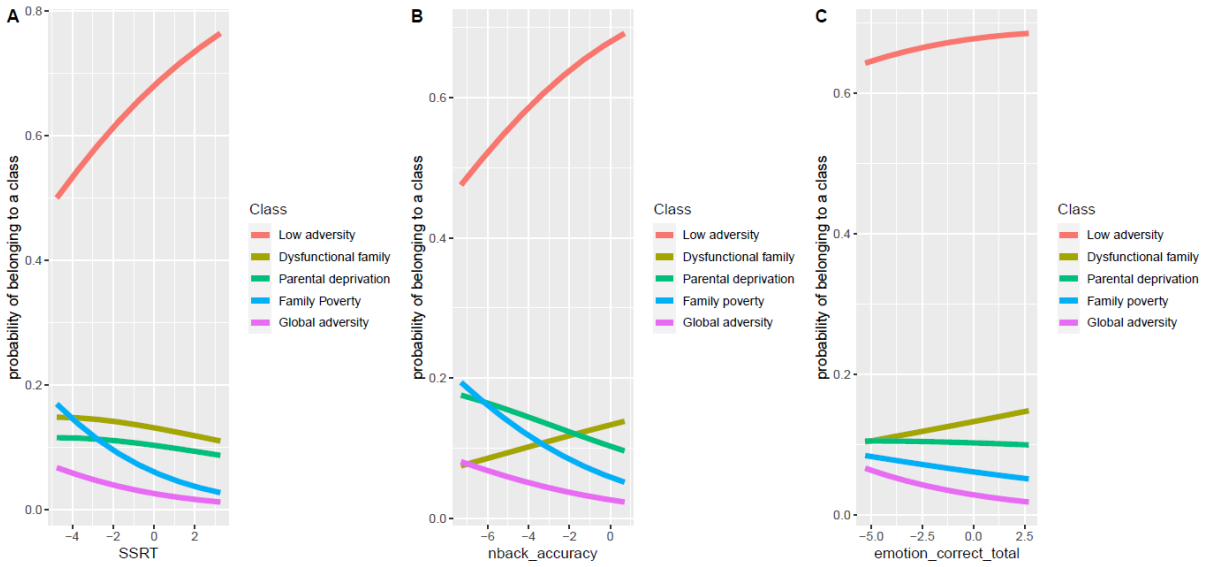


Figure 3.3: Plots of latent class regression in which the probability of belonging to a discrete class membership is predicted by cognitive performance in SSRT (Panel A), N-back task (Panel B) and total emotion correctly identified (Panel C).

To do this, I simultaneously fit each of the three cognitive outcomes (scores of SSRT, N-back and total emotion correctly identified) as covariates into latent class analysis. This approach known as latent class regression, uses these covariates (participants scores in cognitive outcomes) to predict the probability of belonging to discrete class membership. Against a reference low adversity class, results (Figure 3.3 and Table 3.5) revealed that performance in inhibition measured by SSRT predicted the probability of membership to family poverty class (family poverty vs low adversity: beta = -0.282, p = 0.010) but not any other classes (dysfunctional family vs low adversity: beta = -0.090, p = 0.204; parental

deprivation vs low adversity: beta = -0.088, p = 0.204; global adversity vs low adversity: beta = -0.267, p = 0.064). Similarly, performance in working memory measured by N-back task predicted the probability of membership to family poverty (family poverty vs low adversity: beta = -0.213, p = 0.020) but not dysfunctional family (dysfunctional family vs low adversity: beta = 0.030, p = 0.714), parental deprivation (parental deprivation vs low adversity: beta = -0.123, p = 0.057) and global adversity (global adversity vs low adversity: beta = -0.204, p = 0.136). On the other hand, relative to low adversity class, participants' performance in the emotion recognition task did not predict any discrete class membership (dysfunctional family vs low adversity: beta = 0.037, p = 0.602; parental deprivation vs low adversity: beta = -0.015, p = 0.838; family poverty vs low adversity: beta = -0.071, p = 0.532; global adversity vs low adversity: beta = -0.171 , p = 0.231).

Table 3.5

Parameter estimates of latent class regression in which the probability of class membership is predicted by cognitive performance in inhibition, working memory and emotional recognition.

	beta	SE	t	p
Inhibition (SSRT)				
Dysfunctional family vs low adversity	-0.090	0.071	-1.272	0.204
Parental deprivation vs low adversity	-0.088	0.069	-1.270	0.204
Family poverty vs low adversity	-0.282	0.110	-2.568	0.010
Global adversity vs low adversity	-0.267	0.144	-1.851	0.064
Working memory (N-back)				
Dysfunctional family vs low adversity	0.030	0.082	0.367	0.714
Parental deprivation vs low adversity	-0.123	0.064	-1.904	0.057
Family poverty vs low adversity	-0.213	0.091	-2.337	0.020
Global adversity vs low adversity	-0.204	0.136	-1.494	0.136
Total emotion				
Dysfunctional family vs low adversity	0.037	0.071	0.521	0.602
Parental deprivation vs low adversity	-0.015	0.073	-0.205	0.838
Family poverty vs low adversity	-0.071	0.114	-0.625	0.532
Global adversity vs low adversity	-0.171	0.143	-1.199	0.231

Note: SSRT = stop signal reaction time; SE = standard error; class 1 = low adversity; class 2 = dysfunctional family; class 3 = parental deprivation; class 4 = family poverty; class 5 = global adversity

As displayed in Figure 3.3, there is an increasing performance in inhibition (SSRT) as the probability of belonging to low adversity class increases. When compared to low adversity, performance in inhibition increases as the probability of belonging to family poverty class decreases. Along similar lines, there is an increasing performance in working memory (N-back) as the probability of belonging to low adversity class increases. Against this reference class (low adversity), performance in working memory increases as the probability of belonging to family poverty decreases. Performance in emotion recognition task did not substantially vary to predict class membership. These findings suggest that cognitive performance in inhibition (SSRT) and working memory (N-back) varied substantially to predict adversity latent classes specific to low adversity class, and family poverty class.

3.3.4 What are the independent effects of each adversity measures, taking into account the timing of exposure?

To examine the third research question of the independent effects of each adversity measures, I first present in Table 3.6, the result of zero-order correlation involving the binarized scores (ever exposed = 1 vs never exposed = 0) of the 11 adversity measures and all cognitive scores, including the 6 emotion sub-types. To control for the effects of shared variance explained by other adversity predictors, I then fit a multivariate regression model. Results of multivariate regression analysis displayed in Table 3.7 and Figure 3.4a-3.4c revealed that exposure to sexual abuse was associated with poorer performance in inhibition ($\beta = -0.450$, $p = 0.018$) and emotion recognition (total emotion: $\beta = 0.619$, $p = 0.001$; surprise: $\beta = -0.637$, $p<0.001$; anger: $\beta = -0.413$, $p = 0.030$). Exposure to inconsistent caregiving on the other hand was associated with higher performance in working memory ($\beta = 0.125$, $p< 0.001$) and emotion recognition (total

emotion: β = 0.157, p< 0.001; fear: β = 0.126, p = 0.003; anger:β = 0.127, p = 0.003). Exposure to family instability (β = -0.080, p = 0.039) and financial distress (β = -0.132, p =0.006) were both associated with poorer inhibition while exposure to parental separation or divorce (β = -0.115, p = 0.002) was associated with poorer working memory. All other adversity measures yielded little evidence of significant association with cognitive outcomes. To justify the criticism against specificity approach of adversity study, I then compared the results of zero-order correlation and multivariate regression. Result of zero-order correlation showed that neighbourhood stress, for example, was negatively associated with both inhibition and working memory but after controlling for all the adversity variables in the multivariate regression, these significant associations disappeared. This suggests that the effects were driven by the shared variance with financial distress from which neighbourhood stress co-occurred in "family poverty" class in the latent class analysis. Several other significant associations in the zero-order correlation analysis could not hold after controlling for other adversity effects in the multivariate regression (Tables 3.6 & 3.7 or Figure 3.4a-3.4c for full comparison).

Table 3.6

Result of zero-order correlation examining association between binarized (ever exposed vs never exposed) score of each childhood adversity measure and cognitive outcomes

	SSRT	N-back correct	Emotion Total	Happy	Surprise	Fear	Sad	Anger	Disgust
Physical abuse	-0.03	0.00	0.02	-0.02	0.00	0.04*	0.03	0.01	0.00
Sexual abuse	-0.05**	-0.04*	-0.06**	-0.02	-0.06***	-0.03	-0.02	-0.04*	-0.03
Inconsistent caregiving	0.01	0.05**	0.07***	0.02	0.02	0.05**	0.04*	0.06**	0.02
Family instability	-0.05**	-0.01	0.01	0.02	0.01	0.00	0.01	0.02	-0.02
Caregivers abuse	-0.02	-0.01	0.01	-0.01	-0.02	-0.01	0.03	0.01	0.03
Maternal psychopathology	-0.03	-0.02	0.00	0.01	-0.01	0.01	0.01	0.01	-0.02
Maternal victimization	-0.02	-0.04*	-0.02	0.00	-0.02	-0.02	-0.01	-0.02	-0.01
Parental legal problems	-0.02	-0.03	-0.03	-0.01	0.00	-0.04*	0.00	0.00	-0.02
Parental separation/divorce	-0.03	-0.06***	-0.02	0.01	-0.01	-0.03	0.00	-0.02	0.01
Financial distress	-0.07***	-0.06**	-0.03	0.02	0.01	-0.03	-0.05**	-0.01	-0.02
Neighbourhood stress	-0.05**	-0.03	0.00	-0.02	0.02	0.00	0.00	0.00	0.00

Note: *** = significant at p<0.001; ** = significant at p<0.01; * = significant at p<0.05; SSRT = stop signal reaction time.

Table 3.7

Result of multivariate regression analysis examining association between binarized (ever exposed vs never exposed) score of each childhood adversity measure and cognitive outcomes

	SSRT	N-back correct	Emotion Total	Happy	Surprise	Fear	Sad	Anger	Disgust
Physical abuse	-0.027	0.039	0.069	-0.044	0.009	0.123*	0.082	0.011	-0.004
Sexual abuse	-0.450*	-0.322	0.619**	-0.243	-0.637***	-0.264	-0.303	-0.413*	-0.313
Inconsistent caregiving	0.042	0.125**	0.157***	0.047	0.049	0.126**	0.073	0.127**	0.060
Family instability	-0.080*	0.001	0.022	0.034	0.032	0.005	0.020	0.043	-0.052
Caregivers abuse	0.017	0.058	0.079	-0.034	-0.042	-0.010	0.126*	0.061	0.159**
Maternal psychopathology	-0.010	-0.018	0.021	0.029	-0.031	0.032	0.033	0.019	-0.033
Maternal victimization	0.007	-0.050	-0.083	-0.000	-0.024	-0.026	-0.092	-0.056	-0.077
Parental legal problems	0.015	-0.030	-0.101	-0.028	0.012	-0.160*	0.008	0.004	-0.099
Parental separation/divorce	0.007	-0.115*	0.000	0.018	-0.021	-0.040	0.041	-0.054	0.080
Financial distress	-0.132**	-0.083	-0.059	0.058	0.028	-0.054	-0.142**	0.014	-0.044
Neighbourhood stress	-0.078	-0.033	0.023	-0.067	0.082	0.040	0.007	0.002	0.019

Note: *** = significant at p<0.001; ** = significant at p<0.01; * = significant at p<0.05; SSRT = stop signal reaction time.

To determine the effect of timing of these adversity exposures on all cognitive outcomes, I then fit the SLCMA models. By fitting SLCMA, I can examine whether sensitive periods (adversity exposure before age 3 = Very early childhood, 3-5 years = Early childhood, 6-8 years = Middle childhood) or accumulation models best explained the association observed between adversity and cognitive outcomes. In this study, I fit 99 SCLMA models - consisting of each 11 adversity types across all assessment timepoints for each of the 9 cognitive outcomes. That is, each adversity type (e.g. physical abuse by anyone) was modelled with each cognitive outcomes (e.g. inhibition). For each model, I examine the time of adversity exposure or theoretical model (sensitive periods or accumulation) first selected by SLCMA as well as the models within significant threshold ($p<0.05$).

Figure 3.4A

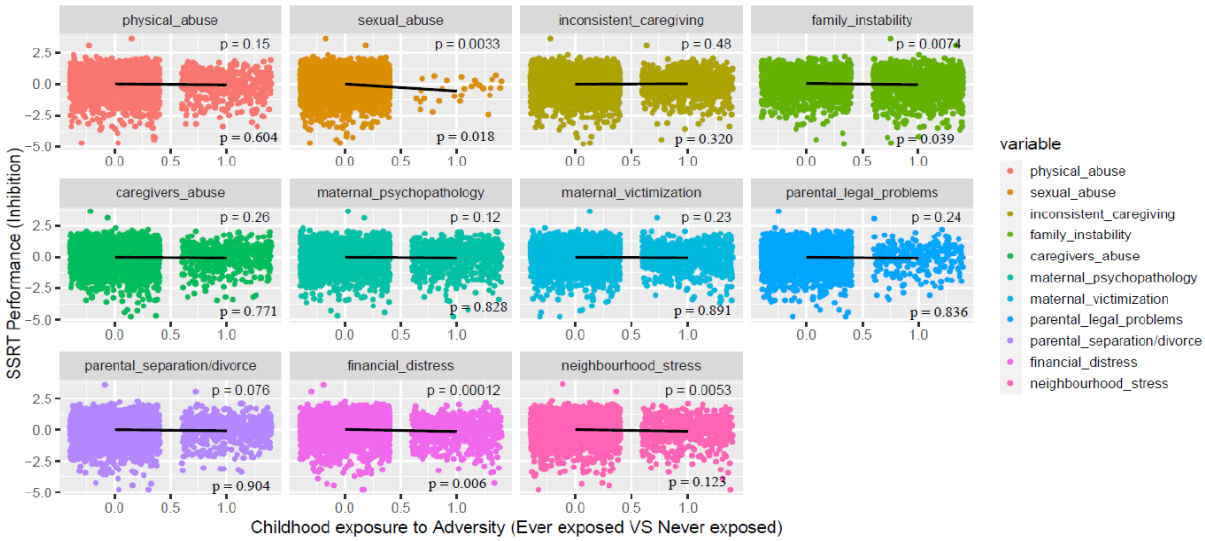


Figure 3.4B

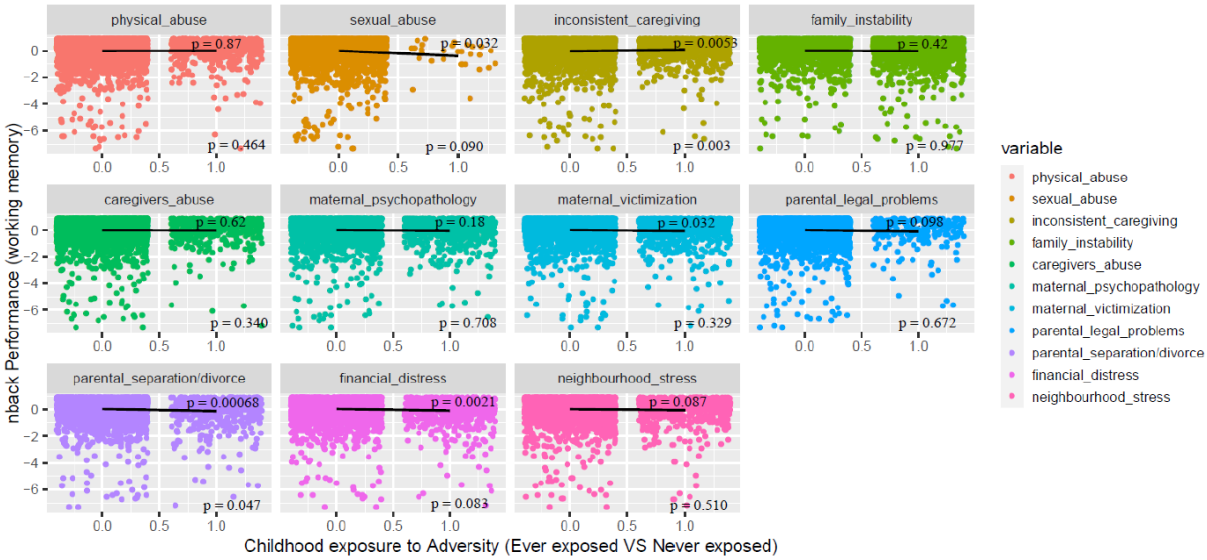
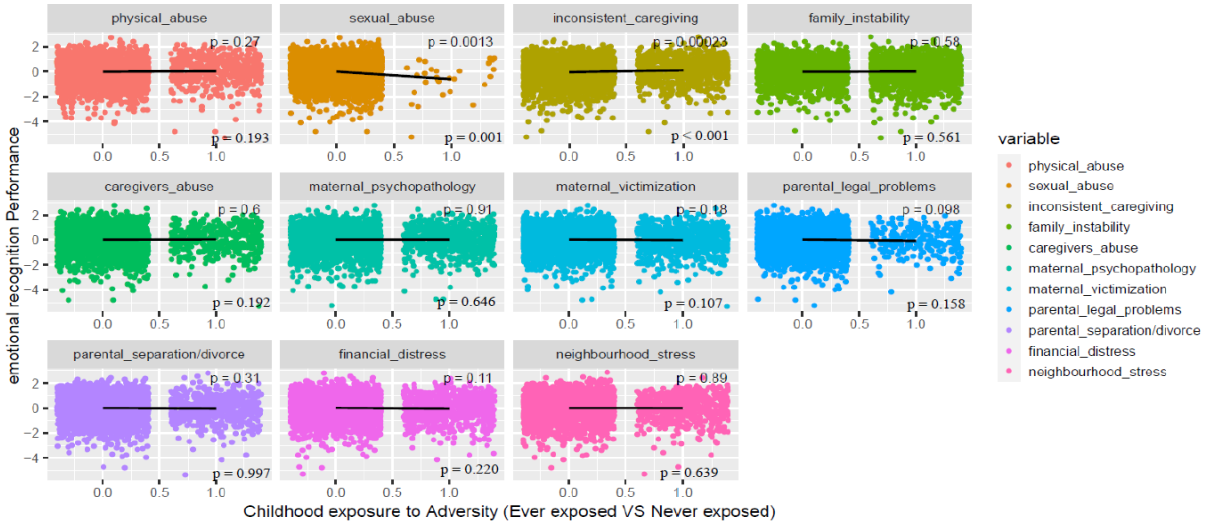


Figure 3.4C



Figures 3.4 A-C shows the association between different childhood adversity measures and cognitive performance in **(A)** inhibition **(B)** working memory **(C)** emotion recognition. PLEASE NOTE: the p-values above the regression lines are the zero-order correlation p values while the p-values below the regression lines are the multivariate regression p-values.

Result of SLCMA shown in Figure 3.5 and Table 3.8 revealed that among the 99 models examined, only 11 of the models first selected by SLCMA reached statistical significance (10 sensitive periods compared 1 accumulation model). Within sensitive periods, very early childhood was first selected in 4 significant models, while early childhood and middle childhood had 5 and 1 significant models respectively. Specifically, exposure to adversity at very early childhood (before age 3) significantly explained greater variability in poorer

working memory performance observed among participants exposed to sexual abuse (age = 2.6 years, p =0.010) and parental separation or divorce (age = 2.9 years, p<0.001) as well poorer performance in the emotion recognition task (total emotions: age = 1.9 years; p = 0.003; fearful emotion: age = 1.9 years, p = 0.016) observed among participants exposed to financial distress. Along similar lines, adversity exposure at early childhood (3-5 years) significantly explained more variability in the association between exposure to maternal psychopathology and poorer recognition of disgust emotion (age = 3.11 years, p = 0.04) while the same timeframe explained greater variability in the higher performance observed among those exposed to inconsistent caregiving in the emotion recognition task: angry faces (age = 3.6 years, p= 0.030), disgust faces (age = 3.6 years, p = 0.039) and total emotions (age = 3.6 years, p = 0.033). On the other hand, variability in poorer SSRT scores was explained by middle childhood exposure among participants exposed to parental separation or divorce (age = 6.1 years, p = 0.026) but accounted for by accumulation model among participants exposed to neighbourhood distress (p = 0.005).

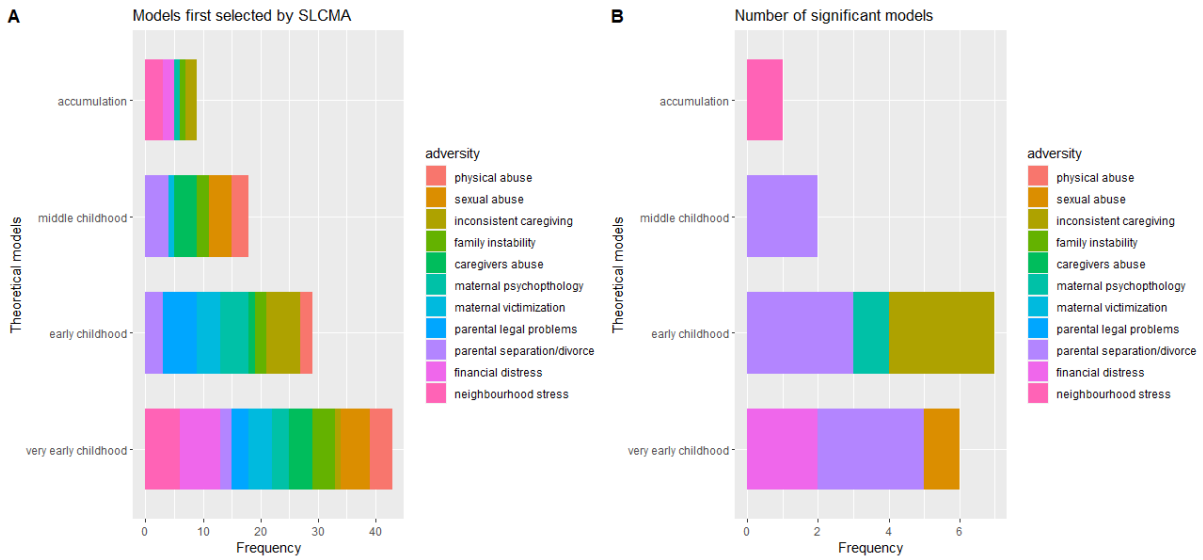


Figure 3.5. The figure shows the results of the structural life course modelling approach comparing two theoretical models of sensitive periods (very early childhood = before age 3; early childhood = 3-5 years; middle childhood = 6-8 years) and accumulation models selected by different adversity types. **Panel A** illustrates the frequency by which these two theoretical models were first chosen by SLCMA. Out of the total 99 models estimated, sensitive periods were first selected by SLCMA models in 90 models (very early childhood = selected by 43 models; early

childhood = 29 models; middle childhood = 18 models) while accumulation was selected in only 9 SLCMA models. **Panel B** displays the SLCMA models that reached significant threshold (i.e. $p<0.05$). Sensitive periods were statistical significant in 10 SLCMA models compared to just 1 model in accumulation.

Notably, parental separation or divorce at all assessment timepoints were significant and contributed substantially to the variability in poorer working memory ability observed in the study sample, suggesting the continuously influential role of full parental support in the development of children's working memory ability across early developmental time course. Overall, these findings provide further evidence of a more time-sensitive effect of childhood adversity on cognitive outcomes, compared to accumulation model. See Figure 3.5 and Table 3.8 for full details.

Table 3.8

Result of SLCMA showing the theoretical model of adversity measures first selected by LAR for all 9 cognitive outcomes

	SSRT	N-back accuracy	Emotion Total	Happy	Surprise	Fear	Sad	Anger	Disgust
Physical abuse	4.9 years	3.6 years	1.6 years	6.9 years	8.7 years	1.6 years	1.6 years	6.9 years	1.6 years
Sexual abuse	8.7 years	2.6 years*	2.6 years	2.6 years	2.6 years	8.7 years	6.9 years	2.6 years	8.7 years
Inconsistent caregiving	3.6 years	Accumulation	3.6 years*	5.9 years	4.9 years	2.6 years	Accumulation	3.6 years*	3.6 years*
Family instability	6.9 years	4.9 years	2.6 years	5.9 years	1.6 years	2.6 years	Accumulation	2.6 years	8.7 years
Caregivers abuse	8 months	2.9 years	6.1 years	6.1 years	6.1 years	6.1 years	2.9 years	8 months	5.1 years
Maternal psychopathology	1.9 years	Accumulation	3.11 years	2.9 years	1.9 years	3.11 years	5.1 years	5.1 years	3.11 years*
Maternal victimization	6.1 years	1.9 years	5.1 years	1.9 years	8 months	5.1 years	1.9 years	5.1 years	3.11 years
Parental legal problems	5.1 years	5.1 years	5.1 years	8 months	8 months	5.1 years	5.1 years	5.1 years	8 months
Parental separation/divorce	6.1 years*	(2.9/6.1/3.11/0.8/1.9/5.1 years)***	6.1 years	3.11 years	3.11yrs*	6.1 years	8 months	6.1 years	5.1 years
Financial distress	Accumulation	Accumulation	1.9 years*	2.9 years	1.9 years	1.9 years*	1.9 years	8 months	1.9 years
Neighbourhood stress	Accumulation*	2.9 years	2.9 years	Accumulation	Accumulation	1.9 years	1.9 years	2.9 years	2.9 years

*** = significant at $p<0.001$; * = significant at $p<0.05$; SSRT = stop signal reaction time. Note that I refer to sensitive periods as very early childhood (adversity exposure before age 3), early childhood (exposure between 3-5 years) and middle childhood (exposure between 6-8 years).

3.3.5 Sensitivity analyses and results

Given the substantial reduction in the study sample size (N=2,965) from the initial ALSPAC enrollment number (N~14,541), I conducted a latent class sensitivity analysis to see how the latent class result compares with the result from the larger sample of participants. There were two conditions for inclusion in the final analytic sample; First, participants mothers have provided data on adversity measures when participants were 8 months old (this is the first timepoint relevant adversity measures were obtained). Second, participants must have completed three cognitive tasks used in the study at age 24. This second condition resulted in the elimination of several participants from the latent class analysis. In the sensitivity analysis, I used a larger sample of 11,309 participants whose mothers provided relevant adversity data starting at 8 months old.

As I did in the main analysis, I first carried out an exploratory analysis involving class 1 to 8 models to determine which of them best explains the adversity data. Similar to findings reported in the primary analysis, class 5 model offered the optimal class solution given that it yielded better estimates (BIC = 114989; entropy = 0.7367487) compared to other rival class models. An inspection of this class model showed that class 1 consisted of 54.07% of the population. I referred to this class 1 (Figure S3, top left) as "low adversity" because members in this class have very low probability of being exposed to any of the 11 adversity measures with less than 19% probability of exposure in all adversity measures except family instability (38%). Class 2 (Figure S3, top centre) is made up of 14.77% of all participants. I referred to this class as "parental deprivation" because members in this class reported 98% probability of being exposed to parental divorce or separation and 90% probability of exposure to family instability. Together, these two measures reflect questions designed to measures the extent to which a developing child has been deprived of parental time and availability. Class 3 (Figure S3, top right) is named "dysfunctional family" because members (12.5%) have medium to high probability of exposure to one or more adversity measures characterized by dysfunctional family rearing. Specifically, members in this class reported relatively high probability of exposure to family instability (61%), caregivers' abuse (51%), maternal psychopathology (44%), maternal victimization (64%) and inconsistent caregiving (34%). Class 4 (Figure S3, bottom left) consists of 9.51% of the population. I called this class "*family poverty"* because participants responded high to financial distress (81%) and neighbourhood disadvantage (52%). These two adversity measures are designed to capture various degrees of socioeconomic

disparities and financial deprivation. Lastly, Class 5 (Figure S3, bottom right) is referred to as "*global adversity*" because members in this class (9.15%) have very high probability of being exposed to all the adversity measures in the study. Probability of exposure to adversity measures in this class range from 17% (sexual abuse) to 95% (family instability). Taken together, these findings from the sensitivity analysis are robust and consistent with the results reported in the primary analysis.

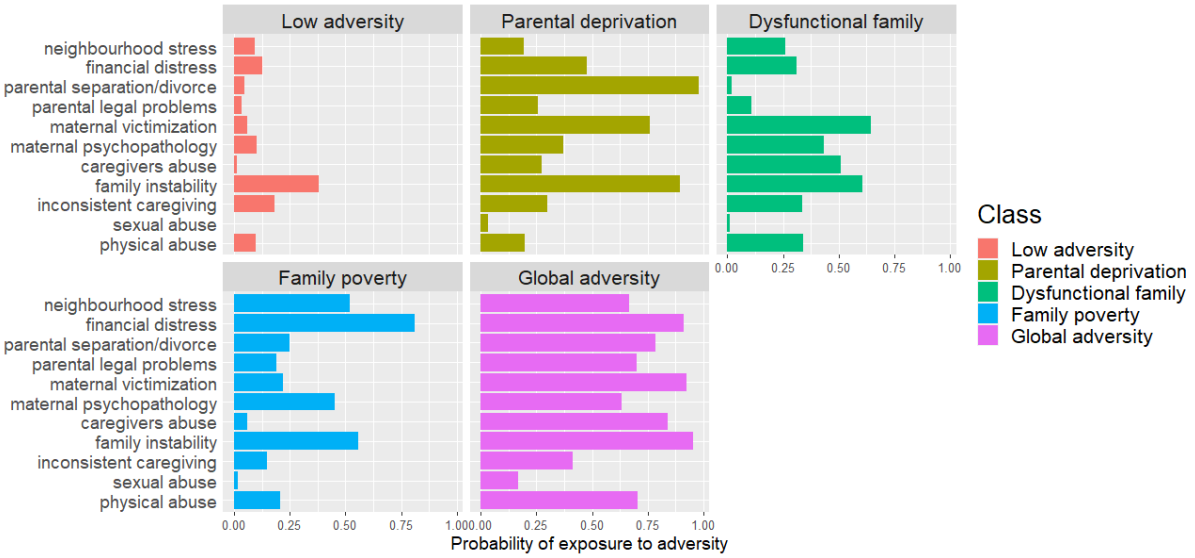


Figure S3: Latent class sensitivity analysis showing the five adversity classes and the corresponding class-conditional response probability for all the adversity measures. The sensitivity results from the unrestricted sample are consistent with findings reported in the primary analysis.

3.4 Discussion

In a large longitudinal sample, this study examined the co-occurrence of adverse childhood experiences in their classes or clusters. Results showed evidence of five classes of adversity in the data, namely: low adversity, dysfunctional family, parental deprivation, family poverty and global adversity. The adversity classes predicted differential performance in various cognitive outcomes, with participants in the family poverty class performing poorer relative to those in the low adversity class in cognitive outcomes specific to inhibition and working memory outcomes. Individual adversity types had distinct effects on cognitive functioning but greater variability in the observed effects was explained by sensitive periods (specific timing of adversity exposure) compared to accumulation hypothesis. These findings highlight the importance of studying childhood adversity in their classes or clusters in other to tease apart the cumulative effects of adversity and obtain a more fine-grained understanding of the specific pathway through which adversity disrupts cognitive functioning.

To begin with, the current study found five classes of childhood adversity which provides empirical evidence of dimensions or subgroups of adversity. As noted in previous studies (McLaughlin et al., 2021; McLaughlin and Sheridan, 2016), the dominant specificity and cumulative risk approaches of adversity studies have some shortcomings, because childhood adversity mostly co-occur and different types of adversity have distinct effects. Thus, by examining adversity in their classes or clusters, I may gain a better understanding of the specific adversity subgroups (classes or clusters) driving specific observed effects. The past studies that have used clustering technique (e.g., latent class analysis) have found between 3 (Ho et al., 2020; Denholm et al., 2013) to 4 (Davies, Read, & Shevlin, 2021; Lacey et al., 2020a; Lacey et al., 2020b; Wadman et al., 2019) classes of adversity. While the number of classes and the corresponding co-occurring adversity types will likely vary across studies based

on the number and severity of individual adversity types examined, there is little doubt that the clustering technique provides an alternative or complementary approach to studying childhood adversity, leading to a more nuanced understanding of the effects of adversity on outcomes, obtained through the pathways of adversity classes. Using latent class approach could further reveal the population distribution of the co-occurring adversity patterns among participants who may be at the greatest health risk and thus, prompt some form of intervention that targets the developmental areas of need for such high risk groups.

Secondly, when I compared cognitive performance among the different adversity classes in the sample, results showed that performance varied substantially across classes. Notably, cognitive performance of participants in the family poverty class was poorer relative to those exposed to low adversity in both inhibition and working memory. This finding was slightly contrary to initial predictions, as I expected participants in the global adversity class to have the worst performance metrics on the cognitive measures. However, poverty has been noted to be one of the most potent predictors of poorer cognitive outcomes in high income countries (Nisbett et al., 2012); many past studies have suggested that the poorer cognitive outcomes observed in people reared in poverty may be comparable to the severely neglected or institutionalised children (Hildyard & Wolfe, 2002). While participants in the global adversity class in this study also reported a substantial proportion of financial distress and did not differ significantly from the low adversity class, it should be noted that the largest concentration of participants reporting financial distress emerged in the family poverty class. Additionally, for some participants living in extreme poverty, financial distress is more likely to have enduring pattern of exposure across childhood than any other adversity types I examined. Thus, it is very likely that participants living in extreme and enduring poverty may have clustered in the family poverty class; and may have a shared pattern of long-lasting financial distress that is different from potentially short-term financial distress reported among

participants in the global adversity class. This may explain the observed significant effects in the family poverty subgroup but not in the global adversity subgroup, despite report of exposure to financial distress as well. These findings further demonstrate the added value of using latent class analysis as a complementary approach to studying childhood adversity as it can use the quantified population distribution of the co-occurring adversity types to examine the extent to which the predicted high risk group perform in developmental measures such as cognition or mental health. Such an approach would provide nuanced insight into the effects of adversity at a clustering level, and thus enable targeted academic or clinical intervention in the developmental area of need among the high risk groups in the population.

While I have no knowledge of previous studies that examined differential cognitive outcomes among adversity subgroups, past work has noted that low socioeconomic status was associated with poorer inhibition, as well as poorer working memory at low cognitive load but not at high cognitive load (John et al., 2019). The low cognitive load working memory outcome used by John and his colleagues is comparable to the 2-back version of the working memory task used in this study, given its relatively lower demand on executive function (compared to a more complex 3-back version). This suggests that the poorer working memory performance observed in the family poverty subgroup may be as a result of difficulties in attuning to basic working memory strategies rather than inability to sustain attention at a more complex level. On the other hand, some studies have found poorer performance in working memory among those exposed to chronic poverty (Evans and Schamberg, 2009; Evans and Fuller-Rowell, 2013). In such work, associations between poverty and cognition were often mediated by childhood chronic stress. Consistent with this, when I separately examined the individual adversity types that co-occurred in the family poverty class (i.e., financial distress and neighbourhood stress), findings showed that associations with poorer inhibition and working memory performance were mostly significant. However, after controlling for the effects of

shared variance from other adversity measures, some of these significant associations disappeared. For example, neighbourhood stress separately was associated with poorer inhibition, but results from multivariate regression analyses suggest that this association was driven by shared variance with financial distress. Also, while financial distress was separately associated with poorer working memory, this association did not reach significance levels after accounting for shared variance with other predictors. These findings further highlight the importance of cluster approaches to the study of adversity's impacts, as dealing with the co-occurrence of adverse childhood experiences can help highlight where associations with specific outcome effects emerged. There were no class differences in the emotional face recognition task, suggesting that the affective processing might not be very sensitive to most non-severe adversity types, thus, the resulting clusters of adversity would not differ between each other.

To justify the criticisms of specificity approaches to studying childhood adversity studies (McLaughlin et al., 2021; Smith & Pollak, 2020; McLaughlin and Sheridan, 2016) due to co-occurring pattern, I compared the results of the associations between each adversity type and cognitive outcomes before and after accounting for shared variance with other adversity measures. Findings showed that some of the significant associations observed between each adversity type and cognitive outcomes disappeared after controlling for shared variance with other adversity predictors. This was principally observed in the working memory measure. For example, the negative association observed for performance on this task with sexual abuse, maternal victimization and financial distress were not significant after accounting for shared variance in multivariate regression. Similarly, neighbourhood stress lost its association with inhibition. These findings suggest that some cognitive tasks (e.g., executive functioning) may be more sensitive to the effects of shared variance from other adversity measures. It is also possible that broader non-severe adversity types may not adversely affect general affective

processing (e.g., emotion recognition) compared to an executive functioning measure (e.g., n-back task).

In an important and novel set of analyses, I compared the theoretical models of sensitive periods and accumulation to ascertain which model has greater explanatory power for the observed effects between adversity and cognitive outcomes. For these comparisons, results showed that the observed variances were predominantly explained by sensitive periods. In all 16 models (estimating different adversity types on cognitive outcomes) that were significant in SLCMA, 15 models were identified by sensitive periods. Consistent with previous study on childhood adversity and DNA methylation (Dunn et al., 2019), sensitive periods at very early childhood (6) and early childhood (7) explained greater number of the observed effects, than middle childhood (2). Accumulation hypotheses were significantly selected in only one model, suggesting that the timing of adversity exposure (sensitive periods), especially during the early childhood period, may be of greater importance; thus, the need for parents and caregivers to safeguard the childhood environment against any potential stressors. Overall, these findings provide additional evidence of sensitive periods of adversity on cognitive outcomes.

The current study should be interpreted in the light of some limitations. First, the adversity measures used in this study were parent-completed, and thus may have been underreported (Holt et al., 2008). Second, because this is a longitudinal study, there may be an attrition effect as certain participants dropped-out overtime. The final analytic sample consists of 2,965 participants who completed the three cognitive tasks at age 24, relative to the larger sample of children (13,988 children) that were initially enrolled. In the ALSPAC study, it was reported that participants from disadvantaged households were more likely to skip follow-ups (Wolke et al., 2009), thus, the generalization of these findings may be limited. Finally, it should be noted that while the study modelled different adversities longitudinally, the cognitive data used in this study was cross-sectional as it was obtained at one time point.

In conclusion, I found evidence of five adversity classes in a population-based sample. These adversity classes had varying level of cognitive performances with poorer performance coming from participants in the family poverty class. I also report the independent effects of each adversity type on cognitive outcomes but it was the timing of exposure to these adversity types (sensitive periods) that appears to explain these observed effects more than the number of times an individual was exposed (accumulation). Examined collectively, results suggest important impacts of adversity that could subsequently inform the development of novel targets for intervention and prevention for high-risk groups.

4 Chapter 4

Trajectories of cortical structures associated with adverse life events across adolescence: A bivariate latent change score approach.

4.1 Introduction

Adverse events in childhood and adolescence have been associated with poorer developmental outcomes. Numerous studies have linked adversity during development to poorer mental health (Gilbert et al., 2009), problem behaviours (Golm et al., 2020; Sonuga-Barke et al., 2017), cognitive deficits (Guinosso, Johnson, & Riley, 2015) and structural alterations in the brain (McLaughlin, Weissman, & Bitrán, 2019; Teicher et al., 2016). Although these findings are robust, very few studies have longitudinally modelled the individual differences in change in the relations between adversity, brain development and cognitive functioning (i.e., how adversity exposure at one timepoint predicts change in brain development or cognitive functioning between two timepoints). Given that all those exposed to adversity in childhood or adolescence do not go on to develop challenges (Ellis et al., 2020), it is imperative to understand the different developmental impact of adverse life events across the lifespan. Thus, using different longitudinal models, the primary aim of this empirical study is to extend the results found in past cross-sectional projects, and more intricately understand long-term

interrelations between adverse life events, brain development and cognitive functioning. Here, I defined adversity as persistent adverse life events that deviate from the expected environment, but which have a lesser degree of severity than some of the previously investigated adversity measures (e.g., institutionalization, extreme neglect, or poverty).

The effects of adversity on cortical and subcortical structures are well documented (Luby, Tillman, & Barch, 2019; Hanson et al., 2015; Hodel et al., 2015; Sheridan et al., 2012; Lupien et al., 2011; Tottenham et al., 2010). For example, child deprivation e.g., institutionalization or poverty (Sheridan & McLaughlin, 2014) as well as mild and uncontrollable stress (Arnsten, 2009; Lupien et al., 2009) have been linked to alterations in the frontoparietal regions, including facets of the prefrontal regions. The effects of adversity on the frontoparietal regions are present at adolescence (Arnsten, 2009; Lupien et al., 2009), with child abuse (Gold et al., 2016; Kelly et al., 2013; Thomaes et al., 2010) or child institutionalization (Mackes et al., 2020; Hodel et al., 2015; McLaughlin et al., 2014) being related to structural brain alterations in various prefrontal and parietal regions. Other studies that examined the association between cortical structures and mild childhood stressors using the early life stress questionnaire found alterations in the anterior cingulate cortex (Baker et al., 2012; Cohen et al., 2006). Given that these cortical structures, especially prefrontal cortex subregions, continue to develop during adolescence (Tamnes et al., 2017), it may make these regions more susceptible to brain attenuations induced by stress compared with other brain areas.

Similar to relations with cortical development, previous studies have shown that adverse life events across childhood and adolescence exacts negative effects on cognitive functioning. There may be common mechanisms through which the effects of adversity manifests on both cognitive and neurodevelopmental processes (Arnsten, 2009). Studies have consistently linked child institutionalization to poorer performance on cognitive tasks (Golm et

al., 2020; Merz et al., 2016), including executive functions, working memory and decision making across the lifespan. Importantly, the prefrontal cortex is similarly implicated in the higher order cognitive processes (Friedman & Robbins, 2022; Stuss, 2011) ranging from planning, decision making, attention, memory and executive functions, indicating a potential pathway through which the effects of adversity commonly manifest on cognitive and brain changes. Previous studies have suggested that exposure to overwhelming stress may trigger accelerated loss of prefrontal cognitive abilities while chronic stress has been linked to structural changes in the prefrontal dendrites (Arnsten, 2009). Functional imaging techniques provide unique methods of establishing this pathway of interrelation between adversity, cognition and brain development. In one such study on reward processing and decision making (Birn et al., 2017), individuals who experienced high levels of community stress (i.e., day-to-day stressors) showed reduced activation in the posterior cingulate, precuneus and insula when processing cues about potential loss and rewards and greater activation in the inferior frontal regions when experiencing loss. This result suggests that childhood adversity may compromise learning abilities, specifically being able to adjust behaviours after one's loss; rather than global deficits in how rewards and punishments are processed. Other studies examining network connectivity (Teicher et al., 2014; Philip et al., 2013) in maltreated children have observed altered connectivity in many frontoparietal networks including in the cingulate, prefrontal, precuneus, and insula. These brain areas are critical to higher-order cognitive abilities such as working memory, emotion regulation, performance monitoring and self-awareness (Lara & Wallis, 2015; Haber & Knutson, 2009; Cavanna & Trimble, 2006). Examined collectively, these findings suggests a potential common pathway through which adversity exposure alters typical trajectories of brain and cognitive development.

While evidence linking adversity to cognitive and neurobiological alterations across human development is well established, important gaps that hinder the long-term inferences of

these associations and interrelations still exist. First, most studies examining the effects of adversity have been cross-sectional and consequently limit the ability to make long-term inferences. Some other studies Mackes et al., 2020; Golm et al., 2020; Mehta et al., 2009 have attempted to use a pseudo-experimental design by following a group of institutionalised children who were adopted to more enriched homes during very early childhood. Yet, such studies are often limited because they involve mostly small samples who had faced extreme adversities and often report high levels of psychopathology. In contrast, the use of population data samples offers an opportunity for researchers to establish stronger links on the effects of adversity due to the availability of large, longitudinal datasets (Rosenberg et al., 2018). Yet, very few published studies have utilized these longitudinal datasets to understand individual differences in change between adversity and brain development. That is, to what extent changes in brain development between two or more assessment timepoints are related to the effects of childhood or adolescence adversity exposure. Secondly, few studies examining the neurobiological effects of adversity have simultaneously examined the multiple morphometric measures of the brain (i.e., volume, surface area and cortical thickness). The preponderance of work has focused on brain volume, surface area or cortical thickness in isolation (cf., Gehred et al., 2021; Mackes et al., 2020; Rinne-Albers et al., 2020). Neurobiological research has shown that these three brain morphometrics are genetically independent and may be sensitive to clinical conditions such as adversity exposure (Storsve et al., 2014). Related studies have equally shown that alterations in the cortical brain volume may be attributable to variations in the surface area rather than cortical thickness (Im et al., 2008; Storsve et al., 2014). In relation to their association with adversity and other clinical sensitive events, one of the few studies that investigated the three brain morphometrics (i.e., volume, surface area and cortical thickness) showed in an exploratory analysis that adversity exposure was associated with reductions in the different portions of the prefrontal cortex volumes and moreso, the reductions

in brain volumes were explained largely by variability in the surface areas than in the cortical thickness (Hodel et al., 2015). The study also showed that alterations linked to adversity were proportionately distributed across the three brain morphometrics (Hodel et al., 2015). In a whole brain analysis, another cross-sectional study found that the association between adversity and the three morphometrics were inconclusive (Mackes et al., 2020) with adversity exposure linked to reduction in the inferior frontal surface area but correlating with greater growth in the inferior temporal volume, surface area and cortical thickness. A further exploration, using longitudinal models to examine and compare these brain morphometrics may provide further insight to their link with adversity. Lastly, although studies have attempted to establish the inter-correlation existing between adversity, cognition and brain development through several methods (e.g., functional imaging analysis), no study, to my knowledge, has longitudinally modelled the relations existing among these constructs.

The purpose of the current study is, therefore, threefold. First, to use a longitudinal model (latent change score) to extend the robust cross-sectional studies linking adversity to attenuations in brain and cognitive development. This change score model can quantify the individual differences in change observed over time among those exposed to adverse life events. This is pertinent given that previous studies have indicated potential nuanced and heterogeneous effects of adversity on cortical structures (Mackes et al., 2020), neural connectivity (Ellwood-Lowe et al., 2021) and cognitive outcomes (Young et al., 2020; Fields et al., 2021; Nweze et al., 2020). Thus, teasing out the portions of developmental trajectories when deficits, or compensatory benefits emerge in the brain or cognitive functioning could be very crucial in understanding the effects of adversity across adolescence. The model also enables me to establish the bidirectionality (i.e., how adversity affect brain and cognitive functions, versus how brain and cognitive outcomes affect adversity on the other hand) which will invariably lead to a more robust conclusion. Most previous studies on adversity were

centred on the more intuitive framework of effects of adversity on developmental processes e.g., brain development and cognitive functioning. Thus, very little is known about how adversity-associated changes in these developmental processes might affect the subsequent perception of prolonged adverse life events given the paucity of adversity studies that have used bi-directional analytic strategies. Few studies that have investigated the role of brain on perceived stress have implicated alterations in the brain frontal regions, particularly the prefrontal frontal cortex (McEwen et al., 2013; Michalski et al., 2017; Moreno et al., 2017). Second, in examining the link between adverse life events and brain development, I capture all three morphometric measures of brain assessments (i.e., volume, surface area and cortical thickness). A simultaneous investigation of all three outcomes will enable me to disentangle the effects of adversity on relatively established brain volumes, compared to the more fine-grained surface area and cortical thickness. In other words, I ask if adversity has equal or disproportionate effects on brain volume, surface area and cortical thickness. Lastly, I attempt to establish the interrelations between adverse life events, cortical brain structures and two cognitive processes of spatial working memory and decision making by examining the mediating effects of both brain and cognitive outcomes using complete longitudinal mediation models. This model tests whether any mediating effects exist in the data for neurobiology or cognition, and if so, further disentangles specific mediating paths. For example, the models allow me to understand if adversity predicts brain alterations which in turn predicts cognitive deficits, or in contrast, if adversity predicts cognitive deficits which in turn predicts brain alterations. Testing these two neurocognitive pathways to adversity would enable a more holistic appreciation of the mediating interrelations between adversity, brain and cognition given previous studies that have suggested common mechanisms through which the effects of adversity manifests on both cognitive and neurodevelopmental processes (Arnsten, 2009). Given findings from previous cross-sectional studies, I predict that adversity will lead to

decrease change in cortical structures across adolescence and these alterations will be equally distributed across the three brain morphometry outcomes I examined. I also predict that both cortical structures and cognitive outcomes (i.e., spatial working memory and decision making) will have mediating interrelations with adversity.

4.2 Methods

4.2.1 Participants

Data were obtained from the IMAGEN project – a European multi-centre longitudinal cohort study that is primarily focused on understanding how biological, psychological and environmental factors interact to shape the brain development and mental health of young people. (See Schumann et al., 2010 for detailed description of study protocols). Data were first collected when the participants were aged 14 but subsequent follow-up assessments have taken place at ages 16, 19 and 22.

The analytic sample consists of 502 participants (Male = 283; Female = 219) who completed all MRI scans, as well as behavioral and cognitive data at ages 14 (Mean =13.978; SD = 0.518), 19 (Mean =18.483; SD =0.725), and 22 (Mean = 21.945; SD = 0.610). Data obtained at age 16 were not included in the analysis because there was no MRI assessment at this time point.

4.2.2 Measures

Adverse life events: Participants completed the 39-item life events questionnaire (Newcomb et al., 1981) and the revised Olweus bully/victim questionnaire (Olweus, 2006) at ages 14, 19 and 22. These measures have been used in previous studies that examined the effects of adversity in this cohort sample (Mackey et al., 2017; Gollier-Briant et al., 2016; Galinowski et al., 2015). The life events questionnaire has 7 subscales: parents and family, accident and illness, sexuality, autonomy, deviance, relocation, and distress. In the first assessment (age 14), the

participants were asked about their lifetime exposure to these events in the questionnaire. But in the follow-up assessments at age 19 and 22, the participants were asked about their exposure to the events since their last IMAGEN visit. In this study, only the negative life events captured in 3 subscales (parents/family, accident/illness, and distress) and consisting of 15-item questions were included in the analysis. These 3 subscales were used in this study because; firstly, they broadly reflect on general negative experiences involving the individuals or their immediate family. Secondly, they represent negative events variables that have been operationalised within the adversity frameworks in the IMAGEN cohort. Lastly, previous studies using the IMAGEN dataset have used these subscales when adversity exposure (Mackey et al., 2017; Gollier-Briant et al., 2016; Galinowski et al., 2015). Relatedly, the bully/victim questionnaire is a widely used questionnaire for the assessment of bullying either as a victim or as a perpetrator in school-aged children. For each of the assessment time, the participants were asked if they have been exposed to bullying in the last 6 months. I included only the victim subscale which has 6 item-questions because they reflect on adversity exposure to an individual. See Supplementary material for chapter 4 for all the item questions in both the subscales of life events questionnaire and bullying questionnaire used in the study. Exposures to any of the item questions in the selected subscales in life events questionnaire or bully/victim questionnaire were initially coded 1, or 0 if no exposure was reported. However, as has been performed elsewhere in the IMAGEN sample (Mackey et al., 2017), I transformed all the individual item scores in the selected subscales of both questionnaires to Z scores and then summed them up to produce a composite adversity score for each timepoint.

Cognitive measures: Cognitive ability was examined with two tasks from the computerized CANTAB battery (Robbins et al., 1994): Spatial working memory task and Cambridge Gambling Task. These cognitive measures were selected because they have been strongly linked to the functions of the brain regions involved in higher cognitive processes e.g.,

prefrontal regions (Funahashi, 2017; Yazdi et al., 2018). In the spatial working memory task, participants were asked to search for a hidden blue token in a number of coloured boxes displayed on the screen, and to open the boxes to see what is inside. Using an elimination strategy, participants were asked to avoid a box where a token had previously been found. Strategy in spatial working memory task corresponds to a sequential search pattern used by the participants when beginning a new search after a token has been found. An efficient strategy requires participants to begin from a predetermined search sequence, beginning with a specific box and return to it after a token has been found (Owen et al., 1990). The task progressively increases in difficulty as the number of boxes presented on the screen increases from 2 to 8. The outcomes in this task are *between errors* which is the number of times participants revisit a box in which token has previously been found, and *strategy* score which is number of distinct boxes used by the participants when beginning a new search. Higher scores in both of these outcomes indicate poor working memory ability. However, I reverse coded the scores, so that higher scores indicate high working memory ability.

In the Cambridge Gambling Task, which measures decision making and risk-taking behaviour, participants were presented with ten boxes, varying in red or blue colours. Participants were told that one of the boxes contained a hidden yellow token and must first, use the appropriate red or blue buttons to choose which box, they think contained the yellow token. Then, beginning with a starting 100 points, all participants will then wager an amount from a range of 5 possible values (5%, 25%, 50%, 75%, and 95% - sometimes presented in ascending or descending order) based on their confidence of the location of a token. If they made the correct decision, the amount will be added to their total points; otherwise, the equivalent value wagered will be deducted from their points. The outcomes analysed in this study include *quality of decision making* (proportion of trials where the correct colour outcome was made; higher score indicates good decision making ability), *risk taking* (proportion of bet points placed after

the most likely outcome was chosen; higher score represents high risk tolerance) and *risk adjustment* (the extent to which betting behaviour is moderated by the ratio of blue to red boxes presented; higher score indicates that participants change total points wagered on each trials depending on the probability of winning).

Structural Magnetic resonance imaging: Structural scans were performed on 3T scanners from different manufacturers (Philips, General Electric, Siemens, Bruker; Schumann et al., 2010).). High resolution 3-dimenional T1 weighted images were acquired using magnetization prepared gradient echo (MPRAGE) sequence, based on the ADNI protocol (http://www.loni.ucla.edu/ADNI/Cores/index.shtml). To account for variations in scanner manufacturer across sites, scanning protocol parameters (e.g., those relating to image contrast or signal-to-noise ratio) were devised and harmonised across all the scanning sites. Scanning site was also included as a covariate in the statistical analyses. Data segmentation of structural MRI was performed using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). For additional information on MRI acquisition protocols and quality control in this IMAGEN cohort, see Schumann et al. 2010. In this study, I analysed 11 derived brain metrics, primarily in the frontoparietal regions in both the left and the right hemispheres because past cross-sectional research findings have shown that adversity exposure is commonly related to differences in these regions (Sheridan & McLaughlin, 2014; McLaughlin et al., 2019). These 11 brain regions include; middle frontal (Edmiston et al., 2010; Herzberg et al., 2018; Hodel et al., 2015; McLaughlin et al., 2014), orbitofrontal (Hanson et al., 2010; Edmiston et al., 2010; Herzberg et al., 2018; Hodel et al., 2015; McLaughlin et al., 2014), anterior cingulate (Herzberg et al., 2018; Hodel et al., 2015; Kelly et a., 2013), inferior frontal (Herzberg et al., 2018; Hodel et al., 2015; Kelly et a., 2013), frontal pole (Herzberg et al., 2018), superior parietal (McLaughlin et al., 2014), superior frontal (Herzberg et al., 2018; Hodel et al., 2015; Kelly et a., 2013), inferior parietal (McLaughlin et al., 2014), precuneus (McLaughlin et al., 2014),

posterior cingulate (McLaughlin et al., 2014) and insula (McLaughlin et al., 2014; Kelly et a., 2013). In addition, I also followed similar exploratory approach used in previous cross-sectional study (Hodel et al., 2015) by examining the volume, surface area and cortical thickness in these regions of interest to see if the alterations linked to adversity are proportionately spread out across these 3 brain morphometrics. It should be also be noted that these selected brain regions, particularly the prefrontal regions are also linked to higher cognitive functions in the brain, specifically working memory and decision making abilities (Birn et al., 2017; Funahashi, 2017; Yazdi et al., 2018). Thus, I equally investigated the mediating interrelations between adversity, cognitive functions of working memory and decision making and these selected brain regions.

4.2.3 Statistical analyses

All statistical analyses were performed in *R* (R Core Team, 2019) and *R Studio* version 4.1.1, within a structural equation modeling framework (Iacobucci et al., 2007). Data for all study constructs were transformed to standardized scores to have a mean centre of zero.

As a requirement for longitudinal analysis (e.g. latent change score model), I began by testing the longitudinal measurement invariance using configural, metric and scalar models. Measurement invariance generally tests whether the constructs measured (e.g., Life events questionnaire) were the same across the three different measurement waves. For each measurement invariance models tested, I first examine fit using the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR). Previous studies (Hu & Bentler, 1999; Browne & Cudeck, 1993) have recommended the following threshold as indicative of good model fit: CFI > 0.90 and RMSEA < 0.08. Secondly, using likelihood ratio test, I then proceed to examine metric

invariance by comparing the configural model against the metric model and scalar invariance by comparing metric model against the scalar model. An insignificant chi-square difference test is an indication of measurement invariance in the construct. In addition to the chi-square difference test, the following fit difference cut-offs have also been suggested as an indication of measurement invariance (Murray et al., 2021; Chen, 2007; Cheung & Rensvold, 2002); ΔCFI > -.010; ΔRMSEA < 0.015, and ΔSRMR < 0.030 (or ΔSRMR < 0.010 for scalar invariance).

Secondly, to examine how individual differences (and changes) in adversity exposure, brain development, and cognitive outcomes may influence one another, I first fit a bivariate latent change score model (Wiedeman et al., 2021; Kievit et al., 2018). In this latent change score models, depicted in Figure 4.1, I examined four different bivariate relations across 3 waves: 1) The association between adverse life events and brain volumes in the frontoparietal regions; 2) The relations between adverse life events and surface area in the frontoparietal regions; 3) The association between adverse life events and cortical thickness in the frontoparietal regions; and 4) The relations between adverse life events and different cognitive outcomes in the spatial working memory and Cambridge gambling tasks. The essential feature of a latent change score model is that it can be used to test for (linear) increases or decreases within the same construct in two adjacent waves (i.e., within-level change). The change score was obtained by regressing the observable score of a given timepoint from the previous timepoint (e.g., Δadversity in T1-T2 or Δadversity in T2-T3, where T1 = Time 1, T2 = Time 2 and T3 = Time 3). In addition, I also used cross-lagged dynamic coupling (i.e., bidirectionality) to test for individual differences in the relations between adversity and linear changes in brain/cognition as well as the relations between brain/cognition and linear change in adversity. In this instance, I examined whether exposure to adversity at T1 predicted a linear change in brain/cognitive scores across T1-T3 or alternatively, whether brain/cognitive scores at T1

predicted a linear change in adversity across T1-T3. In total, I carried out 71 separate analyses of bivariate latent change score model examining association between adverse life events and 11 brain volume metrics in each left and right hemisphere, 11 surface areas metrics in each left and right hemisphere, 11 cortical thickness metrics in each left and right hemisphere and 5 cognitive outcomes. In all models, I controlled for age, sex and sites of recruitment by adding them as covariates in the model. In implementing the latent change score model in *lavaan* (Rosseel, 2012), I used the maximum likelihood estimator. In each bivariate relations, I examine all model fit indices and report the parameter estimates at 0.05 significant threshold.

Finally, using a complete longitudinal mediation model (Jose, 2016), I examine the long-term mediating effects between adverse life events, brain development and cognitive functioning via auto-regressive path models. A complete longitudinal mediation model (shown in Figure 4.2) essentially tests 6 different indirect paths involving all 3 study constructs. However, only two mediating paths are of interest in the current study: adversity T1 => Brain development T2 => cognitive outcome T3 and adversity T1 => cognitive outcome T2 => Brain development T3. Note that all scores at Timepoint 2 and Timepoint 3 are residualised. In the first indirect path, the model tests whether adverse life events score at time 1 predicts brain morphometrics at time 2 and whether this in turn predicts the cognitive score at timepoint 3. In the second indirect path, I reversed the mediator and the outcome and examine if adverse life events score at time 1 predict the cognitive score at timepoint 2, which in turn predicts brain morphometrics at timepoint 3. In implementing this model, I used bias-corrected confidence intervals using 5000 bootstrap permutations. To reduce the number of analyses carried out in the mediation model, I used the sum of the brain metrics in both the left and the right hemisphere rather than analyse each hemisphere separately. In total, I carried out 165 separate mediation model analyses involving 5 cognitive outcomes and the 11 frontoparietal regions testing each metric of the brain volume, surface area and cortical thickness. In implementing

this model in R, I requested for bootstrapped estimation of the indirect effects using bias-corrected confidence intervals at 5000 bootstrap permutations. I report the estimates of the effect sizes with their standard errors and the confidence intervals. Confidence intervals that do not include zero indicate significant indirect effects.

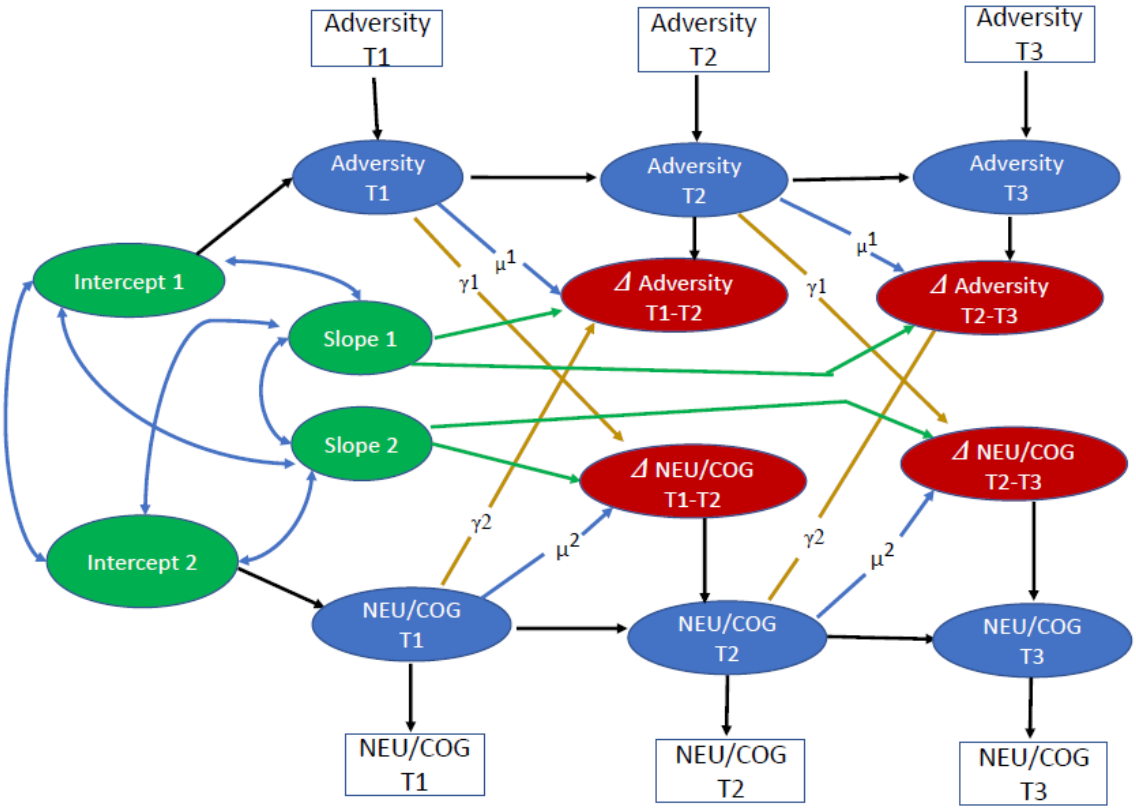


Fig 4.1. A simplified bivariate latent change score model. I examined four bivariate relationships: 1 = relationship between adverse life events and frontoparietal network volume; 2 = relationship between adverse life events and frontoparietal network surface area; 3 = relationship between adverse life events and frontoparietal network cortical thickness; 4 = relationship between adverse life events and cognitive outcomes. In all models, I covaried for age, sex and sites of recruitment. T1 = timepoint 1; T2 = Timepoint 2; T3 = Timepoint 3. NEU = each frontoparietal region tested; COG = each cognitive outcome tested.

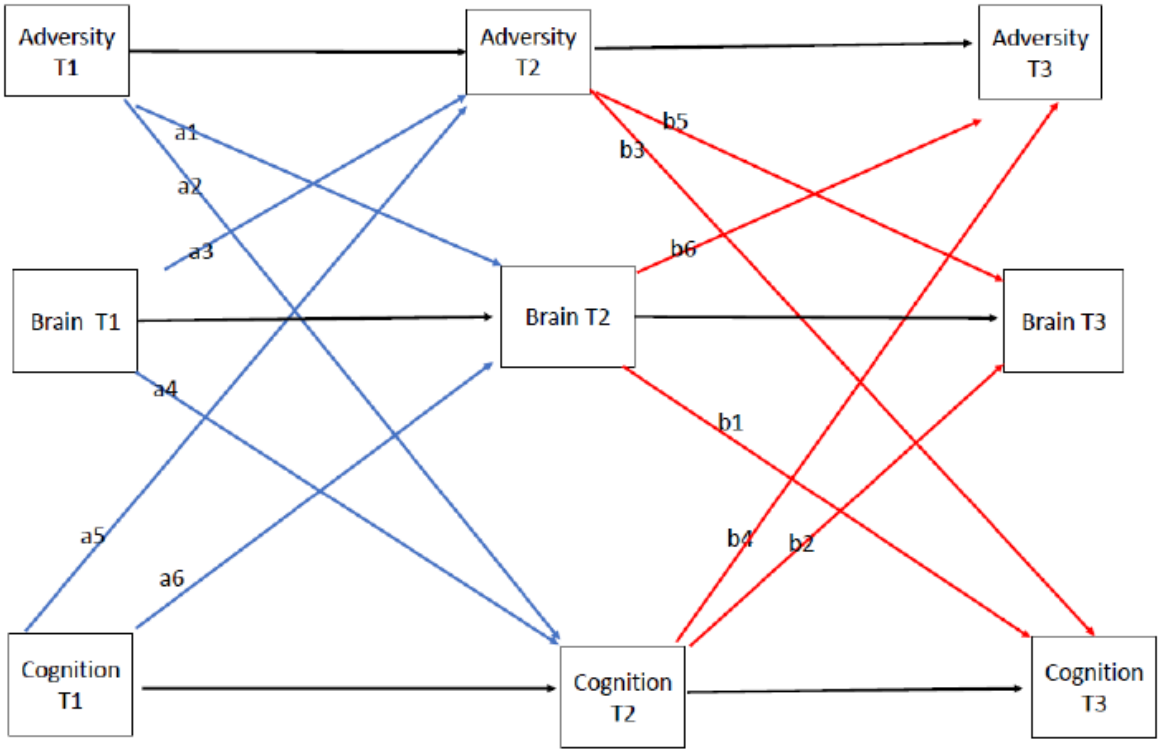


Fig 4.2. Complete longitudinal mediation model. This model investigates 6 possible indirect effects involving all 3 adverse life events, brain and cognitive variables. However, only the first two mediation paths shown in this figure were of interest in the current study. Scores at T2 and T3 are residualised.

4.3 Results

4.3.1 Longitudinal measurement invariance

I present the results of the longitudinal measurement invariance, comparing configural, metric and scalar models of the study measures. As evidence of measurement invariance, I used a non-statistical chi-square test and fit difference within the recommended cut-off: ΔCFI > -.010; ΔRMSEA < 0.015, and ΔSRMR < 0.030 (or ΔSRMR < 0.010 for scalar invariance). As shown in Table 4.1, the model fit of the bullying and life events questionnaires suffered from relatively poor CFI values while other fit indices were within excellent range. The relatively poor CFI values in these questionnaires, particularly in the life events questionnaire may be attributable to the established low inter-item correlation (Newcomb et al. 1986). In addition, ΔCFI in both the subscales of life events questionnaire and the bullying questionnaires was outside the recommended cut-off for the metric model, indicating a lack of metric invariance in all the adversity subscales. However, the scalar invariance held in the bullying questionnaire based on a non-significant chi-square test and fit difference within predefined cut-offs while scalar invariance held in all the subscales of life events questionnaire based on non-significant chi-square test.

On the other hand, the baseline models fit well for both the CANTAB spatial working memory and Cambridge gambling task. The addition of metric constraints was associated with a non-significant chi-square result in the spatial working memory but not in the Cambridge gambling task; however, ΔRMSEA increased beyond the predefined limit for the spatial working memory while all increases and decreases were within predefined limits for the Cambridge gambling task. Scalar invariance held in both spatial working memory and

Cambridge gambling task based on a non-significant chi-square tests and fit difference well within predefined cut-offs. Taken together, while I impose scalar invariance for bullying questionnaire, and the CANTAB measures, findings in the current study should generally be interpreted with caution given the lack of clear measurement invariance in the life events questionnaire.

Table 4.1: Model fits of longitudinal invariance testing									
	Fit			Fit difference versus baseline			Δχ2 Difference test		
Model	CFI	RMSEA	SRMR	ΔCFI	ΔRMSEA	ΔSRMR	Δχ2	df	p
LEQ: Parents and Family subscale									
Configural	0.884	0.037	0.058						
Metric	0.815	0.045	0.063	-0.069	0.008	0.005	26.766	80	<0.001
Scalar	0.828	0.041	0.064	0.013	-0.004	0.001	2.869	88	0.942
LEQ: Accident and illness subscale									
Configural	0.926	0.029	0.032						
Metric	0.863	0.037	0.050	-0.063	0.008	0.018	18.443	45	0.005
Scalar	0.845	0.037	0.052	-0.018	0.000	0.002	11.530	51	0.073
LEQ: Distress subscale									
Configural	0.881	0.028	0.046						
Metric	0.860	0.030	0.047	-0.021	0.002	0.001	10.723	124	0.379
Scalar	0.846	0.030	0.049	-0.014	0.000	0.002	17.241	134	0.069
Bullying: victim subscale									
Configural	0.922	0.029	0.057						
Metric	0.869	0.036	0.061	-0.053	0.007	0.004	26.712	124	0.002
Scalar	0.868	0.035	0.062	-0.001	-0.001	0.001	14.577	134	0.148
Spatial working memory (CANTAB)									
Configural	0.997	0.000	0.008						
Metric	0.997	0.056	0.012	0.000	0.056	0.005	1.124	2	0.57
Scalar	0.999	0.024	0.012	0.002	-0.032	0.000	0.000	4	>0.999
Cambridge gambling task (CANTAB)									
Configural	0.979	0.069	0.055						
Metric	0.974	0.069	0.055	-0.005	0.000	0.000	13.792	19	0.007
Scalar	0.976	0.060	0.055	0.002	-0.009	0.000	0.000	23	>0.999

Table 4.2			
Mean and standard deviation (SD) of relevant demographic, cognitive and brain data across the three waves			
	Mean (SD)	Mean (SD)	Mean (SD)
	Wave 1	Wave 2	Wave 3
Demographic			
Sex	M= 219; F = 283	M= 219; F = 283	M= 219; F = 283
Age	13.978 (0.518)	18.483 (0.725)	21.945 (0.610)
CANTAB			
SWM Strategy	33.476 (5.426)	35.731 (5.918)	21.195 (5.761)
SWM Errors	56.067 (13.456)	63.894 (11.369)	102.982 (10.490)
CGT quality of decision	0.945 (0.078)	0.957 (0.069)	0.971 (0.048)
CGT risk taking	0.527 (0.140)	0.541 (0.125)	0.563 (0.125)
CGT risk adjustment	1.683 (1.039)	1.998 (1.019)	2.168 (0.982)
Brain volume (both hemispheres)			
Middle frontal	49095.29 (8636.80)	46570.165 (6806.821)	45013.267 (6291.685)
Orbital frontal	27285.345 (4126.635)	26252.343 (3089.147)	27407.12 (3062.62)
Anterior cingulate	9873.498 (1913.046)	9713.954 (1575.832)	8969.474 (1469.633)
Inferior frontal	24685.219 (3750.156)	23441.745 (2997.008)	23263.699 (2807.588)
Frontal pole	2319.125 (419.095)	2095.284 (357.140)	2354.410 (379.484)
Superior parietal	29106.661 (4151.615)	27332.596 (3494.912)	26704.992 (3383.698)
Superior frontal	49848.498 (7231.121)	47148.199 (6177.104)	46177.255 (5948.066)
Inferior parietal	31636.476 (4909.638)	29630.645 (4054.452)	27827.319 (3620.887)
Precuneus	22503.669 (3358.433)	21376.313 (2832.298)	20860.968 (2662.028)
Posterior cingulate	7347.494 (1170.426)	7107.309 (1031.666)	6865.147 (901.088)
Insula	14132.253 (1800.248)	13691.410 (1641.206)	14894.390 (1660.356)
Cortical surface area (both hemispheres)			
Middle frontal	16115.715 (2636.346)	16481.55 (2171.08)	16243.355 (2068.934)
Orbital frontal	8599.116 (1286.807)	8773.233 (1021.791)	9309.596 (1016.944)

Anterior cingulate	2916.5478 (531.4816)	3000.998 (483.834)	2807.337 (457.481)
Inferior frontal	7414.767 (1062.593)	7498.197 (901.881)	7540.035 (869.845)
Frontal pole	522.677 (77.013)	513.918 (66.408)	590.336 (66.241)
Superior parietal	11057.259 (1427.673)	11090.339 (1229.972)	10920.871 (1247.024)
Superior frontal	14358.747 (2017.029)	14553.024 (1721.082)	14613.783 (1695.324)
Inferior parietal	10279.618 (1499.736)	10312.249 (1339.871)	9965.137 (1296.762)
Precuneus	7929.530 (1129.312)	7980.468 (1021.551)	7930.131 (997.706)
Posterior cingulate	2413.233 (357.757)	2454.163 (343.760)	2418.719 (314.299)
Insula	4153.358 (503.063)	4149.802 (480.136)	4701.071 (512.625)
Cortical thickness (both hemispheres)			
Middle frontal	10.228 (0.619)	9.802 (0.652)	9.752 (0.573)
Orbital frontal	10.742 (0.639)	10.359 (0.612)	10.479 (0.513)
Anterior cingulate	11.827 (0.963)	11.464 (0.751)	11.306 (0.672)
Inferior frontal	16.387 (0.989)	15.828 (0.864)	15.773 (0.783)
Frontal pole	5.959 (0.647)	5.690 (0.594)	5.518 (0.519)
Superior parietal	4.618 (0.296)	4.408 (0.275)	4.378 (0.231)
Superior frontal	5.808 (0.362)	5.557 (0.419)	5.439 (0.381)
Inferior parietal	5.298 (0.325)	5.072 (0.265)	4.927 (0.222)
Precuneus	5.170 (0.306)	4.965 (0.260)	4.920 (0.201)
Posterior cingulate	5.548 (0.347)	5.329 (0.290)	5.124 (0.264)
Insula	6.526 (0.350)	6.410 (0.267)	6.286 (0.243)
Note: SD = standard deviation; SWM = spatial working memory; CGT = Cambridge gambling task			

4.3.2 Descriptive results

Table 4.2 displays the descriptive statistics of the basic demographic variables, adverse life events measures, cognitive outcomes and the total brain variables in the left and right hemispheres in the volume, surface area and cortical thickness of the selected regions. I present the unstandardized, mean score and standard deviation of these measures. I also present in Table 4.3, zero-order correlations of a paired-wave association between adversity and brain/cognitive outcomes at each measurement wave.

Table 4.3: A zero-order correlation of a paired-wave association between adversity and brain/cognitive outcomes

	Left hemisphere			Right hemisphere		
	Adversity T1	Adversity T2	Adversity T3	Adversity T1	Adversity T2	Adversity T3
Volume						
Middle frontal	-0.03	-0.04	-0.10*	-0.02	-0.01	-0.06
Orbital frontal	-0.04	-0.06	-0.04	-0.03	-0.06	-0.06
Anterior cingulate	-0.06	-0.14**	-0.09*	-0.04	0.00	-0.11*
Inferior frontal	-0.03	-0.01	0.01	-0.06	-0.02	-0.07
Frontal pole	-0.01	0.03	-0.02	-0.04	0.04	-0.08
Superior parietal	-0.08	-0.03	-0.06	-0.06	-0.01	-0.05
Superior frontal	-0.08	-0.01	-0.03	-0.09*	-0.03	-0.05
Inferior parietal	-0.10*	-0.09*	-0.11*	-0.11*	-0.10*	-0.08
Precuneus	-0.07	-0.09*	-0.05	-0.07	-0.06	-0.02
Posterior cingulate	-0.06	-0.09*	0.00	-0.08	-0.04	-0.03
Insula	-0.06	-0.06	-0.02	-0.08	-0.08	-0.02
Surface area						
Middle frontal	-0.03	-0.09*	-0.07	-0.02	-0.08	-0.04
Orbital frontal	-0.02	-0.08	-0.05	-0.03	-0.11*	-0.04
Anterior cingulate	-0.04	-0.14**	-0.09*	-0.04	-0.04	-0.08*
Inferior frontal	-0.03	-0.04	0.01	-0.04	-0.07	-0.05
Frontal pole	-0.04	-0.08	0.02	-0.06	-0.05	-0.02
Superior parietal	-0.06	-0.06	-0.06	-0.04	-0.07	-0.06
Superior frontal	-0.06	-0.06	0.00	-0.08	-0.10*	-0.04
Inferior parietal	-0.07	-0.11*	-0.10*	-0.11*	-0.10*	-0.06
Precuneus	-0.06	-0.08	-0.05	-0.06	-0.09*	-0.03
Posterior cingulate	-0.04	-0.10*	-0.03	-0.09*	-0.08	-0.03
Insula	-0.03	-0.07	-0.02	-0.04	-0.08	-0.02
Cortical thickness						
Middle frontal	-0.03	0.08	-0.05	-0.02	0.10*	0.00

Orbital frontal	-0.09*	0.01	-0.01	-0.01	0.10*	-0.04
Anterior cingulate	-0.02	-0.03	0.05	-0.03	0.05	-0.04
Inferior frontal	-0.02	0.08	-0.02	-0.07	0.09	-0.03
Frontal pole	0.06	0.12**	-0.04	-0.01	0.11*	-0.09*
Superior parietal	-0.04	0.03	0.02	-0.03	0.08	0.07
Superior frontal	-0.06	0.09	-0.03	-0.02	0.13**	-0.02
Inferior parietal	-0.05	0.05	0.02	-0.03	-0.05	0.06
Precuneus	-0.07	-0.04	0.01	-0.06	0.07	0.04
Posterior cingulate	-0.04	0.04	0.05	0.01	0.13	0.00
Insula	-0.11*	-0.02	-0.01	-0.10*	-0.02	-0.04
Cognition						
SWM Strategy	0.02	-0.06	-0.04			
SWM Errors	-0.01	-0.07	-0.04			
CGT decision making	0.01	0.05	-0.07			
CGT risk taking	-0.04	-0.07	0.11*			
CGT risk adjustment	-0.01	-0.01	-0.13**			

4.3.3 Relationship between adverse life events and brain volumes in the frontoparietal regions

To examine the association between adversity and the brain volumes in the frontoparietal regions, I fit a bivariate latent change score model. After controlling for age, sex and sites of recruitment, all models were within the range of excellent fit (fit range: CFI: 0.988 – 0.953; RMSEA: 0.051 – 0.069; SRMR: 0.030 – 0.033) as recommended in previous studies (Chen, 2007; Cheung & Rensvold, 2002). I displayed in Table 4.4 the within-variable changes in the volumes of each cortical structures, the lagged effects of adversity on changes in each frontoparietal brain volume, and the lagged effects of each frontoparietal brain volume on changes in adversity.

Within-level changes*:* In all brain regions examined, there was a significant negative association between brain volumes at baseline and the linear changes in brain volumes at follow-up assessments in both the left and the right hemispheres (all p's<0.001). This implies that greater brain volumes at baseline were associated with decrease change at follow-up assessments.

Lagged effects of adversity on changes in the volumes of frontoparietal regions: Next, I examined if baseline adverse life events scores predicted volumetric changes in frontoparietal regions. Results showed that there was no statistically significant association between baseline adversity and the linear change in brain volume in any of the frontoparietal regions examined, either in the left hemisphere (all p's> 0.134) or in the right hemisphere (all p's>0.050).

***Lagged effects of frontoparietal brain volumes on changes in adversity*:** Relatedly, I investigated if baseline brain volumes in any of the frontoparietal areas were associated with linear change in adversity exposure subsequently reported at follow-ups. As was the case for the lagged effects of adversity, I found no statistically significant evidence of lagged effects of brain volume on adversity in the left hemisphere (all p's > 0.343) or in the right hemisphere (all p's>0.389).

4.3.4 Relationship between adverse life events and brain surface area in the frontoparietal regions

Following similar approach as above, I next examine the individual differences in change between adversity exposure and surface area of frontoparietal regions of interest. Examination of model fit shows that all models were within the range of excellent fit (fit range: CFI: 0.991 – 0.974; RMSEA: 0.048 – 0.074; SRMR: 0.028 – 0.032). Results which are displayed in Table

4.5, present the within-variable change in surface area, the lagged effects of adversity on changes in surface area of each brain regions, and the lagged effects of surface area of each frontoparietal areas on adversity.

Within-level changes*:* Aside from the left insula (p = 0.261), I observed significant negative changes across ages 14-22 for all brain surface area in the frontoparietal regions in both the left and right hemispheres (all p's < 0.05), such that smaller baseline surface area was associated with greater growth across follow-up assessments.

Lagged effects of adversity on changes in the surface area of frontoparietal brain regions: Next, I examined if baseline adversity exposure was associated with linear changes in the surface area of frontoparietal regions at follow-up assessments. Results (displayed in Figure 4.3 and Table 3) showed that greater adversity exposure at baseline was associated with a modest, but significant decrease in the right anterior cingulate in the follow-up assessments (*Std.* β =-0.266, p = 0.036, 95% CI [-0.514, -0.018]). No other significant associations between adversity and frontoparietal surface area were observed in the left hemisphere (all p's > 0.056) or in the right hemisphere (all p's > 0.262).

Lagged effects of surface area at baseline on changes in adversity: Similarly, I examined if baseline brain surface area in any of the frontoparietal areas was associated with change in adversity exposure subsequently reported at follow-ups. I found no evidence of significant association between baseline levels of surface area of frontoparietal regions and linear change in adversity exposure reported at follow-up assessments. This was true for both the left hemisphere (all p's > 0.129) and the right hemisphere (all p's > 0.140).

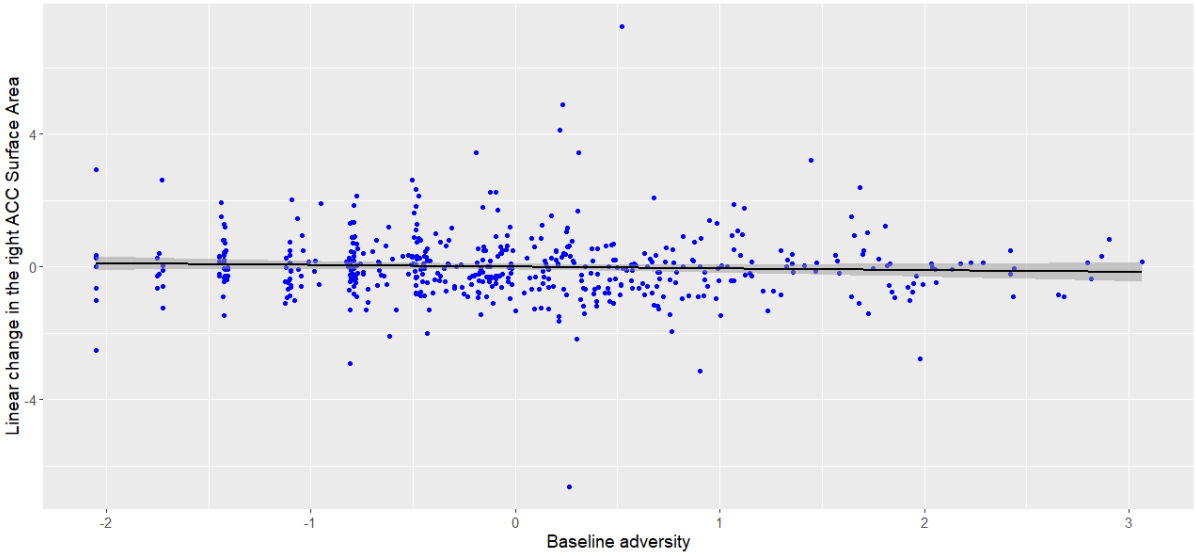


Figure 4.3: Illustrates the association between baseline adversity and linear change in the right anterior cingulate surface area across follow-up assessments. The bivariate latent change score analysis (N=502) revealed that greater baseline adversity was associated with a very modest reduction in the right anterior cingulate surface area at follow-up analysis.

4.3.5 Relationship between adverse life events and brain cortical thickness in the frontoparietal areas

I next examine the relationship between adversity and cortical thickness in each frontoparietal regions. Inspection of model fit revealed that all models were within the range of acceptable fit (fit range: CFI: 985 - 944; RMSEA: 0.046 – 0.090; SRMR: 0.029 – 0.038). I follow a similar strategy used in the two bivariate relationships described above by examining the within-variable change in cortical thickness, the lagged effects of baseline adversity on changes in cortical thickness and the lagged effects of cortical thickness on adversity (shown in Table 4.6).

Within-level changes*:* All baseline cortical thickness in the frontoparietal regions in both the left and right hemispheres were associated with steeper decreases across time (all, $p < 0.05$) with the exception of left anterior cingulate ($p = 0.224$), left posterior cingulate ($p = 0.287$) and right posterior cingulate ($p = 0.992$).

Table 4.4: Bivariate latent change score model of adversity and brain volume						
	Left hemisphere			Right hemisphere		
	Within-level change	Lagged effects of adversity	Lagged effects of volume	Within-level change	Lagged effects of adversity	Lagged effects of brain volume
	Std. β (SE)	Std. β (SE)	Std. β (SE)	Std. β (SE)	Std. β (SE)	Std. β (SE)
Middle frontal	-1.029*** (0.113)	-1.482 (1.232)	0.014 (0.227)	-1.038*** (0.050)	-0.263 (0.224)	-0.002 (0.193)
Orbital frontal	-1.022*** (0.069)	-0.322 (0.336)	-0.037 (0.218)	-1.041*** (0.046)	0.010 (0.240)	0.017 (0.187)
Anterior cingulate	-0.948*** (0.140)	-0.516 (0.694)	-0.022 (0.429)	-1.127*** (0.074)	-0.302 (0.155)	0.045 (0.217)
Inferior frontal	-1.059*** (0.135)	-0.992 (1.490)	0.195 (0.299)	-0.950*** (0.057)	-0.246 (0.247)	0.111 (0.233)
Frontal pole	-1.211***(0.267)	-0.214 (0.838)	0.013 (0.719)	-1.089*** (0.220)	-0.417 (0.592)	-0.409 (0.475)
Superior parietal	-0.934*** (0.071)	0.021 (0.245)	0.007 (0.335)	-0.927*** (0.102)	-0.291 (0.351)	0.095 (0.330)
Superior frontal	-1.045*** (0.104)	-1.041 (0.696)	0.005 (0.168)	-1.070*** (0.070)	-0.571 (0.834)	0.016 (0.210)
Inferior parietal	-0.882*** (0.105)	-0.349 (0.359)	0.083 (0.304)	-0.782*** (0.097)	-0.269 (0.429)	-0.093 (0.355)
Precuneus	-0.943*** (0.070)	0.078 (0.280)	0.185 (0.271)	-0.890*** (0.089)	0.164 (0.331)	-0.027 (0.283)
Posterior cingulate	-1.029*** (0.195)	-0.095 (0.195)	0.350 (0.369)	-0.721*** (0.151)	-0.410 (0.303)	-0.069 (0.362)
Insula	-1.045*** (0.121)	0.133 (0.218)	0.078 (0.356)	-1.012*** (0.154)	0.070 (0.250)	-0.183 (0.406)

Table 4.5: Bivariate latent change score model of adversity and brain Surface area						
	Left hemisphere			Right hemisphere		
	Within-level change	Lagged effects of adversity	Lagged effects of brain surface area	Within-level change	Lagged effects of adversity	Lagged effects of brain surface area
	Std. β (SE)	Std. β (SE)	Std. β (SE)	Std. β (SE)	Std. β (SE)	Std. β (SE)
Middle frontal	-0.973*** (0.045)	-0.366 (0.198)	0.194 (0.158)	-0.945*** (0.053)	-0.172 (0.154)	0.277 (0.188)
Orbital frontal	-0.995*** (0.086)	-0.553 (0.297)	0.107 (0.185)	-0.955*** (0.125)	-0.570 (1.054)	0.248 (0.309)
Anterior cingulate	-0.878*** (0.124)	-0.211 (0.249)	0.229 (0.370)	-1.035*** (0.088)	-0.266* (0.127)	0.354 (0.264)
Inferior frontal	-0.925*** (0.038)	0.077 (0.159)	0.240 (0.200)	-0.872*** (0.071)	-0.092 (0.183)	0.379 (0.258)
Frontal pole	-0.995* (0.477)	0.444 (0.393)	1.599 (1.529)	-1.028*** (0.172)	0.251 (0.324)	0.208 (0.526)
Superior parietal	-0.816*** (0.093)	0.052 (0.180)	0.036 (0.327)	-0.600*** (0.139)	-0.092 (0.325)	0.203 (0.345)

Superior frontal	-0.928*** (0.051)	-0.218 (0.114)	0.263 (0.174)	-0.909*** (0.053)	-0.260 (0.290)	0.303 (0.263)
Inferior parietal	-0.770*** (0.120)	-0.177 (0.236)	0.288 (0.334)	-0.602*** (0.164)	-0.110 (0.303)	-0.103 (0.449)
Precuneus	-0.879*** (0.064)	0.156 (0.272)	0.103 (0.285)	-0.817*** (0.091)	0.052 (0.237)	0.063 (0.323)
Posterior cingulate	-0.683* (0.335)	-0.097 (0.185)	0.888 (0.630)	-0.553* (0.243)	-0.084 (0.246)	0.448 (0.594)
Insula	-0.472 (0.441)	-0.088 (0.359)	-1.579 (1.404)	-0.612* (0.277)	-0.218 (0.330)	-0.167 (0.671)

Table 4.6: Bivariate latent change score model of adversity and brain cortical thickness						
	Left hemisphere			Right hemisphere		
	Within-level change	Lagged effects of adversity	Lagged effects of cortical thickness	Within-level change	Lagged effects of adversity	Lagged effects of cortical thickness
	Std. β (SE)	Std. β (SE)	Std. β (SE)	Std. β (SE)	Std. β (SE)	Std. β (SE)
Middle frontal	-1.839*** (0.294)	-0.684 (1.418)	-0.202 (0.325)	-0.824*** (0.084)	-0.178 (0.362)	-0.306 (0.220)
Orbital frontal	-0.623** (0.232)	0.230 (0.273)	-0.934 (0.483)	-1.086*** (0.076)	0.317 (0.318)	-0.398* (0.186)
Anterior cingulate	0.428 (0.638)	-0.120 (0.729)	-0.774 (1.044)	-1.042*** (0.086)	0.012 (0.274)	-0.273 (0.212)
Inferior frontal	-1.043** (0.320)	-1.020 (1.741)	-0.065 (0.542)	-0.860*** (0.097)	-0.081 (0.406)	-0.304 (0.237)
Frontal pole	-0.855*** (0.168)	-0.133 (0.366)	-0.769 (0.511)	-1.004*** (0.112)	-0.476 (0.589)	-0.141 (0.289)
Superior parietal	-0.978*** (0.081)	-0.101 (0.458)	0.109 (0.278)	-1.071*** (0.059)	-0.157 (0.372)	0.012 (0.214)
Superior frontal	-1.822* (0.770)	-0.423 (0.928)	-0.430 (2.019)	-1.957*** (0.035)	-0.246 (0.453)	-0.151 (0.149)
Inferior parietal	-0.985*** (0.099)	-0.207 (0.403)	-0.011 (0.278)	-1.101*** (0.095)	-0.296 (0.400)	0.258 (0.288)
Precuneus	-1.003*** (0.104)	0.069 (0.322)	0.019 (0.339)	-1.187*** (0.064)	0.261 (0.278)	-0.103 (0.184)
Posterior cingulate	-0.377 (0.355)	-0.446 (0.551)	-0.793 (0.696)	-0.004 (0.438)	-0.578 (0.483)	-1.153 (0.765)
Insula	-0.798** (0.291)	-0.395 (0.404)	0.804 (0.519)	-1.037*** (0.290)	-0.310 (0.518)	-0.298 (0.510)

Lagged effects of adversity on changes in the cortical thickness of frontoparietal regions: I then examined whether adversity at baseline was associated with increases or decreases in cortical thickness. I found no evidence of significant association between baseline adversity level and linear change in cortical thickness at follow-ups in both left ($p > 0.327$) or right ($p > 0.230$) hemispheres.

Lagged effects of cortical thickness on changes in adversity: Next, I examined whether baseline cortical thickness was associated with linear change in adversity exposure reported across follow-up assessments. Results showed that baseline right orbitofrontal thickness was associated with a marginal but significant negative change in adversity level at the follow-up assessments (*Std.* β = -0.398, p = 0.032, 95% CI = [-0.762, -0.034]). This implies that greater right orbitofrontal cortical thickness at age 14 predicted a small decrease in adversity exposure reported at ages 19 and 22. No other significant associations were observed in the left (all p's> 0.052) or right (all p's> 0.131) hemispheres.

4.3.6 Relationship between adverse life events and different cognitive outcomes

The last bivariate relationship I examined was the association between adversity and different cognitive outcomes in the spatial working memory and Cambridge gambling tasks. The cognitive variables tested include: strategy and between error scores in the spatial working memory task, as well as quality of decision making, risk taking and risk adjustment in the Cambridge gambling task. Model inspection showed that all models fit well (fit range: CFI: 0.988 – 0.958; RMSEA: 0.034 – 0.067; SRMR: 0.029 – 0.033). Results shown in Table 4.7 revealed that with the exception of risk adjustment (p = 0.151), smaller baseline cognitive scores were associated with significant incremental linear change across the two follow-up assessments (all p's<0.01). However, there was no significant association between baseline

adversity score and linear changes in any of the cognitive outcome (all p's> 0.333), or vice versa (all p's> 0.076).

Table 4.7: Bivariate latent change score model of adversity and cognitive outcomes			
	Within-level change	Lagged effects of adversity	Lagged effects of Cognition
	Std. β (SE)	Std. β (SE)	Std. β (SE)
SWM Strategy	-0.709** (0.222)	-0.380 (0.530)	0.450 (0.440)
SWM Errors	-1.696*** (0.297)	-0.049 (0.152)	0.992 (0.562)
CGT quality of decision making	-0.981*** (0.173)	-0.413 (0.427)	-0.058 (0.373)
CGT risk taking	-0.962*** (0.169)	-0.242 (0.381)	0.806 (0.474)
CGT risk adjustment	-0.721 (0.503)	-0.473 (0.869)	-1.478 (2.309)

4.3.7 Mediation analysis

Lastly, through autoregressive path models, I completed longitudinal mediation analyses of adversity, brain metrics and cognitive outcomes. Depicted in Figure 4.2, there are potentially 6 indirect paths involving these 3 variables. I however report only two paths relevant to the research questions. In the first of these two indirect path analyses, I examined if adversity at Time 1 predicts residualised brain score at Time 2 and if this in turn predicts cognitive performance at Time 3. Results presented in Table 4.8, showed that no significant indirect associations were observed for this first indirect path involving adolescent adversity exposure brain variables (volume, surface area and cortical thickness) and cognitive outcomes. The confidence intervals of each of these mediation models included zeros, indicating they were not statistically significant. Similarly, I examined a second indirect path of effects, by reversing the mediators and outcomes. This second model examined if adversity at Time 1 predicts cognitive performance at Time 2 which in turn predicts brain volume, surface area or cortical thickness at Time 3. Similar to the first set of mediation analyses, I found no evidence of any

indirect association involving this path, as the confidence intervals in each mediation model included zero, indicating a lack of significant indirect effects.

Table 4.8. Complete longitudinal mediation analysis showing indirect effects of different brain regions (path 1) or cognitive functioning (path 2) in the relationship between adolescent adversity exposure, brain development and cognitive functioning. Bias corrected 95% confidence intervals indicate no significant mediating effect in any of the models or paths examined.

	Indirect effects	Brain Volume		Surface area		Cortical Thickness	
		β	95%CI	β	95%CI	β	95%CI
	SWM strategy						
1st path	Adversity T1 =>Middle frontal T2 => SWM strategy T3	0.002	-0.001, 0.010	0.000	-0.006, 0.003	0.000	-0.008, 0.006
2nd path	Adversity T1 => SWM strategy T2 => Middle frontal T3	0.001	-0.001, 0.005	0.000	-0.001, 0.003	0.002	-0.002, 0.011
1st path	Adversity T1 =>Orbitofrontal T2 => SWM strategy T3	0.002	-0.001, 0.010	-0.001	-0.007, 0.002	0.002	-0.003, 0.010
2nd path	Adversity T1 => SWM strategy T2 => Orbitofrontal T3	-0.001	-0.005, 0.001	0.000	-0.004, 0.001	0.000	-0.003, 0.004
1st path	Adversity T1 =>anterior cingulate T2 => SWM strategy T3	0.000	-0.007, 0.007	-0.001	-0.007, 0.004	0.000	-0.003, 0.005
2nd path	Adversity T1 => SWM strategy T2 =>anterior cingulate T3	0.000	-0.001, 0.005	0.000	-0.003, 0.001	0.001	-0.001, 0.009
1st path	Adversity T1 =>inferior frontal T2 => SWM strategy T3	0.001	-0.002, 0.006	0.000	-0.004, 0.002	-0.001	-0.010, 0.006
2nd path	Adversity T1 => SWM strategy T2 => inferior frontal T3	0.000	-0.001, 0.004	0.000	-0.002, 0.002	0.002	-0.002, 0.010
1st path	Adversity T1 =>frontal pole T2 => SWM strategy T3	0.000	-0.002, 0.007	-0.001	-0.010, 0.001	-0.001	-0.009, 0.005
2nd path	Adversity T1 => SWM strategy T2 => frontal pole T3	0.001	-0.001, 0.007	0.000	-0.006, 0.001	0.002	-0.002, 0.009
1st path	Adversity T1 =>superior parietal T2 => SWM strategy T3	-0.001	-0.009, 0.004	0.000	-0.004, 0.002	0.000	-0.009, 0.006
2nd path	Adversity T1 => SWM strategy T2 => superior parietal T3	0.000	-0.001, 0.004	0.000	-0.001, 0.003	0.002	-0.002, 0.008
1st path	Adversity T1 =>superior frontal T2 => SWM strategy T3	0.001	-0.002, 0.007	0.000	-0.004, 0.002	0.001	-0.006, 0.010
2nd path	Adversity T1 => SWM strategy T2 => superior frontalT3	0.001	-0.001, 0.005	0.000	-0.004, 0.000	0.002	-0.002, 0.011
1st path	Adversity T1 =>inferior parietal T2 => SWM strategy T3	0.000	-0.001, 0.004	0.000	-0.004, 0.001	-0.001	-0.010, 0.001
2nd path	Adversity T1 => SWM strategy T2 => inferior parietal T3	0.000	-0.001, 0.004	0.000	-0.001, 0.003	0.002	-0.002, 0.009
1st path	Adversity T1 =>Precuneus T2 => SWM strategy T3	0.000	-0.003, 0.005	0.000	-0.002, 0.003	0.000	-0.002, 0.005
2nd path	Adversity T1 => SWM strategy T2 => Precuneus T3	0.000	-0.001, 0.004	0.000	-0.002, 0.001	0.001	-0.002, 0.007
1st path	Adversity T1 =>Posterior cingulate T2=>SWM strategy T3	0.000	-0.002, 0.004	0.000	-0.003, 0.002	0.002	-0.001, 0.009
2nd path	Adversity T1 => SWM strategy T2=>posterior cingulate T3	0.000	-0.001, 0.005	0.000	-0.002, 0.002	0.001	-0.001, 0.008
1st path	Adversity T1 =>insula T2 => SWM strategy T3	0.000	-0.002, 0.002	0.000	-0.002, 0.003	0.001	-0.001, 0.007
2nd path	Adversity T1 => SWM strategy T2 => insula T3	0.001	-0.001, 0.005	0.000	-0.001, 0.004	0.002	-0.002, 0.009
	SWM between errors						
1st path	Adversity T1 =>Middle frontal T2 => SWM errors T3	0.000	-0.002, 0.006	0.000	-0.003, 0.002	0.000	-0.008, 0.007

2nd path	Adversity T1 => SWM errors T2 => Middle frontal T3	0.000	-0.001, 0.003	0.000	-0.001, 0.002	0.001	-0.003, 0.008
1st path	Adversity T1 =>Orbitofrontal T2 => SWM errors T3	-0.001	-0.008, 0.001	0.000	-0.001, 0.006	0.000	-0.007, 0.007
2nd path	Adversity T1 => SWM errors T2 => Orbitofrontal T3	0.000	-0.003, 0.001	0.000	-0.001, 0.003	0.000	-0.005, 0.001
1st path	Adversity T1 =>anterior cingulate T2 => SWM errors T3	0.000	-0.003, 0.004	0.000	-0.005, 0.001	0.001	-0.001, 0.009
2nd path	Adversity T1 => SWM errors T2 =>anterior cingulate T3	0.000	-0.002, 0.002	0.000	-0.003, 0.001	0.000	-0.002, 0.005
1st path	Adversity T1 =>inferior frontal T2 => SWM errors T3	0.000	-0.006, 0.002	0.000	-0.001, 0.003	-0.002	-0.011, 0.004
2nd path	Adversity T1 => SWM errors T2 => inferior frontal T3	0.000	-0.002, 0.001	0.000	-0.003, 0.001	0.000	-0.002, 0.007
1st path	Adversity T1 =>frontal pole T2 => SWM errors T3	0.000	-0.007, 0.003	-0.001	-0.008, 0.002	-0.001	-0.011, 0.004
2nd path	Adversity T1 => SWM errors T2 => frontal pole T3	0.000	-0.002, 0.006	0.000	-0.003, 0.002	0.000	-0.001, 0.005
1st path	Adversity T1 =>superior parietal T2 => SWM errors T3	-0.001	-0.009, 0.004	0.000	-0.004, 0.002	-0.001	-0.009, 0.006
2nd path	Adversity T1 => SWM errors T2 => superior parietal T3	0.000	-0.004, 0.001	0.000	-0.004, 0.001	0.000	-0.002, 0.005
1st path	Adversity T1 =>superior frontal T2 => SWM errors T3	-0.002	-0.011, 0.001	0.000	-0.002, 0.005	-0.002	-0.011, 0.006
2nd path	Adversity T1 => SWM errors T2 => superior frontal T3	0.000	-0.002, 0.001	0.000	-0.003, 0.001	0.001	-0.003, 0.008
1st path	Adversity T1 =>inferior parietal T2 => SWM errors T3	0.000	-0.004, 0.001	0.000	-0.001, 0.004	-0.002	-0.012, 0.001
2nd path	AdversityT1 => SWM errors T2 => inferior parietal T3	0.000	-0.001, 0.002	0.000	-0.001, 0.002	0.000	-0.001, 0.006
1st path	Adversity T1 =>Precuneus T2 => SWM errors T3	-0.001	-0.008, 0.001	0.000	-0.007, 0.001	0.000	-0.001, 0.007
2nd path	Adversity T1 => SWM errors T2 => Precuneus T3	0.000	-0.001, 0.004	0.000	-0.001, 0.002	0.000	-0.002, 0.006
1st path	Adversity T1 =>Posterior cingulate T2=>SWM errors T3	0.000	-0.002, 0.003	0.000	-0.002, 0.002	0.003	-0.001, 0.010
2nd path	Adversity T1 => SWM errors T2=>posterior cingulate T3	0.000	-0.001, 0.004	0.000	-0.002, 0.001	0.001	-0.006, 0.009
1st path	Adversity T1 =>insula T2 => SWM errors T3	0.000	-0.002, 0.003	0.000	-0.001, 0.005	0.000	-0.006, 0.002
2nd path	Adversity T1 => SWM errors T2 => insula T3	0.000	-0.002, 0.001	0.000	-0.003, 0.001	0.000	-0.003, 0.005
	CGT quality of decision making (QDM)						
1st path	Adversity T1 =>Middle frontal T2 => CGT QDM T3	0.001	-0.001, 0.008	0.000	-0.002, 0.003	0.002	-0.003, 0.012
2nd path	Adversity T1 => CGT QDM T2 => Middle frontal T3	-0.001	-0.007, 0.001	0.000	-0.004, 0.001	0.000	-0.009, 0.003
1st path	Adversity T1 =>Orbitofrontal T2 => CGT QDM T3	0.001	-0.001, 0.007	0.000	-0.001, 0.003	0.003	-0.001, 0.013
2nd path	Adversity T1 => CGT QDM T2 => Orbitofrontal T3	-0.002	-0.009, 0.001	-0.002	-0.008, 0.001	-0.001	-0.010, 0.002
1st path	Adversity T1 =>anterior cingulate T2 => CGT QDM T3	0.000	-0.004, 0.004	0.000	-0.004, 0.001	0.002	-0.001, 0.010
2nd path	Adversity T1 => CGT QDM T2 =>anterior cingulate T3	-0.001	-0.007, 0.001	-0.001	-0.005, 0.000	0.000	-0.004, 0.008
1st path	Adversity T1 =>inferior frontal T2 => CGT QDM T3	0.000	-0.002, 0.005	0.000	-0.001, 0.003	0.002	-0.003, 0.013
2nd path	Adversity T1 => CGT QDM T2 => inferior frontal T3	-0.002	-0.009, 0.001	-0.001	-0.006, 0.001	-0.001	-0.012, 0.002

1st path	Adversity T1 =>frontal pole T2 => CGT QDM T3	0.001	-0.001, 0.007	0.000	-0.004, 0.002	0.000	-0.006, 0.008
2nd path	Adversity T1 => CGT QDM T2 => frontal pole T3	-0.002	-0.011, 0.001	-0.002	-0.011, 0.001	-0.001	-0.007, 0.002
1st path	Adversity T1 =>superior parietal T2 => CGT QDM T3	0.000	-0.005, 0.006	0.000	-0.005, 0.001	0.003	-0.003, 0.014
2nd path	Adversity T1 => CGT QDM T2 => superior parietal T3	-0.002	-0.009, 0.001	-0.001	-0.006, 0.001	-0.001	-0.009, 0.002
1st path	Adversity T1 =>superior frontal T2 => CGT QDM T3	-0.001	-0.007, 0.001	0.000	-0.001, 0.003	-0.001	-0.010, 0.006
2nd path	Adversity T1 => CGT QDM T2 => superior frontal T3	-0.001	-0.009, 0.001	-0.001	-0.005, 0.001	-0.001	-0.012, 0.001
1st path	Adversity T1 =>inferior parietal T2 => CGT QDM T3	0.000	-0.003, 0.002	0.000	-0.001, 0.004	0.002	-0.001, 0.012
2nd path	Adversity T1 => CGT QDM T2 => inferior parietal T3	-0.002	-0.009, 0.001	-0.001	-0.005, 0.001	-0.002	-0.012, 0.001
1st path	Adversity T1 =>Precuneus T2 => CGT QDM T3	0.000	-0.005, 0.002	0.000	-0.005, 0.001	0.001	-0.001, 0.008
2nd path	Adversity T1 => CGT QDM T2 => Precuneus T3	-0.001	-0.008, 0.001	-0.001	-0.005, 0.001	-0.001	-0.010, 0.001
1st path	Adversity T1 =>Posterior cingulate T2=> CGT QDM T3	0.000	-0.004, 0.001	0.000	-0.002, 0.003	0.000	-0.003, 0.006
2nd path	Adversity T1 => CGT QDM T2=>posterior cingulate T3	-0.002	-0.010, 0.001	-0.002	-0.008, 0.001	-0.001	-0.012, 0.002
1st path	Adversity T1 =>insula T2 => CGT QDM T3	0.000	-0.002, 0.002	0.000	-0.001, 0.004	0.000	-0.001, 0.006
2nd path	Adversity T1 => CGT QDM T2 => insula T3	-0.001	-0.006, 0.001	-0.001	-0.006, 0.001	-0.001	-0.009, 0.001
	CGT risk taking						
1st path	Adversity T1 =>Middle frontal T2 => CGT QDM T3	0.000	-0.004, 0.004	0.000	-0.004, 0.002	-0.004	-0.014, 0.001
2nd path	Adversity T1 => CGT risk taking T2 => Middle frontal T3	-0.001	-0.007, 0.001	-0.002	-0.007, 0.001	0.002	-0.001, 0.011
1st path	Adversity T1 =>Orbitofrontal T2 => CGT risk taking T3	0.000	-0.006, 0.001	0.000	-0.004, 0.002	-0.003	-0.014, 0.001
2nd path	Adversity T1 => CGT risk taking T2 => Orbitofrontal T3	0.000	-0.004, 0.001	0.000	-0.004, 0.001	0.000	-0.002, 0.007
1st path	Adversity T1=>anterior cingulate T2 =>CGT risk taking T3	0.000	-0.003, 0.003	0.000	-0.005, 0.001	0.000	-0.005, 0.003
2nd path	Adversity T1=>CGT risk taking T2 =>anterior cingulate T3	-0.001	-0.006, 0.001	-0.001	-0.005, 0.001	0.000	-0.003, 0.006
1st path	Adversity T1 =>inferior frontal T2 => CGT risk taking T3	0.000	-0.006, 0.002	0.000	-0.002, 0.003	-0.002	-0.012, 0.004
2nd path	Adversity T1 => CGT risk taking T2 => inferior frontal T3	-0.001	-0.006, 0.001	-0.001	-0.006, 0.000	0.001	-0.002, 0.010
1st path	Adversity T1 =>frontal pole T2 => CGT risk taking T3	0.001	-0.001, 0.009	-0.001	-0.007, 0.001	-0.001	-0.008, 0.005
2nd path	Adversity T1 => CGT risk taking T2 => frontal pole T3	0.000	-0.003, 0.005	-0.001	-0.009, 0.001	0.001	-0.001, 0.008
1st path	Adversity T1 =>superior parietal T2 => CGT risk taking T3	0.002	-0.003, 0.010	0.001	-0.001, 0.007	-0.001	-0.009, 0.006
2nd path	Adversity T1=> CGT risk taking T2 => superior parietal T3	0.000	-0.002, 0.005	0.000	-0.002, 0.003	0.000	-0.003, 0.005
1st path	Adversity T1 =>superior frontal T2 => CGT risk taking T3	0.000	-0.006, 0.002	0.000	-0.003, 0.002	-0.006	-0.018, 0.001
2nd path	Adversity T1 => CGT risk taking T2 => superior frontal T3	0.000	-0.004, 0.001	-0.001	-0.005, 0.001	0.001	-0.001, 0.010
1st path	Adversity T1 =>inferior parietal T2 => CGT risk taking T3	0.000	-0.001, 0.004	0.000	-0.004, 0.001	-0.002	-0.012, 0.001

2nd path	Adversity T1 => CGT risk taking T2 => inferior parietal T3	0.000	-0.004, 0.001	0.000	-0.004, 0.001	0.000	-0.007, 0.002
1st path	Adversity T1 =>Precuneus T2 => CGT risk taking T3	0.000	-0.005, 0.003	0.000	-0.004, 0.002	0.000	-0.005, 0.002
2nd path	Adversity T1 => CGT risk taking T2 => Precuneus T3	0.000	-0.003, 0.002	0.000	-0.001, 0.004	-0.001	-0.007, 0.001
1st path	Adversity T1=>Posterior cingulate T2=>CGT risk taking T3	0.000	-0.002, 0.006	0.000	-0.004, 0.003	0.000	-0.003, 0.005
2nd path	Adversity T1=>CGT risk taking T2=>posterior cingulate T3	0.000	-0.005, 0.001	-0.001	-0.006, 0.001	0.001	-0.001, 0.010
1st path	Adversity T1 =>insula T2 => CGT risk taking T3	0.000	-0.002, 0.002	0.000	-0.004, 0.001	-0.001	-0.007, 0.001
2nd path	Adversity T1 => CGT risk taking T2 => insula T3	0.000	-0.001, 0.005	0.000	-0.004, 0.002	0.002	-0.001, 0.011
	CGT risk adjustment						
1st path	Adversity T1 =>Middle frontal T2 => CGT risk adjust T3	0.000	-0.006, 0.002	0.000	-0.002, 0.005	0.003	-0.002, 0.012
2nd path	Adversity T1 => CGT risk adjust T2 => Middle frontal T3	0.000	-0.003, 0.004	0.000	-0.005, 0.001	0.001	-0.001, 0.009
1st path	Adversity T1 =>Orbitofrontal T2 => CGT risk adjust T3	0.000	-0.002, 0.005	0.000	-0.002, 0.005	0.003	-0.001, 0.012
2nd path	Adversity T1 => CGT risk adjust T2 => Orbitofrontal T3	-0.001	-0.006, 0.001	-0.001	-0.005, 0.001	0.001	-0.001, 0.009
1st path	Adversity T1=>anterior cingulate T2 =>CGT risk adjust T3	0.000	-0.002, 0.002	0.000	-0.001, 0.005	0.002	-0.001, 0.011
2nd path	Adversity T1=>CGT risk adjust T2 =>anterior cingulate T3	-0.001	-0.008, 0.001	-0.001	-0.008, 0.001	0.003	-0.001, 0.014
1st path	Adversity T1 =>inferior frontal T2 => CGT risk adjust T3	0.000	-0.005, 0.002	0.000	-0.001, 0.003	0.001	-0.006, 0.008
2nd path	Adversity T1 => CGT risk adjust T2 => inferior frontal T3	-0.001	-0.007, 0.001	-0.002	-0.007, 0.001	0.002	-0.001, 0.011
1st path	Adversity T1 =>frontal pole T2 => CGT risk adjust T3	0.001	-0.001, 0.008	-0.001	-0.007, 0.001	0.001	-0.005, 0.008
2nd path	Adversity T1 => CGT risk adjust T2 => frontal pole T3	-0.001	-0.010, 0.001	-0.003	-0.013, 0.002	0.001	-0.001, 0.007
1st path	Adversity T1 =>superior parietal T2 => CGT risk adjust T3	0.000	-0.006, 0.006	0.000	-0.005, 0.001	0.002	-0.004, 0.009
2nd path	Adversity T1=> CGT risk adjust T2 => superior parietal T3	-0.001	-0.007, 0.001	-0.001	-0.006, 0.001	-0.001	-0.007, 0.001
1st path	Adversity T1 =>superior frontal T2 => CGT risk adjust T3	0.000	-0.002, 0.006	0.000	-0.002, 0.003	0.002	-0.005, 0.010
2nd path	Adversity T1 => CGT risk adjust T2 => superior frontal T3	-0.001	-0.006, 0.001	-0.001	-0.005, 0.000	0.001	-0.001, 0.008
1st path	Adversity T1 =>inferior parietal T2 => CGT risk adjust T3	0.000	-0.001, 0.005	0.000	-0.003, 0.001	0.001	-0.002, 0.007
2nd path	Adversity T1 => CGT risk adjust T2 => inferior parietal T3	-0.001	-0.008, 0.001	0.000	-0.005, 0.001	-0.002	-0.010, 0.001
1st path	Adversity T1 =>Precuneus T2 => CGT risk adjust T3	0.000	-0.002, 0.005	0.000	-0.004, 0.001	0.001	-0.001, 0.007
2nd path	Adversity T1 => CGT risk adjust T2 => Precuneus T3	-0.001	-0.006, 0.001	-0.001	-0.006, 0.001	0.000	-0.004, 0.003
1st path	Adversity T1=>Posterior cingulate T2=>CGT risk adjust T3	0.000	-0.006, 0.003	0.000	-0.004, 0.005	0.000	-0.002, 0.006
2nd path	Adversity T1=>CGT risk adjust T2=>posterior cingulate T3	-0.002	-0.009, 0.002	-0.002	-0.010, 0.002	0.001	-0.001, 0.009
1st path	Adversity T1 =>insula T2 => CGT risk adjust T3	0.000	-0.002, 0.002	0.000	-0.001, 0.005	0.001	-0.001, 0.007
2nd path	Adversity T1 => CGT risk adjust T2 => insula T3	-0.002	-0.008, 0.001	-0.002	-0.007, 0.001	0.001	-0.002, 0.008

Cl = Confidence intervals; CGT = Cambridge Gambling Task; QDM = Quality of Decision Making; risk adjust = risk adjustment; T1 = Timepoint 1; Time 2= Timepoint 2; T3 = Timepoint 3

4.4 Discussion

In a three-wave longitudinal cohort sample, this study used a latent change score model to examine the bivariate relationships between adverse life events and the trajectories of 3 brain morphometric measures (i.e., volume, surface area and cortical thickness) in the frontoparietal regions. Using similar analytic approaches, I also investigated the association between adversity exposure and various cognitive outcomes. This analytic strategy allows me to test the bidirectional effects of individual differences in change in the relations between adversity, brain development and cognitive outcomes. As such, this study examine if adversity predicts changes in outcomes and/or if these outcomes predict change in adversity. After controlling for age, sex and sites of recruitment, results showed that baseline adversity levels at age 14 predicted a marginal decrease in the surface area of the right anterior cingulate cortex at follow-up assessments. Similarly, greater baseline cortical thickness of right orbitofrontal cortex predicted a small, but significant decrease in the levels of adversity exposure reported at follow-up assessments. I found no evidence of significant relations between adversity and volumetrics of the frontoparietal regions or cognitive outcomes. In a separate analysis, I used longitudinal mediation models to further explore interrelations between adversity, brain morphometrics and cognitive outcomes, exploring two potential indirect paths – indirect effects of brain morphometrics and indirect effects of cognitive outcomes. Statistical models showed no evidence of indirect effects in any of the two indirect paths that I examined.

Examining these findings, there are a number of important connections to note related to previous studies. First, I found evidence of lagged effects of adversity on right anterior cingulate surface area, as well as lagged effects of right orbitofrontal thickness on adversity. I must caution that these associations are very modest in nature. Due to its protracted neurodevelopment, portions of prefrontal cortex are presumed to be more vulnerable to

adversity exposure in childhood (Arnsten, 2009; Lupien et al., 2009). Supporting this assumption, previous studies investigating prefrontal regions have shown some of the most consistent alterations following adversity compared to many other brain regions (Mackes et al., 2020; Gold et al., 2016; Hodel et al., 2015; McLaughlin et al., 2014). The reduced change in right anterior cingulate surface area, observed in this study, is also consistent with a few other cross-sectional studies that have found altered anterior cingulate volume following adversity (Hanson et al., 2012; Jensen et al., 2015; Ansell et al., 2012). However, there have been a number of studies focused on anterior cingulate surface area that have not noted associations with adversity exposure (Mackes et al., 2020, Rinne-Albers et al., 2020). Related to the lagged effects of right orbitofrontal cortical thickness on adversity observed in this study, there are not any existing longitudinal studies, to my knowledge, examining the bi-directional effects of adversity and brain morphometrics. All previous cross-sectional studies have examined how adversity predicts brain development (and not vice versa). Nonetheless, there have been multiple studies linking adversity to alterations in orbitofrontal cortical thickness (Bounoua, et al., 2020; Monninger et al., 2019; McLaughlin et al., 2014) while few studies have linked the frontal regions, particularly the prefrontal cortex to perceived adversity exposures (McEwen et al., 2013; Michalski et al., 2017; Moreno et al., 2017). These findings might prompt different interpretations of those past results, especially if future longitudinal work continues to link orbitofrontal cortical thickness to adversity perceptions.

At a broad level, I noted only modest associations between dversity exposure and the three brain morphometrics measured in this study. This stands in stark contrast with the widespread structural alterations in frontoparietal regions reported elsewhere (Mackes et al., 2020; Gold et al., 2016; Hodel et al., 2015; McLaughlin et al., 2014; Kelly et al., 2013; Teicher, 2006; Cohen et al., 2006; Baker et al., 2012; Thomaes et al., 2010). There are multiple explanations for these potential discrepancies. First, most of these past studies recruited

participants who have been exposed to extreme forms of adversity (e.g., institutionalization, severe maltreatment). These types of extreme stress or adversity have been linked to higher likelihood of developing psychopathology. This is in contrast to the current study, which examined a general population, representative cohort. It is likely that the adversity exposure that was measured here (i.e., general lower level environmental and family stressors) do not exert as much impact on brain development, as the more extreme adversities examined in past published reports. An alternative explanation to the small, non-significant effects observed in this study may also be related to the longitudinal modeling used in the study. My study approach was designed to capture increases or decreases present in the bivariate and bi-directional relations between adversity and the brain morphometrics. As such changes are often based on auto-regressive assumptions (i.e., differences in scores between two timepoints), significant effects may be less likely to be observed compared to the robust alterations previously reported in cross-sectional studies. Results of the paired-wave correlational analysis between adversity exposure and the brain morphometrics which showed widespread significant associations, appeared to support this point. A third possible explanation may be the developmental timing of adversity in this study. Although the study asked about the lifetime exposure to adverse life events at 14, later adversity measurements at ages 19 and 22 primarily centered on adverse life events that had happened since the time of a participant's last study visit. Previous work on the sensitive periods of adversity (Marini et al., 2020; Dunn et al., 2019) have observed that effects of adversity on outcomes are greater when exposures occur in very early childhood (than in later childhood). Past cross-sectional studies on brain development and adversity have commonly focused on samples with adversity exposure in the very early years of life (i.e., institutionalization at age 1-3). This idea is further strengthened by a previous work in a community-based sample (Birn et al., 2017). Although a functional imaging study, findings showed that those with high levels of childhood stress had more altered brain

activations including in many frontoparietal regions during fMRI task designed to measure risk taking and decision making relative to a comparison group that ranked low on stress level. More importantly, the effects observed in their study were completely driven by childhood stress, rather than current (adult) stress level. Another recent study (Gehred et al., 2021) showed that prospectively ascertained childhood stress had larger and widely distributed effects on brain alterations compared to retrospective childhood stress reported in adulthood. Taken together, these past studies collectively suggest the intensity of reported adversity exposure and also the developmental time of adversity exposure may explain the limited effects observed in this study.

Additionally, by simultaneously examining three brain morphometric measures, I probed if adversity has equally distributed or disproportionate effects on brain volume, surface area and cortical thickness. Based on the findings observed in this study, the answer to this question is, presently, inconclusive. I observed no bivariate relationship between brain volume and adversity and reported lagged effects of adversity on the surface area of right anterior cingulate as well as lagged effects of right orbitofrontal cortical thickness on adversity. However, the very small nature of these effects does not convince me to make any concrete conclusion in this regard. Almost all previous studies have examined these three brain morphometrics separately in relation to how they are altered by adversity. And the only studies that have simultaneously examined at least two of these three morphometrics have reported equally distributed alterations in cortical surface area and thickness (Gehred et al., 2021), regional specific alterations (e.g., smaller right inferior frontal volume and surface area Mackes et al., 2020) or no alterations at all (Rinne-Albers et al., 2020). More studies are needed before I can concretely ascertain the extent of widespread alterations in all three brain morphometrics following adversity.

Lastly, I examined if complete longitudinal mediation models can provide insight into the neurocognitive pathways potentially mediating the interrelations between adversity, brain and cognitive outcomes. In doing so, I examine two crucial indirect paths – first, the path from which the effects of adversity on brain morphometrics at earlier assessments reflects on cognitive functioning later on; and an alternative path where the effects of adversity on cognition at an earlier wave impacts the brain development at the later assessment. I found no evidence of indirect association in any of the two indirect paths I reported. While adversity is known to predict alterations in the prefrontal cortex and cognitive abilities, I have no knowledge of studies that have examined their mediating effects. And most knowledge about their interrelations come from functional imaging studies. Additional work is needed to further confirm the absence of neurocognitive mediating effects. Possible reasons for the lack of indirect effects observed may mirror explanations for limited effects observed in the bivariate latent change analysis. For example, all brain and cognitive scores at timepoint two and timepoint three were residualised and as been noted (Jose, 2016), such highly auto-regressive paths of mediation analysis would ordinarily diminish any potential indirect effects present in the data. I encourage future studies that would similarly probe this longitudinal mediating effect.

4.4.1 Limitation of the study

The most significant limitation of the current study is the lack of clear longitudinal measurement invariance in the adversity measures. Although all subscales of the bullying and life events questionnaires used for adversity measurements were within the cut-off of metric or scalar measurement invariance through either predefined fit difference threshold or likelihood ratio test (See table 4.1), however, the CFI fit of these subscales suffered considerably from

poor values. Possible reasons for the relatively poor CFI values observed in the adversity measures maybe down to the nuances in the measurement protocols. For example, the life events questionnaire at baseline was based on lifetime retrospective reports where the participants were asked if they had been exposed to a particular negative event and to indicate the age or time of exposure. Although, subsequent questions at follow-up assessments were framed to reflect experiences that had occurred after the baseline measurement, (and in-between each follow-up assessments), however, the retrospective adversity responses provided at baseline might have biased the model fit of measurement invariance analysis in a substantial way. Alternative reason for the considerably poor CFI scores may be due low inter-item correlation which have been noted in the life event questionnaire (Newcomb, Huba, & Bentler, 1981), especially given that all other fit indices for these adversity measures were within excellent range.

4.4.2 Conclusion

I found that baseline adversity was associated with a decrease in the right anterior cingulate surface area. I also found that greater right orbitofrontal cortical thickness at baseline was related to a small decrease in reported adversity at follow-up assessments. Both of these effects reported in this study were very marginal. These findings to some extent provide an additional empirical and longitudinal backing to the widespread alterations of brain morphometrics previously reported in the literature.

5 Chapter 5

5.1 General discussion

The purpose of this thesis is to use longitudinal modelling to understand the complexities of adverse childhood experiences and their long-term effects on mental health, cognitive abilities, and cortical brain structures. In doing this, I utilized three large population cohort samples, namely, the Millennium Cohort Study (MCS, N = 13,287), Avon longitudinal study of parents and children (ALSPAC, N = 2,965), and IMAGEN cohort sample (N = 502). Each of the three population cohort samples provided a unique dataset suited to examine pertinent research questions that are crucial towards enhancing the understanding of the intricacies of childhood adversity. Below, I integrate the key findings across these empirical studies and articulate recommendations for future directions. I end this chapter by highlighting the strengths and limitations of this thesis.

In chapter two, I attempted to understand the cumulative and time-specific mediating effects of childhood mental health across ages 3-14 in the relation between early-life adversity and cognitive functioning. Findings showed that adversity exposure at age 3 was associated with poorer mental health across all timepoints (3, 5, 7, 11 and 14) and poorer cognitive performance in spatial working memory and vocabulary at ages 11 and 14 respectively. More importantly, when I examined the indirect pathways between adversity, mental health and cognitive functioning, I found that mental health across ages 3-11 (mediation pathways) cumulatively explained 59% of the total effects between adversity and poorer spatial working

memory performance at age 11. Similarly, poorer mental health across ages 3-14 (mediation pathways) accounted for 70% of the total effects between adversity and poorer performance in vocabulary at age 14.

These findings of chapter two are particularly interesting, especially in the context of forging resilience and adaptive skills after adversity. Earlier in the introduction, I highlighted findings that showed that individuals can develop resilience or adaption to adversity by developing some protective factors which can help buffer the effects of adversity on several developmental outcomes. This empirical chapter did not set out to test ways individuals exposed to adversity can build protective factors, but in attempting to address my research questions, the study revealed an important insight into one potential mechanism through which effects of adversity on cognitive abilities manifest. For example, adversity may lead to protracted periods of poorer mental health across childhood, and this lasting poor mental health in childhood adds up and manifests in poorer cognitive abilities such as learning and memory. Previous study has shown that internalizing and externalizing behaviours (similar to those measured in Strengths and Difficulties Questionnaire) were associated with poorer academic performance across adolescence (Van der Ende, Verhulst, & Tiemeier, 2016). This is not very surprising given that inattention and distractibility which are inherent symptoms of externalizing behaviours are likely to affect the cognitive processes needed to excel in learning and standard tests. This begs the question, if the mental health conditions of children exposed to adverse life experiences are improved through some sort of intervention, would that foster academic and cognitive resilience in those children? I strongly encourage future research in this direction.

In chapter three, I analyzed data from the Avon longitudinal study of parents and children, consisting of 2,965 participants. Primary analysis investigating presence of adversity subgroups showed evidence of 5 adversity subgroups/classes, namely, low adversity,

dysfunctional family, parental deprivation, family poverty and global adversity. Further analysis seeking to establish a pathway to cognitive functioning among the adversity subgroups showed that these subgroups performed differentially in the key cognitive outcomes with participants in family poverty performing poorer, relative to participants in low adversity in both inhibition and working memory outcomes. In a separate analysis, this study revealed that the effects of each individual adversity types on cognitive outcomes were mostly consistent with the observed class performance in which they co-occurred. That is, financial distress, for example, was one type of adversity that formed the family poverty subgroup, and this adversity type was associated with poorer cognitive outcomes, similar to the poorer performance observed among participants in the family poverty subgroup. Consistent with previous studies (Dunn et al., 2017; Dunn et al., 2018; Dunn et al., 2019), sensitive periods at very early childhood, compared to accumulation hypothesis, explained more variability in the observed effects between childhood adversity and cognitive outcomes.

The findings in this study are fascinating as they provided support for dimensional models of childhood adversity (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014; McLaughlin & Sheridan, 2016; McLaughlin et al., 2021), despite recent criticisms (Smith & Pollak, 2020). Essentially, findings provided evidence that adversity can be quantified into discrete subgroups, and thus, an alternative perspective to studying childhood adversity that takes into account the independent and co-occurring effects of multiple adverse experiences. As I highlighted in chapter 1, poverty has been noted to be one of the most potent predictors of poorer cognitive outcomes in high income countries (Nisbett et al., 2012), with some studies suggesting that the poorer cognitive outcomes observed in people reared in poverty may be comparable to the severely neglected or institutionalised children (Hildyard & Wolfe, 2002). Although based on the evidence from this study, I would not want to go that far to make this extreme comparison but it was nonetheless fascinating to observe participants in

the family poverty subgroup perform poorer than all other subgroups, including those in the global adversity subgroup who, unfortunately, reported a significant exposure to almost all adverse childhood experiences I examined. Although I did not observe poorer cognitive performance among participants in global adversity subgroup compared to those in low adversity, but that does not imply that those with multiple exposures to adversity are better insulated from the effects of adversity compared to those living in poverty. What I imply is that since the largest number of participants reporting financial distress clustered in this family poverty subgroup, and had poorer cognitive abilities compared low adversity, it provides additional insight into the poorer cognitive competence of individuals exposed to poverty which has been highlighted in previous research.

Another important implication of this poorer cognitive performance from participants in the family poverty subgroup in relation to previous studies, is that it offers insight about potential cross-cultural differences in response to poverty. As I noted above, while living in poverty or low socioeconomic conditions is associated with poorer cognitive outcomes in high-income countries, one of the studies I conducted in Nigeria, on the contrary, showed that children who had experienced parental deprivation (i.e. mostly lived with foster parents either as a result of family poverty or parental death) had better performance in working memory but not inhibition or cognitive flexibility (Nweze et al., 2020). My colleagues and I had reasoned that deprived school children in Nigeria may have developed better working memory abilities as a pathway to social mobility, given the emphasis (by teachers or guardians) of academic hard work as a means of achieving career success. We attempted to replicate these patterns in more recent work, but experienced poor reliability for the socioeconomic status index questionnaire that we administered; this meant study findings were not clearly interpretable. Nonetheless, I would encourage future studies to probe these possible cultural nuances in cognitive attenuations among school children living in poverty using diverse samples of both

low- and high-income countries. This is because if these cultural nuances are well established, they may have implication on interventions aimed at poverty alleviation or more specific programmes targeted at improving the developmental outcomes of children living in poverty. For example, a very recent study in the United States showed evidence of changes in brain activity indicative of acquisition of cognitive skills by infants whose mothers received unconditional and routine financial aid (Troller-Renfree et al., 2022). If the conclusion I reached in my study on Nigerian parentally deprived children is true, then a more appropriate and effective intervention programme in Nigerian samples would be to offer scholarship aids to the best performing deprived school children, with the aim of not only providing adequate support for the brilliant minds through the course of their academic training but also as a motivation for the rest of the school children to work harder towards earning such scholarship. This, no doubt requires further empirical enquiries and is in fact, one of my proposed future works.

In chapter four, I analysed a subset of the IMAGEN cohort sample consisting of 502 participants across three data timepoints as I attempted to longitudinally understand the long-term interrelations between adverse life events, cortical development and cognitive functioning. Compared to my two empirical studies described in this thesis, i.e. chapter 2 and chapter 3, this was a very dynamic study in quite a number of ways. First, the sample was particularly representative, consisting of participants in 8 European cities (4 countries). The other two studies had utilized only British population samples. Second, I analysed data of cortical brain structures, and cognitive outcomes and examined how these developmental processes may be impacted by adversity across 3 timepoints. My other empirical studies had not previously analysed brain data. Third, although my first 2 empirical studies were fairly rigorous, these works were no match for the complexity of the auto-regressive models and measurements that characterized this chapter 4.

In the first main analysis in this chapter 4, I used latent change score models to understand individual differences in change in the relationship between adversity and volume, surface area and cortical thickness of frontoparietal brain regions as well as the relationship between adversity and cognitive processes of working memory and decision making. In doing this, I tested bidirectionality, i.e., how adversity predicts changes in these outcomes versus how the outcomes lead to change in reported adversity level. Results showed that among all the cortical brain structures examined, baseline adversity level only predicted a modest decrease in the right anterior cingulate surface area in the follow-up assessment. On the other hand, baseline right orbitofrontal cortical thickness predicted a marginal decrease in reported adversity at follow-ups. These effects are very modest, even without correcting for multiple comparison. There was no association between adversity and volumes of the cortical structures or cognitive outcomes. In the second main analysis, I used complete longitudinal mediation models to test any indirect neurocognitive effects linking adversity to cortical brain structures and cognitive functions. This mediation model can test for 6 indirect pathways that contain all three variables but I had interest in only two mediating pathways – the path from which adversity at timepoint 1 predicts cortical structures at timepoint 2, which in turn predicts cognitive outcomes at timepoint 3 or the alternative path where adversity at timepoint 1 predicts cognitive outcomes at timepoint 2, which in turn predicts cortical structures at timepoint 3. Results of this longitudinal mediation model showed no evidence of indirect effects in the two neurocognitive pathways that linked adversity with brain and cognitive outcomes.

Although I have discussed these findings extensively in chapter 4, but I would like to highlight a few unique implications of this work. First, findings appear to shed light on the impact of adversity on brain alterations, particularly in the prefrontal regions which have consistently been implicated in the previous cross-sectional studies (Hanson et al., 2012; Jensen et al., 2015; Ansell et al., 2012). Although, the magnitude of effects observed in this study are

smaller than have been reported in the cross-sectional studies, suggesting that potential long-term impact of adversity on brain structures may likely be more modest than previously noted. Second, I also appreciate how the timing of adversity exposure reported in this chapter would have contributed to the modest effects observed on cortical brain structures. In chapter one, I highlighted the possible influence of timing of adversity exposure as a potential explanation for the variations in the developmental outcomes. I also made reference to a number of studies (Dunn et al., 2017; Dunn et al., 2018; Dunn et al., 2019) that showed that adversity exposure occurring in very early childhood accounted for most of the variance of adversity's effects (compared to later adversity exposure or even other theoretical models of accumulation or recency). I did in fact, test these theoretical models of sensitive periods and accumulation on multiple cognitive outcomes in chapter 3 (Nweze et al., 2023), and found consistency with the reports of Dunn and colleagues. In reference to timing, the adversity exposure reported in chapter 4 of this thesis was obtained across ages 14-22 (although baseline adverse life events were retrospectively reported at age 14 and could have included occurrences at earlier childhood as well), a period when adversity is believed to have milder effects on outcomes. This may be a possible explanation for the modest effects reported in chapter 4. For this reason, I encourage future studies that can replicate these models of measurements on brain-cognitive outcomes, using more severe adversity measures that were prospectively captured at early childhood. Finally, I particularly urge all readers to tread with caution when interpreting the results of chapter 4, given that the life events questionnaire used lacked clear longitudinal measurement invariance.

Examined collectively, the overall story from my thesis suggest that the effects of childhood adversity are endearing and continue to adversely manifest on a range of developmental outcome many years after the initial exposure. Given that almost all previous studies in the field are cross-sectional, and little was previously known about the long-term effects of

adversity on developmental outcomes. Motivated to find answers on the long-term effects of adversity, this formed the central research question in this thesis. Findings from all the three empirical studies undertaken in this thesis were in support for long-lasting effects of childhood adversity on developmental outcomes. While I discussed below, the real-world implications of these findings and some limitations that impeded my ability to tell a single story across these empirical studies, but when examined collectively, this thesis supports previous cross-sectional studies that have implicated childhood adversity to alterations in mental health, cognitive functioning and cortical brain development.

5.1.1. Implication of these findings

The findings from this thesis shed further light on the negative impact of adverse childhood experiences on different developmental outcomes, specifically on mental health, cognitive functioning and brain development. As noted in the introduction of the thesis, these three outcomes were the most robustly investigated developmental outcomes linked to adversity and numerous cross-sectional studies have implicated adversity to deficits or alterations in these outcomes. However, given the limitations of cross-sectional studies, further longitudinal studies were warranted in other to establish their long-term associations. Thus, the need to employ longitudinal modelling on these variables of interest.

These findings were mostly consistent with results of cross-sectional studies and one implication of this consistency is the need for a sustained policy to support individuals who are at the highest risk of adversity childhood experiences. As shown in the chapter 3, this could be individuals who are living in chronic and extreme poverty as well as individuals who are unfortunate to have accumulated multiple adversities, leaving them even more vulnerable to the negative impact of such adversities. Government policies that could identify such high-risk individuals from the general population at very early age and provide the adequate and time-

sensitive support, may go a long way in ameliorating the impact of adversity and provide a path to satisfactory life outcomes among such vulnerable individuals.

Examples of government support could include but not limited to greater mental health support, and educational mentoring. I must note that I am not a clinician and I was not trained to be a clinician in my PhD training, but given one of my thesis findings which showed that mental health strongly mediated the effects of childhood adversity on cognitive functioning over a long period of time, this is could be a pointer that with better mental health outcome for children exposed to childhood adversity, their cognitive outcome could invariably improve. Among other ways of improving mental health, families who have been identified to be at the highest-risk should be encouraged to seek for clinical help. Getting adequate clinical help could help improve family relations, alleviate psychological stress and promote wellbeing. With better family relations, the mental health of high-risk children may be improved and they will be in better position to concentrate on their academic responsibilities.

Academic mentoring targeted at these high-risk children may go a along way in directing them to the right path of better life outcomes. In addition to getting mental health support, policies that subsidize or freely avail mentoring services to these individuals may be as helpful as the as the academic training they receive in schools. This is because sometimes, it may take a mentor who has been through adversity and who overcame a specific or broader adversity to be able to support other children or adolescents who are currently struggling from their own adversity. Also, within the connivence of academic training, I equally recommend that teachers and trainers pay special attention to the potential high-risk children (if they were adequately screened and identified prior to their admission) and thus provide them with the additional support they may require to excel in their studies.

5.1.2 Considerations for multiple comparison corrections

As can be observed in the empirical studies undertaken in this thesis, I did not correct for multiple comparisons despite including multiple variables in each of the empirical studies reported in this thesis. There were some theoretical and statistical considerations I put into context before reaching this decision. While every good scientist should be wary of inflated findings or effects which are likely a result of type 1 error and thus can not be replicated, I believe that it is equally important not to overlook real effects incurred from multiple testing correction. So many studies have warned against the danger of type 11 error and argued that the traditional multiple comparison correction methods may not be as effective in reducing type 1 error as have been previously suggested (Groenwold et al., 2021; Gelman et al., 2012). One study noted that the theoretical premise for multiple comparison in the universal null hypothesis that chance is the first-order explanation for observed phenomenon is undermined by the basic premise of empirical research about laws of natural observation (Rothman, 1990). A more recent opinion piece offered more nuances in making statistical choice for correcting for multiple comparison (Lakens, 2016). The author in this piece argued that the only situation that would warrant multiple testing correction is if the statistical tests carried out test a single theory, which will lead authors to accept the hypothesis (Lakens, 2016). Thus, theoretical inference (from tests) is as important as the number of statistical tests done, when thinking about whether to carry out multiple testing correction or not. Such that researchers analysing the effectiveness of drug intervention with t-test or anova may need to correct for multiple testing as it will lead them decide whether drug (treatment group) is more effective than placebo or other controls, and this is fundamentally different compared to other researchers using multi-level modelling where no correction for multiple testing may be warranted given that such models are based on partial pooling (shifting estimates toward each other) which inherently address the multiple

comparison problems (Gelman et al., 2012). It was on these collective basis that I made the statistical choice not to correct for multiple comparison in these studies given that all the three empirical studies undertaken in this thesis were based on multi-level modelling approaches. In addition, I also used a modest interpretation of the observed effects and more importantly, by reporting all the statistical tests I ran or explored, rather than report those that showed statistical significance, I equally promoted transparency in research which is as important as any other methodological considerations.

5.1.3 Strengths and limitations of this thesis

The strengths of this thesis across the three empirical studies are intertwined with the limitations of the previous studies which I described extensively in the introduction of this thesis and to a lesser extent, at each empirical chapter. Principally, the use of longitudinal measurement design across the three empirical studies, especially in chapter 4, provided some novel insights into the long-term consequences of adversity on developmental processes that have not been observed yet in any published empirical studies. In addition, all the empirical studies reported in this thesis utilised large-scale population sample sizes which provided sufficient power to detect any effect in the data. These population cohort samples measured mild forms of adverse childhood experiences, that differed substantially from the severe adversity types (e.g., abuse, neglect) that dominated early adversity studies. Some of the population cohorts, precisely the IMAGEN cohort, reported in chapter 4, was truly representative, at least regionally, as initial samples comprised of adolescents in England, Ireland, France and Germany. This representation can only enhance the generalizability of the findings reported in that study.

Despite these enormous strengths, this thesis still has limitations. As is common in many longitudinal cohort sample, attrition as a result of participants drop out overtime was a noticeable limitation of these empirical studies presented in this thesis. Given that individuals who faced higher adverse childhood experiences (e.g., poverty) are more likely to drop out in longitudinal cohorts (Connelly & Platt, 2014), even the most initial representative sample may be biased significantly by such drop out. Although I used multiple imputations to account for missing data when it is defensible to do so, nonetheless, across all three empirical studies, sample sizes analysed were subsets of larger samples who began the studies at the first assessment point. Secondly, as I noted in the beginning of this chapter, I selected relevant cohort datasets to provide meaningful tests of theoretical models, but I also had to strike a balance to ensure that each selected cohort study had all relevant datasets needed to robustly test these theories and research questions. For example, when I wanted to investigate the long-term interrelations between adversity, cortical brain structures and cognitive outcomes, I needed a cohort sample that has all the data of interest across multiple timepoints. However, as I observed across all studies, no cohort sample will likely have all the desirable data of interest and as result, I have to be amenable in what questions I can ask in each cohort and at the same being cautious in the conclusion that I draw given this limitation. For example, the conclusion I made in chapter 4 would have been more robust and conclusive if I had the luxury of using the rich adversity data available in chapter 3. Nonetheless, this limitation does not detract from the complex and rigorous measurements and statistical designs that addressed those pertinent questions.

Lastly, as can be observed from the three empirical chapters of this thesis, the operational definition of childhood adversity slightly varied for each chapter and the age adversity was assessed was also different for each study. For example, adversity was measured before age 3 in the first empirical study in chapter 2 and measured between ages 8 months to

8.7 years for the second empirical study in chapter 3. The adversity measures used in both empirical studies are the commonly investigated childhood adversity measures in the field and all fall within the standard definition of childhood adversity (Dunn et al., 2018; 2019; McLaughlin, 2016; Kessler et al., 2010). However, the adversity measures for the third empirical study in chapter 4 (defined as adverse life events) slightly differed from the conceptualisation of adversity in the other two empirical chapters in this thesis in terms of severity of adversity. Although the item questions for the first (Parents and Family subscale) and second (Accident and illness subscale) subscales of the life events questionnaires used in study 3 (chapter 4) are similar to the adversity measures I analysed in either study 1 (chapter 2) or study 2 (chapter 3), however, the 3 subscale (Distress subscale) as well as the bullying questionnaire were slightly different from the adversity measures used in my earlier empirical studies. This subtle variation is down to the different datasets used in this thesis as I utilised available adversity data that are closest to how adversity has been operationalised in the literature in the different cohort datasets that I analysed in this thesis. In addition, adversity was also assessed at three measurement timepoints for study 3, spanning across the whole of adolescence period (ages 14, 19 and 22) and assessed up to 7 times across childhood for study 2. These are in contrast to the single early childhood timepoint assessment obtained for study 1. These differences in timing of adversity measurement should be equally considered given previous study that showed that early adversity exposure has more detrimental impact on developmental outcomes than later adversity exposure (Dunn et al., 2019). While the results of each of these adversity measures offered very informative findings on the impact of adversity, the varying severity and developmental time of measurement should be taken into perspective when interpreting the results across the three empirical chapters in this thesis and in relation to other findings in the field. Another important point to note is related to differences in population sample. Data for study 1 and study 2 came from the British population cohort

studies while data for the study 3 was derived from different European samples, which also included a sample of British adolescents. There were also differences in attrition levels across these three cohort studies. For example, in the data analysed in my thesis, there was about 23% attrition level in the MSC cohort sample, over 79% in the ALSPAC cohort and about 76% in the IMAGEN cohort. These huge differences in attrition levels were driven by methodological and statistical considerations I employed. For example, in the ASLAPC sample (study 2), cognitive data was obtained at age 24, so many years after the adversity variables were measured, leading to many drop out from participants with available adversity data at childhood. In the IMAGEN cohort, considerations were given to complete dataset given reliability problems associated with large missing data in neurobiological studies. Thus, these differences in attrition levels should be taken into account given likelihood that specific population demographics (e.g., people of low socioeconomic status) may be more affected by drop out in longitudinal studies (Wolke et a., 2009). Lastly, the three studies investigated different outcomes. For example, study 1 examined mental health, study 2 examined cognitive outcomes and study 3 investigated brain outcomes. While there are no inherent limitations associated with investigating these different outcomes in this thesis (given that they are the most investigated developmental outcomes in cross-sectional studies), the variations in examined outcomes, along with other caveats noted above, hindered my ability to tell a single story in this thesis about the long-term effects of childhood adversity.

5.1.4 Conclusion

Across three empirical studies, this thesis reported some new and insightful findings. Firstly, I found that mental health difficulties across childhood accounted for ~59% and ~70% of effects

of early-life adversity on poorer performance in spatial working memory and vocabulary respectively. I therefore suggested that the cognitive competence in vulnerable children may be enhanced if their mental health could be deliberately given more clinical attention. Secondly, I found consistent evidence in support of the dimensional models of adversity, which I tested with latent class analysis. A further latent class regression analysis in the same study showed that cognitive performance was worse for participants in family poverty subgroup; even poorer than the subgroup that has been exposed to nearly all adversity types. I queried in chapter 5 of this thesis if children in different population samples (e.g., Western European countries Vs African countries) might respond to adversity in a different ways, given one of my earlier studies that showed that (parentally) deprived children in Nigeria showed better working memory abilities. Thirdly, I present consistent longitudinal evidence that support previous cross-sectional claims that adversity is associated with attenuations in brain cortical structures. This was clearly described in chapter 4, where I reported significant decrement in the right anterior cingulate surface area attributable to adolescent adversity exposure. Although the effects are small compared to those reported in cross-sectional studies, leading me to ask if the long-term effects of adversity on cortical brain structures may indeed be more modest than researchers had previously noted?

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Supplementary materials

Supplementary material for chapter 2

Table S2.1: Descriptive statistics and intercorrelations of the study variables in model 1

				Predictor		**Mediators**				**Outcome**
	Measures	**Mean**	**SD**	1	2	3	4	5	6	7
1	Adversity Age 3	-0.069	1.807	-						
2	SDQ Age 3	9.563	5.289	0.33	-					
3	SDQ Age 5	7.262	4.974	0.31	0.56	-				
4	SDQ Age 7	7.386	5.356	0.30	0.51	0.67	-			
5	SDQ Age 11	7.745	5.858	0.29	0.44	0.55	0.64	-		
6	Global MH Age 11	-1.232	1.338	0.11	0.12	0.16	0.20	0.31	-	
7	Total error SWM: Age 11	35.788	18.750	0.12	0.14	0.17	0.18	0.20	0.06	-

Note: SDQ = Strength and Difficult Questionnaires; SWM = spatial working memory; SD = Standard deviation; Adversity scores were derived from the first component of the PCA.

Table S2.2: Descriptive statistics and intercorrelations of the study variables in model 2

				Predictor		Mediators					Outcome	
	Measures	**Mean**	**SD**	1	2	3	4	5	6	7	8	9
1	Adversity Age 3	-0.109	1.783	-								
2	SDQ Age 3	9.490	5.240	0.33	-							
3	SDQ Age 5	7.176	4.939	0.30	0.55	-						
4	SDQ Age 7	7.313	5.312	0.29	0.51	0.66	-					
5	SDQ Age 11	7.621	5.797	0.29	0.44	0.55	0.65	-				
6	SDQ Age 14	8.185	5.972	0.27	0.39	0.49	0.56	0.66	-			
7	Global MH Age 11	0.001	1.332	0.11	0.12	0.15	0.20	0.30	0.25	-		
8	Global MH Age 14	-1.267	1.576	0.11	0.05	0.07	0.08	0.14	0.25	0.30	-	
9	Word Activity Age 14	7.053	2.624	-0.11	-0.16	-0.17	-0.18	-0.17	-0.19	-0.07	-0.01	-

Note: SDQ = Strength and Difficult Questionnaires; SD = Standard deviation; MH = Mental Health; Adversity scores were derived from the first component of the PCA.

Supplementary material for chapter 3

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Supplementary material for chapter 4

Adversity: Life events questionnaire (Newcomb, Huba, & Bentler, 1981) and the revised Olweus bully/victim questionnaire (Olweus, 2006) were both used in operationalizing adversity. The following are the subscales and item questions used in life events questionnaire: (note that at baseline assessment, they were asked if these events ever occurred but in the two later follow-up assessments, they were asked if the events occurred since their last IMAGEN assessments).

Parents and Family subscale

1. parents divorced
2. family had money problems
3. Parents argued or fought
4. Mother/father remarried
5. Parent abused alcohol

Accident and illness subscale

1. A close family member had a severe accident or a severe illness
2. Given medication by my doctor
3. Death of a relative you are close to
4. I had a serious accident or illness (e.g. broke leg)

Distress subscale

1. Face broke out with pimples
2. My parents/guardians made me see a therapist
3. Thought about harming yourself
4. Ran away from home
5. Got poor exam results
6. Gained a lot of weight

In bully/victim questionnaire, participants were asked how often have the following situations occurred in the past 6 months?

1. I was bullied at school (a student/ peer said or did nasty or unpleasant things to me).
2. I was called mean names, was made fun of, or teased in a hurtful way by a student/ peer.
3. A student/ peer left me out of things on purpose, excluded me from their group of friends or completely ignored me
4. I was hit, kicked, pushed or shoved around, or locked indoors by a student/ peer.
5. I have been bullied by a teacher.
6. I have been bullied by a family member.