Strengthening causal inference in understanding the relationship between childhood adversity and adolescent psychopathology

Athena Ru Wern Chow

Magdalen College, University of Oxford

Supervisors: Professor Lucy Bowes, Dr Jessie Baldwin,

& Professor Jane Barlow

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Abstract

Adverse childhood experiences (ACEs) are a global public health concern, with robust evidence linking ACEs to lasting mental, physical, and psychosocial difficulties across development. Yet despite the proliferation of ACE research over the past two decades, (1) no universal paradigm for operationalising ACEs exists, (2) the extent to which these associations are confounded by pre-existing vulnerabilities remains uncertain, and (3) addressing genetic confounding represents an ongoing challenge. This thesis aims to strengthen causal inference in understanding the relationship between childhood adversity and adolescent psychopathology by applying data-driven, quasi-experimental, and genetically informed methods on contemporary longitudinal cohorts from the UK and US.

Chapter 1 reviews the current literature on ACEs and psychopathology, highlighting conceptual and methodological limitations in the field. Chapter 2 applies an exploratory data-driven approach to identify underlying dimensions of adversity across UK and US cohorts – parental threat, deprivation, and victimisation – and finds that victimisation emerges as the strongest predictor of adolescent psychopathology. Chapter 3 uses propensity score matching to strengthen causal inference about the effects of individual ACEs, revealing victimisation and emotional adversities as robust predictors of psychopathology even after accounting for early life vulnerabilities. In contrast, associations with household-level adversities were substantially attenuated, suggesting they were largely explained by pre-existing confounding. Chapter 4 introduces the novel approach of genetically adjusted propensity score (GAPS) matching to address measured genetic confounding. It reveals gene–environment correlations between polygenic scores and ACE exposures, and further demonstrates that victimisation and emotional adversities predict psychopathology independently of both genetic and environmental confounding. While associations with household-level adversities largely diminished once confounding was addressed, parental psychopathology was no longer significantly associated with adolescent psychopathology after GAPS adjustment, suggesting genetic confounding. Finally, Chapter 5 synthesises these findings, discusses theoretical and practical implications, and outlines directions for future research.

Overall, this thesis advances the study of childhood adversity by: (1) clarifying how ACEs can be meaningfully operationalised through data-driven dimensions, (2) strengthening causal inference using quasi-experimental methods, and (3) addressing genetic confounding with a novel genetically informed design. Together, these contributions provide a more rigorous foundation for understanding how childhood adversity shapes adolescent psychopathology, over and above measured confounding from genetic and environmental influences.

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"And now these three remain: faith, hope, and love. But the greatest of these is love."

(1 Corinthians 13:13)

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Publications

Published journal articles

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Journal articles in preparation

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Table of Contents

Table of Figures

List of Tables

1 Introduction

1.1 A brief overview of ACE research

Adverse childhood experiences (ACEs) constitute a global public health issue that transcends cultural, geographical, and socioeconomic borders. Large-scale systematic reviews and meta-analyses have demonstrated transnational associations between ACEs and elevated risks for psychopathology, chronic health conditions, and substance abuse throughout the life course, with annual health costs associated with ACEs in Europe and North America estimated to be $581 billion and $748 billion USD respectively (Bellis et al., 2019; Hughes et al., 2017). Outside of the Western, educated, industrialised, rich, and democratic (WEIRD) context (Henrich et al., 2010), the economic burden associated with ACEs has been estimated to be between $194 billion and $206 billion for countries in the East Asia and Pacific region (Fang et al., 2015). Although likely underestimated due to a considerable lack of data from low- and middle-income country (LMIC) regions, a budding growth of non-Western research has observed comparable dose-response relationships between ACEs and poor mental and physical health outcomes in LMIC settings such as Malaysia (Ahmed et al., 2015), the Philippines (Ramiro et al., 2010), Mexico (Kremer et al., 2018), and Burkina Faso, Ghana, Malawi, and Uganda (Kabiru et al., 2010).

The public health burden associated with childhood adversity underscores the urgent need for research that identifies modifiable mechanisms, informs effective interventions, and improves developmental outcomes for vulnerable children. Accordingly, the field of ACE research has expanded rapidly over the past two decades. A recent bibliometric analysis identified 789 ACE-related studies published between 1998 and 2018 – more than half of which appeared in just the last three years of that period (Struck et al., 2021). The foundation of ACE research is widely attributed to the landmark Adverse Childhood Experiences Study, which not only coined the now ubiquitous term 'ACE' but also established the cumulative risk score model for understanding the long-term impact of childhood adversity (Felitti et al., 1998). Interestingly, the basis of this study

originated from counterintuitive findings at an obesity clinic, where patients were dropping out despite making successful progress in losing weight (Felitti, 2002). This inexplicable pattern prompted principal investigator Dr Vincent Felitti to interview the dropouts, leading to a startling and tragic discovery: more than half had been sexually abused in childhood. For many, obesity was not merely a health condition but a protective mechanism to shield themselves from further harm. As one patient explained, *"Overweight is overlooked, and that's the way I need to be"* (Felitti, 2002). Felitti later described this as a public health paradox, wherein behaviours typically regarded by society as intractable public health problems were often, for the affected individuals, maladaptive solutions to cope with unresolved trauma (Felitti, 2019).

Spurred by the striking prevalence of childhood sexual abuse and recognising the need for population-level data to generalise these findings, Felitti partnered with the Centres for Disease Control and Prevention (CDC) to launch a formal epidemiological investigation into the prevalence and long-term health outcomes of ACEs in the US population (Felitti et al., 1998). The CDC-Kaiser ACE Study produced groundbreaking insights into the cumulative impact of childhood adversity on adult health. Amongst the 9,508 original respondents, more than half reported at least one ACE, and one in four reported exposures to two or more ACEs. Crucially, ACEs were found to co-occur and exert dose-response effects: individuals with four or more ACEs faced substantially higher risks for a range of negative health outcomes, including 4- to 12-fold increases in depression, suicide attempt, substance use, and alcoholism; 2- to 4-fold increases in smoking and poor self-rated health; and 1.4 to 1.6-fold increases in physical inactivity and severe obesity. Moreover, the number of ACEs experienced displayed strong graded relationships with leading causes of adult morbidity, including cancer, heart disease, and chronic lung disease.

The first wave of the ACE Study assessed seven ACEs as exposures to childhood abuse (emotional, physical, sexual abuse) and household dysfunction (substance abuse, mental illness, mother treated violently, criminal behaviour in household) according to the existing measurement

tools at the time (Felitti et al., 1998). Soon after, this list of ACEs was expanded to include parental separation or divorce (Anda et al., 1999), as well as physical and emotional neglect (Dong et al., 2004), giving rise to the ten classic ACEs that have since become the cornerstone of ACE research. Subsequently, researchers have called for an expansion beyond the original ACEs towards a 'second generation of ACE research', including additional adversities such as peer victimisation, spanking, poverty, and exposure to community or collective violence (Finkelhor et al., 2015; Karatekin & Hill, 2019; Merrick et al., 2017; Mersky et al., 2017). Reflecting this expanded perspective, the World Health Organisation's Adverse Childhood Experiences International Questionnaire (ACE-IQ) includes items on parental death, peer violence, community violence, and exposure to war, in addition to the original 10 ACEs (World Health Organisation, 2020).

While expanding the definition of adversity beyond the original 10 ACEs has undoubtedly stimulated research and deepened our understanding of how early childhood adversity shapes psychopathology, it is important to set boundaries around what constitutes an ACE to prevent the construct from becoming overly broad. Without conceptual boundaries, the term 'ACE' risks losing discriminant validity and predictive power in research; in policy and practice, an overly broad construct may impede the design of targeted interventions and resource prioritisation. The World Health Organisation (WHO) refers to ACEs as the most intensive and frequently occurring sources of stress that children may suffer early in life (World Health Organisation, 2020). Although the WHO definition of childhood adversity acknowledges the recurring nature of ACEs, it still lacks an articulation of the *severity* which pushes an intensive, stressful event past the boundary into what constitutes an adverse childhood experience. This thesis is guided by a working definition of childhood adversity from McLaughlin (2016), which considers ACEs to be experiences which represent a deviation from the expectable environment and require significant adaptation by the developing child via their psychological, social, and neurobiological systems. An "expectable" environment entails sufficient sensory (e.g., visual, auditory, tactile, proprioceptive) and cognitive input (e.g., language, memory, attention, reasoning), as well as warm, responsive caregiving during

sensitive periods to lay the foundation for healthy neurocognitive development (Fox et al., 2010). In the context of ACEs, deviations from the expectable environment may manifest as an absence of expected inputs (e.g., the absence of a primary caregiver would deprive the child of their physical and emotional needs) or the presence of unexpected inputs (e.g., the presence of violence would threaten the physical and emotional integrity of the child). Thus, this working definition provides a conceptual anchor while still allowing flexibility in how childhood adversity may manifest across different contexts (e.g., household, school, neighbourhood). In **Chapter 2**, I include a broader range of neighbourhood and community-level ACEs using an exploratory dimensional framework, as this approach enables the identification of naturally occurring latent patterns within the population. In **Chapters 3 and 4**, however, I focus specifically on the original 10 ACEs (where data were available) to facilitate a critical evaluation of whether previous research – the majority of which replicated the original ACE Study – may have overestimated or underestimated the causal effects of ACEs on psychopathology.

Various theoretical frameworks have been posited to explain how early childhood adversity influences mental health, cognition, and socioemotional development. Amongst the most influential frameworks are the Dimensional Model of Adversity and Psychopathology (DMAP), which distinguishes between threat and deprivation as distinct pathways to psychopathology (McLaughlin et al., 2014); attachment theory, which links disrupted attachment bonds to maladaptive socioemotional development (Ainsworth & Bowlby, 1991); social learning theory, which proposes that children may model dysfunctional behaviours from abusive caregiving environments (Bandura & Walters, 1977); and allostatic load theory, which explains how chronic stress dysregulates neuroendocrine systems over time (McEwen, 2000).

The Dimensional Model of Adversity and Psychopathology (DMAP) proposes that different dimensions of adversity – namely, threat and deprivation – influence psychopathology through distinct neurocognitive mechanisms (McLaughlin & Sheridan, 2016). Threat involves the

presence or risk of harm (e.g., physical abuse, domestic violence), whereas deprivation reflects an absence of expected cognitive and social inputs in the environment (e.g., poverty, neglect). DMAP posits that threat-related experiences primarily disrupt socioemotional processes such as emotion regulation and fear learning, whereas deprivation undermines cognitive development, including memory, language, and executive functioning (Lambert et al., 2017; Machlin et al., 2019; McLaughlin, 2016; McLaughlin et al., 2016). These mechanistic distinctions have received some support from neuroimaging studies which showed that children exposed to threat-based ACEs showed heightened reactivity to threatening cues in emotion and fear-related regions such as the amygdala, hippocampus, and medial cortex, whereas children exposed to deprivation displayed neural systems adapted towards a less complex environment, evidenced by reduced volume and cortical thickness in frontoparietal regions implicated in working memory and cognitive control (McLaughlin et al., 2019). However, heightened stress-response circuitry is not specific to threat but has also been observed after deprivation experiences, and frontoparietal cortical reduction is not specific to deprivation as it has likewise been observed after experiences of threat (Smith & Pollak, 2021). For example, both physical abuse and maternal deprivation have been shown to be associated with structural and functional alterations in amygdala-prefrontal circuitry (Gee et al., 2013; VanTieghem & Tottenham, 2017). Nevertheless, these findings position DMAP as a useful framework for understanding how different types of adversity may shape neurodevelopment via distinct pathways and contribute to psychopathology.

Attachment theory is grounded on the idea that caregiver sensitivity during the critical early years shapes children's internal working models, i.e., cognitive-affective schemas that guide how they perceive themselves, others, and future relationships (Ainsworth & Bowlby, 1991). Secure attachments, fostered in safe and nurturing environments, promote positive developmental outcomes including self-regulation, social competence, and psychological wellbeing (Groh et al., 2017). In contrast, caregiving marked by abuse or neglect disrupts attachment formation, increasing vulnerability to socioemotional difficulties and long-term mental health problems

(Rutter et al., 2007; Sonuga-Barke et al., 2017). Research has shown that maltreated children are more likely to develop insecure or disorganised attachment styles, which can impair their ability to regulate emotions and navigate social relationships (Cicchetti et al., 2006; Groh et al., 2017). These processes were illustrated in the English and Romanian Adoptees Study, which followed the developmental trajectories of Romanian children adopted into the UK after experiencing severe institutional deprivation. Compared to English adoptees, Romanian children exhibited higher rates of disinhibited attachment as well as delays in physical growth, cognitive development, and socioemotional functioning (Rutter, 1998). Disinhibited attachment persisted into middle childhood and was associated with special education and mental health service use, peer and conduct problems, and elevated symptoms of autism spectrum disorder (Rutter et al., 2007). In young adulthood, those with prolonged institutional exposure continued to show higher rates of disinhibited social engagement, emotional dysregulation, and poorer educational and occupational outcomes (Sonuga-Barke et al., 2017). Together, these findings demonstrate how disrupted attachment during sensitive periods can leave lasting impairments on psychosocial functioning.

Social learning theory posits that children learn vicariously by observing and imitating the behaviours of role models around them (Bandura & Walters, 1977), with the seminal Bobo doll experiment demonstrating how even brief exposure to aggressive behaviour can lead to its subsequent imitation (Bandura et al., 1961). In home environments marked by abuse or domestic violence, children are regularly exposed to maladaptive models of behaviour that may normalise aggression and emotional volatility. These behaviours may become internalised as acceptable strategies for dealing with stress, conflict, and interpersonal relationships (Kim et al., 2019; Lichter & McCloskey, 2004). Children exposed to violence often develop hostile attribution biases, interpreting ambiguous cues as threats and responding aggressively (Dodge & Crick, 1990). Over time, these learned behaviours may be generalised across contexts, increasing the risk for aggression, delinquency, and externalising problems (Maxfield & Widom, 1996; Milaniak & Widom, 2015; Moylan et al., 2010). Longitudinal studies have shown that children who were

maltreated or raised in violent households were more likely to condone and perpetrate intimate partner violence, underscoring the potency of social learning processes in perpetuating aggression across generations (Ehrensaft et al., 2003; Lichter & McCloskey, 2004; Milaniak & Widom, 2015). These intergenerational patterns of violent socialisation, often termed the 'cycle of violence', highlight how adversity can be perpetuated through the modelling and normalisation of maladaptive behaviours (Maxfield & Widom, 1996; Milaniak & Widom, 2015).

Allostatic load theory provides a biological framework for understanding how chronic stress may become biologically embedded. Allostasis refers to the body's capacity to maintain stability through change by activating coordinated responses across the nervous, endocrine, and immune systems – particularly the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis (Danese & McEwen, 2012; McEwen, 2000). While adaptive in the short term, prolonged activation of these systems under chronic adversity can lead to allostatic load, i.e., the cumulative 'wear and tear' on the brain and body (McEwen, 2000). Childhood adversity (e.g., maltreatment, neglect, deprivation) has been linked to smaller prefrontal cortex volume, HPA axis dysregulation, altered cortisol secretion, and elevated inflammation (Danese et al., 2009; Danese & McEwen, 2012; Finlay et al., 2022), although it is worth noting that effect sizes for the associations between early adversity and inflammatory markers are small and mostly driven by studies conducted in infancy and adolescence (Kuhlman et al., 2020). While many maltreated children exhibit elevated cortisol, those who are chronically maltreated or bullied may display blunted cortisol responses, suggesting a compensatory down-regulation of the stress response system (Danese & McEwen, 2012; Ouellet-Morin et al., 2011). Crucially, allostatic load can persist long after the adversity has ceased. For example, the Romanian adoptees exposed to over six months of institutionalised deprivation showed HPA axis dysregulation even 20 years later, displaying a distinct lack of cortisol awakening response compared to the less-deprived Romanian adoptees and non-deprived English comparison group (Kumsta et al., 2017). Longitudinal studies have also linked early allostatic load to elevated risk for depression, PTSD, and cardiovascular

disease in adulthood (Danese & McEwen, 2012; Finlay et al., 2022). Thus, allostatic load theory elucidates the biological pathways through which early adversity may become embedded in the brain and body, potentially shaping mental and physical health across the life course.

Taken together, these theoretical frameworks provide multi-level explanations – neurocognitive, behavioural, social, and biological – for understanding how adverse childhood experiences influence developmental trajectories. As each framework highlights distinct primary pathways through which early adversity can become developmentally embedded, tensions inevitably arise between the theories' competing claims. For example, a child raised in a loving but impoverished home may display lower cognitive abilities yet maintain a secure attachment style; in this case, DMAP would predict elevated risk for psychopathology whereas attachment theory would not. While attachment theory treats caregiver relationship quality as the primary mechanism, DMAP postulates that environmental threat alone – even in the presence of a warm parent-child relationship – can still give rise to psychopathology. Nevertheless, by recognising these theoretical frameworks and their respective assumptions, researchers can develop a more holistic understanding of the complex, multi-causal aetiology of mental health outcomes following early adversity. Moreover, instead of activating a singular developmental pathway, it is more plausible that ACEs generate a developmental cascade of effects (Masten & Cicchetti, 2010), wherein biological stress responses, recalibrated neural circuits, disrupted attachment processes, and maladaptive social learning interact over time and across systems to contribute to psychopathology. Yet, theoretical collisions between these frameworks surface when deciding how ACEs should be operationalised: for instance, DMAP's distinction between threat and deprivation suggests that ACEs should be categorised into distinct dimensions of adversity, while allostatic load theory implies ACEs can be aggregated together given its hypothesis that cumulative stress exposure underlies the development of psychopathology, regardless of adversity type. Hence, the operationalisation of ACEs remains a major challenge in the field – a challenge which I explore in greater detail in the next section.

1.2 The challenge of operationalising ACEs: No universal paradigm

To facilitate rigorous research, public policy, and clinical practice, it is vital that ACEs are operationalised in meaningful and appropriate ways. However, there is not yet a universal paradigm to measure and classify ACEs, and a considerable impediment to progress in this field has been the lack of consistent operationalisation across studies (Berman et al., 2022). Three distinct paradigms have emerged from the body of ACE literature over the past 25 years: the cumulative risk approach, the specificity approach, and the dimensional approach (Kim & Royle, 2024; Lacey & Minnis, 2020).

The cumulative risk approach sums the number of ACEs experienced (e.g., abuse, neglect, domestic violence) into a single risk score. Each ACE is typically binarized as a score of 1 versus 0 and then aggregated into a total risk score ranging from 0 (no exposure) to 10 (exposure to multiple ACEs). Although the CDC-Kaiser ACE Study is widely recognised as the study which disseminated this approach, the cumulative risk approach to measuring childhood adversity was in fact pioneered by Sir Michael Rutter in the Isle of Wight Study (Rutter, 1978). Rutter calculated a family adversity index by summing exposures to family-related ACEs (e.g., marital discord, low socioeconomic status, parental criminality, maternal psychopathology, placement in foster care) and demonstrated that children with scores of four or more ACEs had the highest risk of conduct disorders (e.g., aggression, delinquency). Correspondingly, the ACE Study found that individuals who had been exposed to four or more ACEs had up to 12-fold increased risks for depression, suicide attempt, and substance abuse in adulthood (Felitti et al., 1998). Numerous studies have endeavoured to replicate the cumulative risk score of the ten ACEs from the ACE Study, resulting in a wealth of literature demonstrating a strong graded relationship between the number of ACEs experienced and detrimental health outcomes (Bellis et al., 2018, 2019; Hughes et al., 2017; Kim & Royle, 2024). For example, longitudinal studies across the UK, US, Australia, New Zealand, and South Africa have shown that the risk for depression, anxiety, self-harm, and suicidality increases in proportion to the number of adversities experienced in childhood (Baldwin et al., 2021; Cluver

et al., 2015; Danese et al., 2009; Dube et al., 2001; Hu et al., 2017; Merrick et al., 2017; Thompson et al., 2019).

The simplicity and predictive power of the cumulative risk approach has been instrumental in raising public awareness and influencing policies and interventions. However, this approach has significant limitations. First, by aggregating different ACEs as a sum score, the cumulative risk approach inherently assumes that all adversities are equally impactful on later health outcomes, which is a highly tenuous assumption (Lacey & Minnis, 2020; McLaughlin & Sheridan, 2016). Different types of ACEs have been shown to impact physical and mental health in differential ways, with childhood maltreatment subtypes (e.g., emotional abuse) and peer victimisation emerging as stronger predictors of psychiatric symptoms over and above other household dysfunction ACEs (Cecil et al., 2017; Sayyah et al., 2022; Westermair et al., 2018). Furthermore, children with disparate experiences of adversity might be assigned the same score regardless of the specific clustering of ACEs. For instance, a child who experienced emotional, physical, and sexual abuse would be assigned the identical score of three as another child who experienced parental psychopathology, divorce, and substance abuse. Crucially, as the summative nature of the cumulative risk approach implicitly assumes that all ACEs influence development via the same pathways, it fails to provide a mechanistic explanation of *how* different ACEs increase the risk for poor health and development (Lacey & Minnis, 2020; McLaughlin & Sheridan, 2016). Thus, although the cumulative risk approach provides an efficient tool to identify at-risk individuals, its lack of specificity obscures the mechanisms through which ACEs predict specific outcomes, limiting its use in understanding the causal pathways of risk and resilience.

The specificity approach, or the individual ACE approach, focuses on examining the unique effects of a single adversity. In contrast to the cumulative risk approach, the specificity approach recognises that not all ACEs are equal in impact and enables the identification of potential mechanisms underlying each ACE and outcome (Kim & Royle, 2024; Lacey & Minnis,

2020). The main advantage of the specificity approach is its ability to compare the strength of associations between individual ACEs and specific outcomes, which facilitates the development of targeted interventions aiming to address the specific needs associated with each type of adversity. For example, when data from the CDC-Kaiser ACE Study was reanalysed using the specificity approach, emotional abuse emerged as the ACE conferring the largest risk for attempted suicide in adulthood compared to the other ACEs (Merrick et al., 2017). This study found that emotional abuse, emotional neglect, and household mental illness showed the strongest associations with depressive symptoms, whereas the strongest risk factors for drug and alcohol use in adulthood were emotional abuse, household substance abuse, and household mental illness. Importantly, while most experiences of childhood maltreatment demonstrated significant associations with mental health outcomes when examined individually, few unique effects remained after modelling them simultaneously, highlighting the significant role of shared variance in driving the effects of childhood maltreatment on psychopathology (Cecil et al., 2017).

Therein lies the main limitation of the specificity approach: it disregards the unfortunate reality that ACEs tend to co-occur frequently and chronically (Debowska et al., 2017; Hughes et al., 2017; Kim & Royle, 2024; Smith & Pollak, 2021). Common patterns of comorbidity include maltreatment subtypes (e.g., co-occurring abuse and neglect in physical, emotional, or sexual forms), as well as child abuse with various forms of family violence (Appel & Holden, 1998; Debowska et al., 2017; Hamby et al., 2010). Emerging research also suggests that there may be synergistic effects of specific ACE pairs; for instance, the pairing of sexual abuse with other ACEs significantly increases the risk of negative health outcomes beyond the sum of individual ACEs, with synergistic effects varying by gender and age group (Briggs et al., 2021; Putnam et al., 2020). Thus, while the specificity approach enhances our understanding of the unique effects of individual ACEs, it does not reflect the real-world complexity of childhood adversity, which often involves clusters of co-occurring ACEs that may interact in compounding or synergistic ways.

As discussed in the previous section, the dimensional approach groups interrelated ACEs into categories, or 'dimensions', according to the notion that they share a latent underlying construct, proposing that dimensions of adversity differentially influence emotional, cognitive, and neurological development via distinct mechanisms. The Dimensional Model of Adversity and Psychopathology (DMAP) distils ACEs into core underlying dimensions of threat (e.g., abuse) and deprivation (e.g., neglect), with each dimension encompassing ACEs that reflect the underlying dimension to varying degrees (McLaughlin & Sheridan, 2016). Additional dimensions of harshness and unpredictability have been subsequently incorporated into DMAP by McLaughlin and colleagues as they acknowledged that threat and deprivation are not the sole dimensions of adversity (Berman et al., 2022; Ellis et al., 2022; McLaughlin et al., 2021), although these two dimensions remain the focus in most research applying the dimensional approach (Kim & Royle, 2024; Lacey & Minnis, 2020; Lian et al., 2022). Notably, DMAP accounts for the comorbidity of ACEs by arguing that even amidst co-occurring experiences of threat and deprivation, the unique effects of each dimension can be isolated as each dimension impacts psychopathology via distinct mechanisms (Sheridan & McLaughlin, 2014). Specifically, DMAP proposes that early experiences of threat influence later psychopathology via disruptions in socioemotional processing, whereas deprivation disrupts executive functioning to in turn, impact psychopathology (Lambert et al., 2017; Machlin et al., 2019; McLaughlin, 2016; McLaughlin et al., 2016). Certain neuroimaging studies support these claims, showing distinct neural correlates of the different dimensions: threat is associated with heightened amygdala reactivity and reduced volume in emotion-related brain regions, while deprivation is linked to reduced cortical thickness in regions supporting higher-order cognition (McLaughlin et al., 2019). However, existing research on the neurodevelopmental correlates of childhood adversity has mostly employed small, heterogeneous samples and cross-sectional designs, highlighting the need for larger samples and longitudinal datasets in order to combat heterogeneity and lack of statistical power (McLaughlin et al., 2019). There is some longitudinal evidence that adverse childhood experiences of threat and deprivation may increase

the risk for internalising and externalising psychopathology in adolescence through distinct mediational pathways of emotional dysregulation and verbal abilities (Miller et al., 2018; Milojevich et al., 2019). A recent longitudinal analysis of the UK Millennium Cohort Study found no direct effect of either threat or deprivation on psychological distress in adolescence; however, significant indirect effects of threat and deprivation did emerge via pathways of emotion regulation and cognitive ability (Ning et al., 2023). Ning et al. (2023) speculated potential explanations for these unexpected findings (e.g., reporting bias from child reports of psychopathology in their study, as opposed to parent reports in most of the previous literature) and cautioned that the indirect effects were ultimately small, indicating limited benefits if emotion regulation or cognitive ability were targeted in interventions aiming to improve the mental health of children exposed to ACEs.

Just as there is no universal paradigm for operationalising ACEs, there is likewise no consensus on how best to derive the dimensions of childhood adversity. Researchers have applied various approaches ranging from factor analysis, latent class analysis, and network analysis (Lacey & Minnis, 2020; Lian et al., 2022; Sheridan et al., 2020), with most studies applying confirmatory approaches (e.g., confirmatory factor analysis, CFA) to validate the threat and deprivation dimensions of DMAP (Awada et al., 2023; Lian et al., 2022; Miller et al., 2021; Ning et al., 2023). However, confirmatory approaches such as CFA rely on pre-defined categorisations of ACEs, potentially biasing results and obscuring naturally occurring patterns in the data. For example, two independent studies, both informed by the DMAP framework, applied CFA to the same population dataset yet arrived at different dimensional structures (Awada et al., 2023; Sisitsky et al., 2023). Thus, I argue that exploratory data-driven methods should be used in lieu of confirmatory methods, which can be biased by *a priori* categorisations of ACEs. In **Chapter 2**, I demonstrate the utility of exploratory factor analysis in deriving meaningful dimensions of childhood adversity across two population cohorts.

Therefore, although the dimensional approach is promising, it comes with its own set of methodological caveats: it is challenging to replicate dimensions across populations when using

longitudinal datasets, and because mechanistic knowledge is still at an early stage, mechanisms can be difficult to translate into practice (Lacey & Minnis, 2020). Moreover, DMAP has faced criticism for categorising ACEs as 'fuzzy categories' that are unlikely to map onto neurobiological systems discretely (Smith & Pollak, 2021). Smith and Pollak (2021) argued that DMAP's categorisation of ACEs into distinct dimensions oversimplifies the complex and overlapping nature of adverse experiences, as many ACEs inherently possess dual elements of threat and deprivation. For instance, the experience of child abuse would typically be classified as an experience of threat, but an abusive parent might also deprive their child of physical (e.g., food and sleep) and emotional (e.g., love and belonging) needs. Conversely, growing up in extreme poverty would typically be classified under the dimension of deprivation, but the inadequate nutrition from food insecurity would naturally also threaten the child's survival. This critique underscores a broader methodological debate in classifying childhood adversity: whether ACEs should even be grouped into categories (or dimensions) that are assumed to be sufficiently homogeneous to justify generalisation (Kim & Royle, 2024).

Amidst these ongoing scholarly debates over how best to operationalise childhood adversity, an equally critical methodological challenge underlying the field of ACE research is determining whether the relationships between ACEs and detrimental outcomes reflect causality. Much of the existing literature has relied on correlational, cross-sectional, or retrospective designs (Hughes et al., 2017; Kim & Royle, 2024; Lacey & Minnis, 2020), which limit the ability to infer causal relationships. To advance the field, a shift from correlational approaches to causal inference is needed to uncover the causal pathways through which ACEs exert their effects, in order to inform more targeted and effective prevention and intervention strategies. In the following section, I introduce key concepts in causal inference and outline how the effects of ACEs can be delineated within a causal inference framework.

1.3 Delineating effects of ACEs within a causal inference framework

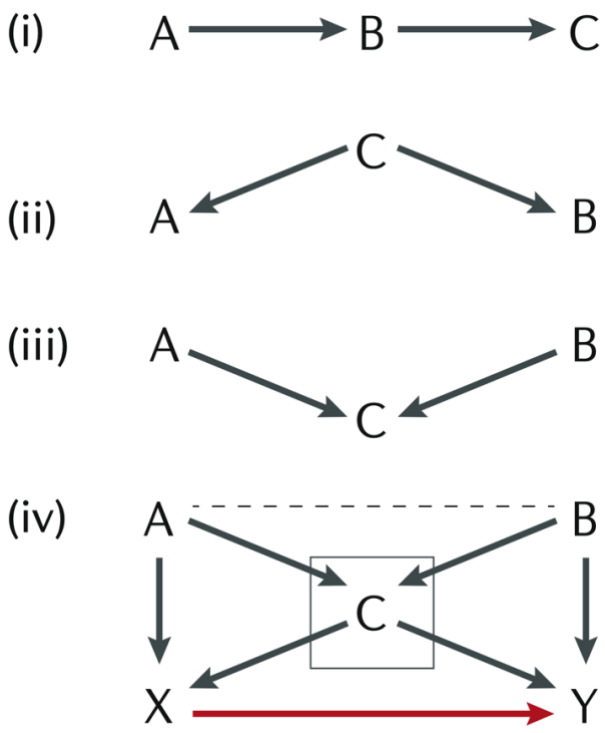
Causal inference methods offer innovative tools to delineate and isolate the causal effects of childhood adversity on psychopathology from measured confounding. All causal inference methods aim to approximate the *counterfactual* scenario, the ideal (but impossible) scenario where an individual is simultaneously exposed and non-exposed to a risk factor (Hernán, 2004; Pingault et al., 2018). Causal effects are defined in terms of counterfactuals; essentially, a causal effect is defined as a difference in outcomes between the exposed factual scenario (e.g., experiencing emotional neglect) and the non-exposed counterfactual scenario (e.g., not experiencing emotional neglect) within the same individual. Since the counterfactual scenario is inherently unobservable in reality and only one outcome can be observed for a given individual (either they experience the ACE or they do not), causal inference methods estimate the counterfactual scenario with novel statistical techniques that allow for causal inference under reasonable assumptions (Pingault et al., 2018). For example, in the twin design, a non-exposed twin approximates a natural counterfactual match to their exposed twin (McGue et al., 2010).

Within the causal inference framework, it is fundamental that the assumption of *exchangeability* is met, i.e., when exposed and non-exposed groups are balanced with respect to all confounders (Hernán, 2004; Hernán & Robins, 2024; Pingault et al., 2018). In other words, exchangeability means that the risk of psychopathology in the non-exposed group would have been the same as the psychopathology risk in the ACE-exposed group had the non-exposed group received the same ACE exposure. Confounding can thus be defined as the lack of exchangeability between the exposed and non-exposed groups (Hernán & Robins, 2024). Other key assumptions that should be met to derive the causal effect estimate include: *positivity* (all individuals have a probability greater than zero of being assigned to each of the treatment levels, e.g., exposed or non-exposed); *no interference* (the potential outcome for any individual is not dependent on the exposure status of another individual); and *consistency* (the effect of the exposure on the outcome should be consistent in all occasions). Taken together, the assumptions of exchangeability,

positivity, no interference, and consistency are collectively known as the identifiability assumptions of causal inference (Hernán & Robins, 2024; Naimi & Whitcomb, 2023).

These concepts underlying causal inference are illustrated in the directed acyclic graphs (DAGs) in **Figure *1.1***, which provides graphical depictions of causal relationships among variables (Pearl, 1995). DAGs represent variables as *nodes* connected by an *arc* or *edge*, which are single headed arrows indicating the direction of causal relationships between variables; they are 'acyclic' because no directed paths in the graph form a closed loop (Greenland et al., 1999). In **Figure *1.1*** (i), A → B → C is a directed causal path where A causes B, and B causes C. For example, childhood emotional neglect (A) could cause depressive symptoms in adolescence (B), which could subsequently lead to substance abuse in adulthood (C).

Figure 1.1 DAGs depicting basic causal structures, from Pingault et al. (2018).



In **Figure *1.1*** (ii), A ← C → B is a *backdoor path* where A is associated with B through C. A backdoor path, or a *confounding pathway*, is a non-causal path between exposure (A) and outcome (B) that is linked through their common cause (C), a *confounder* (Hernán & Robins, 2024). If left

open or 'unblocked', this backdoor path creates a spurious association between A and B, even in the absence of a causal path A → B (Pingault et al., 2018). For example, parental mental health problems (C) could be a confounder of the relationship between childhood emotional neglect (A) and depressive symptoms (B), because parental mental health problems may be a common cause of both the exposure and the outcome (A ← C → B). This is also an example of passive gene-environment correlation, as parental mental health problems might create an environment where the parent neglects their child's emotional needs (C → A), in addition to passing on the genetic predisposition for depression to their child (C → B). In this scenario, parental mental health problems would generate a correlation between emotional neglect and depressive symptoms, even if the causal pathway A → B did not exist. Due to parental mental health problems acting as a confounder, the risk of depression in the non-exposed group is no longer the same as the risk of depression in the emotionally neglected group had the non-exposed group received the same exposure to neglect. The assumption of exchangeability is thus violated by the confounder C as the exposed and non-exposed groups are no longer exchangeable, resulting in a biased estimate of A → B.

Backdoor paths can be closed or 'blocked' by conditioning on a variable along a confounding pathway (Greenland et al., 1999; Hernán & Robins, 2024). If we condition on parental mental health problems (e.g., through multivariable adjustment, matching, or stratification), this will remove the confounding bias by blocking the open pathway A ← [C] → B. In DAG notation, conditioning is typically represented by drawing a box around the conditioned variable. By conditioning on confounders of an association between an exposure and an outcome (i.e., blocking all backdoor paths between A and B), *conditional exchangeability* can be achieved where exchangeability holds in each level of a confounder (Hernán & Robins, 2024; Pingault et al., 2018). For example, parent mental health problems can be conditioned on through propensity score matching by estimating each individual's propensity for exposure to emotional neglect, given a set of observed confounders (including parental mental health). Individuals with similar propensities

for emotional neglect – based in part on whether their parent had mental health problems – can then be matched and compared on their psychopathology outcomes. Once all measured confounders are balanced across the exposed and non-exposed groups (thus achieving conditional exchangeability), this effectively reduces spurious associations, and we can infer a causal effect of the relationship between emotional neglect (A) and depressive symptoms (B) that is no longer confounded by parental mental health problems (C).

In **Figure *1.1*** (iii), the path A → C ← B is blocked because the two arrowheads collide at C. C is a *collider* which blocks the flow of association along the path on which it lies, and thus A is no longer associated with B through C (Hernán & Robins, 2024). However, causal graph theory has proven that conditioning on a collider opens the previously blocked pathway A → [C] ← B and creates a spurious correlation between A and B (Greenland et al., 1999; Hernán & Robins, 2024). For example, cognitive ability (C) could be a collider in this scenario as emotional neglect might hinder cognitive development (A → C) and adolescents with depressive symptoms might struggle academically, which could worsen their cognitive test performance (B → C). Conditioning on cognitive ability (C) would create a spurious association between emotional neglect (A) and depressive symptoms (B) even if no causal relationship exists between them. Suppose we condition on cognitive ability (e.g., stratifying by cognitive ability in the analysis). In examining only individuals with high cognitive ability, the likelihood is that to achieve high cognitive ability even under the circumstances of experiencing emotional neglect (A = 1), these individuals will be less likely to also have depressive symptoms (B = 0) as both emotional neglect and depressive symptoms tend to reduce cognitive ability (C). Moreover, individuals without exposure to emotional neglect (A = 0) might still exhibit depressive symptoms (B = 1) and maintain high cognitive ability (C) as other factors independent of emotional neglect (e.g., genetic predisposition) could contribute to both depression and cognitive ability. This results in a case of *collider bias*, i.e., a spurious distorted association between emotional neglect and depressive symptoms (in which high emotional neglect is associated with low depressive symptoms and vice versa) that is entirely

due to conditioning on the collider C, rather than reflecting a true causal relationship between A and B.

Finally, **Figure *1.1*** (iv) exemplifies how DAGs can guide researchers in adjusting for confounding while avoiding unintended effects of collider bias and spurious correlations. By conditioning on C in an attempt to block the backdoor path X ← [C] → Y, this simultaneously unblocks the path X ← A--B → Y and confounds the path X → Y because C is a collider on the path A → [C] ← B. Through consulting the DAG, we can clearly see that the path between X → Y (in red) is confounded, and the solution is to block this newly opened path by conditioning on either A or B (Pingault et al., 2018). By blocking all backdoor paths between X and Y (essentially by conditioning on C *and* A or B), this achieves *d-separation* (i.e., directional separation) where X is d-separated from Y (Greenland et al., 1999; Hernán & Robins, 2024; Pearl, 1995). In other words, X is conditionally independent from Y given the set of conditioning variables in the DAG, and we can derive an unconfounded estimate of the causal relationship between X → Y.

In sum, DAGs provide a valuable framework for modelling complex relationships between interrelated variables, making them particularly well-suited to ACE research. DAGs enable researchers to delineate hypothesised causal pathways, identify potential confounders, and design strategies to mitigate bias. However, even the most meticulously constructed DAGs are limited by their inclusion of measured confounders. A major challenge in observational research is unmeasured confounding, particularly when it arises from genetic predispositions that may influence both exposure to adversity and later psychopathology outcomes. Amongst the available methods to strengthen causal inference, genetically informed methods offer a promising avenue to address unobserved confounding from genetic variation (Pingault et al., 2018). In the following section, I outline the rationale for applying genetically informed causal inference methods to disentangle the potentially causal effects of childhood adversity from underlying genetic and environmental confounding.

1.4 The need for genetically informed causal inference methods

Emerging evidence suggests that children exposed to ACEs may exhibit an elevated risk for psychopathology, in part due to pre-existing genetic and environmental vulnerabilities (Baldwin, Sallis, et al., 2023; Baldwin, Wang, et al., 2023; Ratanatharathorn et al., 2021; Schoeler et al., 2019). This does not imply that ACEs have no direct detrimental impact on children's mental health; instead, it highlights the importance of accounting for genetic and environmental confounding to avoid overestimating the causal impact of ACEs on mental health outcomes. Deriving more accurate estimates of the impact of ACEs on psychopathology has important implications for social policy and intervention design. First, more accurate estimates can inform intervention targets by identifying ACEs with the strongest evidence for potentially causal effects on mental health outcomes. Second, more accurate estimates can inform anticipated effect sizes of preventative ACE interventions, to set realistic expectations for intervention efficacy and inform sample size calculations (e.g., for randomised controlled trials of ACE interventions). For example, if a moderate estimate of increased risk is found between emotional neglect and adolescent depression, parenting interventions targeting emotional neglect can anticipate a corresponding, but not complete reduction in psychopathology risk. Third, more accurate estimates can refine calculations of the health and economic burden of ACEs (Baldwin, 2021; Grummitt et al., 2024), thereby supporting policymakers in allocating resources more efficiently in large-scale prevention strategies.

Genetic confounding occurs when genetic factors affecting the environmental exposure (e.g., child maltreatment) also affect the outcome (e.g., depression). Hereditary vulnerabilities may inflate the associations between ACEs and psychopathology, and this often manifests through gene-environment correlation (rGE), i.e., when an individual's genotype influences their exposure to particular environmental experiences (Jaffee & Price, 2007). For example, in the case of passive rGE, parents contribute both genes and the caregiving environment to their children. A parent with a genetic predisposition for depression may not only pass on the genetic risk but also shape an adverse environment that independently increases the child's risk for psychopathology (Rice et

al., 2013). With evocative rGE, children with a genetic predisposition for externalising problems may be more likely to evoke harsh parenting or victimisation by peers (Marceau et al., 2013; Schoeler et al., 2019; Sellers et al., 2020). Active rGE can also occur when an individual actively chooses an environment that is compatible with their genotype; for example, a child who is genetically prone towards risk-taking may seek out delinquent peers (TenEyck & Barnes, 2015). Growing evidence from genetically informed studies supports rGE, demonstrating that children's own genetic predispositions for psychiatric disorders are correlated with a higher likelihood of experiencing adversities (Baldwin, Sallis, et al., 2023; Sallis et al., 2021; Schoeler et al., 2019; Zwicker et al., 2020). Crucially, this does not negate the genuine harm caused by ACEs, but it suggests that a proportion of the observed associations between ACEs and mental health problems may be attributable to shared genetic factors rather than a purely environmental causal pathway.

If the observed associations between ACEs and psychopathology are partially genetically confounded, the true causal contribution of ACEs may be smaller than suggested by non-genetically informative studies. As such, Baldwin, Sallis, et al. (2023) argued that even successful primary prevention of ACEs may only partially reduce children's risk of psychopathology, since underlying genetic vulnerabilities would remain. From a policy and intervention perspective, this underscores the need for strategies that address heritable vulnerabilities for psychopathology in ACE-exposed children. Hence, there is a need for genetically informed causal inference methods to enable more accurate estimation of the causal effects of ACEs. A rich toolbox of causal inference methods exists to account for co-occurring genetic and environmental vulnerabilities (Pingault et al., 2018). Within this toolbox, some of the most classic tools available are family-based designs (e.g., twin or sibling differences, children of twins, and adoption designs), which exploit the genetic relatedness between family members to disentangle the independent effects of ACEs from genetic and environmental confounding, thereby strengthening causal inference in observational research (Pingault et al., 2018; Sellers et al., 2022).

Twin and sibling designs approximate the counterfactual scenario in which an individual is both exposed and unexposed to a risk factor, by using their co-twin or sibling as a natural match (Pingault et al., 2018). When two members of a twin or sibling pair are discordant in their exposure to a risk factor, researchers can infer causality by comparing outcomes between the exposed and unexposed member. Monozygotic (MZ) twins share nearly 100% of their genetic material (Bruder et al., 2008), whereas dizygotic (DZ) twins and non-twin siblings share approximately 50% (Pingault et al., 2018; Sellers et al., 2022). Thus, genetic confounding is essentially controlled for in MZ twins, yielding more stringent causal estimates than DZ twins or sibling pairs (Pingault et al., 2018). Twins and sibling designs also control for shared environment confounding, based on the assumption that being raised in the same household exposes both pair members to the same shared environmental factors (e.g., family income). The discordant twin design has provided robust evidence that childhood adversity likely plays a causal role in the development of psychopathology. Twin studies using prospective reports of early adversity have found that physical maltreatment predicts later antisocial behaviour (Jaffee et al., 2004), and that peer victimisation is associated with increased symptoms of depression, anxiety, hyperactivity, and conduct problems (Singham et al., 2017). Similarly, twin studies relying on retrospective self-reports have demonstrated that childhood maltreatment is linked to elevated psychopathology, even after accounting for shared family background and genetic risk (Baldwin, Wang, et al., 2023; Capusan et al., 2016; Lecei et al., 2019; Schaefer et al., 2017). The twin design is considered more stringent than the sibling design because twins are matched in age and typically experience more similar early environments, whereas siblings born at different times may be exposed to different family and population-level risks (Sellers et al., 2022). However, the age difference between siblings can be leveraged to offer insights; for example, the discordant sibling design has shown that advanced paternal age at birth is associated with increased risk of offspring psychiatric disorders and academic difficulties (D'Onofrio et al., 2014). Overall, twin and sibling designs are powerful tools to account for genetic and shared environmental confounding. Their key limitation is they cannot eliminate non-shared

environmental confounding, which may bias the observed associations between exposure and outcome (Pingault et al., 2018). Nevertheless, this can be mitigated by using rich phenotypic datasets to adjust for relevant non-shared environmental confounders.

The Children of Twins (CoT) design extends the classic twin design to disentangle genetic and environmental contributions to intergenerational transmission. It leverages the fact that children of MZ twins share the same degree of genetic relatedness (50%) with both their biological parent and their parent's co-twin, i.e., their aunt or uncle (McAdams et al., 2014; Sellers et al., 2022). Children of DZ twins share, on average, 25% of their genes with their aunt or uncle. By comparing the strength of parent-child correlations with avuncular (aunt/uncle – niece/nephew) correlations, researchers can infer the source of intergenerational transmission in CoT (McAdams et al., 2014). If the parent-child correlation exceeds the avuncular correlation, this indicates environmental transmission of parental effects above and beyond familial confounding. If MZ avuncular correlations exceed DZ avuncular correlations, this points to genetic transmission. If MZ and DZ avuncular correlations are similar, there is no evidence for genetic transmission (McAdams et al., 2014). CoT studies have revealed that some intergenerational transmissions are likely to be genetic in nature, such as psychosis (Gottesman & Bertelsen, 1989) and parental substance use, where most associations with offspring substance use and psychopathology were accounted for by familial confounding (McAdams et al., 2014; Waldron et al., 2009). Other childhood adversities appear to reflect environmental transmission, such as parental depression and anxiety, parental separation, marital discord, and family conflict, which continued to predict offspring psychopathology even after adjustment for familial confounding (D'Onofrio et al., 2007; Eley et al., 2015; McAdams et al., 2014; Silberg et al., 2010). However, as with the classic twin design, CoT cannot control for non-shared environmental confounding, and its statistical power is often limited because large, multigenerational twin samples with rich phenotypic data are rare. Power limitations are particularly problematic for highly heritable traits (e.g., substance abuse), where discordant twin pairs are uncommon so correlations have to be estimated from a small subset of

the sample, increasing the risk of underpowered analyses (McAdams et al., 2014). Thus, a methodological caveat of CoT and twin studies is that their utility depends on sufficient within-pair discordance in the exposure of interest.

Adoption designs compare associations between genetically related and unrelated parent-offspring pairs. Because adopted children are genetically unrelated to their adoptive parents, this design effectively removes confounding from passive gene-environment correlation (Pingault et al., 2018). Associations between the child and biological parents suggest hereditary genetic effects, whereas associations with adoptive parents suggest environmental rearing effects. In line with findings from twin studies, adoption studies have demonstrated a significant environmental component in the link between parental depression and adolescent psychopathology (McAdams et al., 2014; Tully et al., 2008). For example, maternal depression was found to increase the risk of lifetime major depression and disruptive disorders in both adopted and non-adopted adolescents, with adopted adolescents showing elevated risk despite being genetically unrelated to their mothers (Tully et al., 2008). Crucially, these findings do not negate the role of genetic factors in depression; rather, they indicate that maternal depression confers an environmental liability for offspring psychopathology that cannot be explained by genetic inheritance, highlighting the importance of addressing environmental mechanisms in preventive interventions for families with depressed parents. In contrast, adoption research on parental substance abuse and offspring ADHD points to genetic transmission: ADHD risk was similarly elevated in the offspring of biological parents with drug abuse regardless of whether they reared their children, but not in the offspring of adoptive or step-parents with drug abuse (Kendler et al., 2016). Together, these examples illustrate the utility of the adoption design in disentangling genetic from environmental transmission. The main limitation of the adoption design is it does not control for environmental confounding, thus it is necessary to adjust for observed environmental confounders when using this design (Pingault et al., 2018). Additionally, researchers using the adoption design may be limited by the risk

exposures available for study, given that adoption agencies often selectively (and appropriately) place children in safe, nurturing adoptive homes (Sellers et al., 2022).

In sum, genetically informed family-based designs provide powerful tools to account for genetic and shared environmental confounding. As each design has its distinct assumptions, strengths, and limitations, triangulating across designs can enhance causal inference, since findings that converge across different methodological approaches are stronger than findings from any individual design (Baldwin, Wang, et al., 2023; Lawlor et al., 2016; Munafò & Davey Smith, 2018). However, family-based designs face notable constraints when applied to ACEs. Many adversities affect all children in a family, making it rare to identify discordant twin or sibling pairs. Twin studies often detect very few discordant cases (Jaffee et al., 2004), and official records may have difficulties ascertaining whether one or both siblings were exposed (Jonson-Reid et al., 2010). Adoption studies are also less feasible for studying ACEs since the selective screening processes tend to exclude high adversity backgrounds, reducing both exposure prevalence and representativeness (Jaffee, 2017; Van IJzendoorn et al., 2009). As a result, family-based studies are often underpowered due to small, selective samples (McAdams et al., 2014), and many rely on retrospective self-reports which may be subject to recall bias and likely identify distinct groups of individuals from prospective reports (Baldwin et al., 2019). Taken together, these issues make traditional family-based designs less suitable for studying ACEs as opposed to other environmental exposures (e.g., smoking or alcohol consumption).

Quasi-experimental designs that match ACE-exposed children with socio-demographically similar, unexposed children therefore offer a more feasible method than family-based designs in estimating the causal effects of childhood adversity on psychopathology (Jaffee, 2017). Propensity score matching (PSM) is particularly well-suited for studying ACEs because it allows researchers to approximate the counterfactual conditions of a randomised controlled trial – by matching exposed and unexposed individuals on measured confounders – while working within the ethical

and practical constraints of natural observational settings. As PSM does not require genetically related participants, it can be applied on population datasets, improving statistical power and generalisability beyond what is typically possible in family-based designs. In **Chapter 3**, I demonstrate the utility of PSM in inferring the causal effects of individual ACEs on adolescent psychopathology within a large, representative population cohort.

To account for genetic confounding, recent innovations in genome wide association studies (GWAS) enable researchers to calculate polygenic scores, i.e., individual-level scores of genetic propensity for a given trait (Pingault et al., 2018). As increasingly advanced statistical methods and data from GWAS have become rapidly available to the scientific community, this has prompted a paradigm shift from a reliance on traditional family-based designs to the integration of molecular genetic methods in developmental psychopathology (Sellers et al., 2022). Polygenic scores have their methodological limitations: they currently explain only a small proportion of variance in most psychiatric phenotypes, show limited specificity because of widespread pleiotropy (i.e., when a single genetic variant influences multiple phenotypic traits), and do not generalise well across ancestries, reflecting the Eurocentric bias in GWAS discovery samples (Duncan et al., 2019; Mei et al., 2022; Mills et al., 2020). Nevertheless, in the context of ACE research, polygenic scores provide a feasible way to account for measured genetic confounding in large, unrelated population samples, bypassing the low discordance rates and small sample sizes that constrain family-based designs. Moreover, polygenic scores can be integrated with PSM to yield a genetically adjusted propensity score (GAPS) that accounts for measured genetic and environmental confounding (Silver et al., 2022). In **Chapter 4**, I demonstrate the novel approach of GAPS matching, which to my knowledge, has not previously been applied to investigate the effects of childhood adversity on adolescent psychopathology.

While genetically informed causal inference methods are often framed as a means of addressing genetic confounding, the incorporation of genetic data in this thesis extends beyond

improving statistical adjustment for bias. Genetic confounding provides insight into why adversity clusters within families and across generations (i.e., intergenerational transmission), and why children with similar ACE histories can follow markedly different psychopathology trajectories, including resilience – reflecting multifinality arising from the dynamic interplay of biopsychosocial factors across development (Cicchetti & Rogosch, 1996). Evidence that exposure to ACEs is partially heritable highlights the reality that childhood adversity is not randomly distributed across populations (Madigan et al., 2023), but is shaped and perpetuated by intergenerational processes in which genetic, environmental, and structural factors give rise to, or protect from, childhood adversity. Thus, while some children inherit a 'double whammy' of advantageous genetic and environmental influences (Wertz et al., 2023), others experience compounded genetic vulnerabilities alongside adverse environments, underscoring the need for targeted, family-level, and structural interventions to disrupt intergenerational cycles of adversity and psychopathology.

Genetic risk is probabilistic rather than deterministic, and can be buffered or exacerbated by environmental context (Schoeler et al., 2019). Policies and interventions can therefore mitigate inherited vulnerabilities by increasing access to protective resources across multiple domains, including mental health and parenting support for caregivers, educational and extracurricular opportunities for children, economic support for families (e.g., cash transfers), and community-based resources that strengthen safety nets and child protection services (Bhatia et al., 2021). From an ethical perspective, it is crucial that genetic confounding is interpreted in a non-stigmatising and non-deterministic manner, recognising that both genetic vulnerabilities and adverse environments contribute probabilistically to psychopathology risk, while maintaining a focus on improving adverse social and structural conditions (Kelly-Irving & Delpierre, 2019). From a clinical perspective, although polygenic scores currently lack predictive accuracy for individual-level outcomes (Baldwin et al., 2021), understanding gene-environment interplay can still inform case formulation and treatment. For example, awareness of evocative and passive rGE may help clinicians identify child or parental characteristics that perpetuate adversity, while recognition of

intergenerational transmission can support integrated mental healthcare that addresses the needs of multiple family members (Wertz & Lewis, 2023). To conclude, genetically informed methods not only strengthen causal inference by reducing confounding, but also inform ethical interpretation, clinical practice, and policy responses to childhood adversity by increasing awareness of heritable vulnerabilities and strengthening the case for earlier, more targeted efforts to break cycles of intergenerational trauma and mental health problems.

1.5 Thesis aim and structure

This thesis focuses specifically on adolescent mental health outcomes, in line with the growing recognition of adolescence as a sensitive period of psychosocial and neurobiological development (Blakemore & Mills, 2014; Cheng et al., 2024; Fuhrmann et al., 2015; Larsen & Luna, 2018). It is during adolescence that many psychiatric disorders first emerge, coinciding with the rapid maturation of neural systems involved in emotion regulation, reasoning, and reward processing (Paus et al., 2008). Adolescence marks a stage where peer relationships become more influential, social sensitivity is heightened, and individuals learn to navigate increasingly complex social environments (Blakemore & Mills, 2014). Amidst this period of heightened socio-emotional vulnerability, adolescence also offers a critical window for second chances, where policies and interventions have the potential to counteract early adversity, redirect developmental trajectories towards better outcomes, and generate lasting benefits for health and wellbeing that extend far beyond adolescence into adulthood (Patton et al., 2016).

The overarching aim of this thesis is to strengthen causal inference in understanding the relationship between childhood adversity and adolescent psychopathology. To achieve this aim, this thesis addresses three key challenges in ACE research: 1) the lack of a universal paradigm for operationalising ACEs; 2) the uncertainty regarding the extent to which associations between ACEs and psychopathology are confounded by pre-existing vulnerabilities; and 3) the challenge of addressing genetic confounding.

Chapter 2 addresses the first challenge by using a data-driven approach to derive meaningful dimensions of childhood adversity. By replicating a preregistered exploratory factor analysis across two contemporary longitudinal population cohorts, the UK Millennium Cohort Study (MCS) and the US Adolescent Brain Cognitive Development (ABCD) Study, I examine whether distinct dimensions of ACEs can be identified across the two populations and whether they are differentially associated with internalising and externalising symptoms in adolescence.

Chapter 3 addresses the second challenge by applying propensity score matching to examine whether individual ACEs remain associated with depression and anxiety symptoms, high psychological distress, self-harm, and suicide attempt in adolescence, after adjusting for a comprehensive set of early life confounders within a quasi-experimental framework. Using data from the UK MCS, I apply the specificity approach to provide granular insight into whether certain ACEs pose a greater risk for psychopathology than others.

Chapter 4 addresses the third challenge by introducing genetically adjusted propensity score (GAPS) matching, a novel approach that integrates polygenic scores into propensity score models. Building on my phenotypic findings from the UK MCS, I examine gene-environment correlations between genetic vulnerabilities and ACE exposures, then apply GAPS matching to strengthen causal inference about the effects of ACEs on adolescent psychopathology, independent of measured genetic and environmental confounding.

Together, the empirical Chapters 2, 3, and 4 leverage rich, multi-informant, longitudinal data from contemporary developmental cohorts and employ complementary approaches – data-driven, quasi-experimental, and genetically informed methods – to advance a more rigorous understanding of how childhood adversity shapes adolescent psychopathology. Finally, **Chapter 5** synthesises the findings across the empirical chapters, considers their theoretical and practical implications, and outlines directions for future research.

2 Exploring data-driven dimensions of adversity

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2.1 Abstract

Background: There is not yet a consensus on the best way to operationalise adverse childhood experiences (ACEs). I used data-driven methods across two population cohorts to examine if there were meaningful dimensions underlying ACEs, and whether the dimensions were differentially associated with increased risk of adolescent psychopathology.

Methods: Participants were 18,539 British children from the UK Millennium Cohort Study (MCS) and 11,876 American children from the US Adolescent Brain Cognitive Development Study (ABCD). A wide range of ACEs (e.g., abuse, neglect, parental psychopathology, peer victimisation) were measured prospectively from infancy to mid-adolescence. Internalising and externalising symptoms were assessed with child and/or parent reports during adolescence.

Results: This preregistered exploratory factor analysis revealed four latent dimensions in the MCS (parental threat, deprivation, victimisation, and parental discipline) and ABCD (parental threat, deprivation, victimisation, and traumatic events). All dimensions except deprivation were associated with increased risk for internalising and externalising symptoms. Over and above the other dimensions, victimisation was more strongly associated with internalising (MCS β = .34, 95% CI 0.33–0.36; ABCD β = .11, 95% CI 0.10–0.13) and externalising (MCS β = .31, 95% CI 0.30–0.33; ABCD β = .13, 95% CI 0.11–0.15) symptoms.

Conclusions: Across two distinct populations, I found that ACEs can be captured by common underlying dimensions of parental threat, deprivation, and victimisation, as well as additional sample-specific dimensions. My findings expand dimensional theories of childhood adversity by suggesting that in addition to threat and deprivation, victimisation is a distinct dimension of adversity that has the strongest associations with adolescent psychopathology.

2.2 Introduction

Adverse childhood experiences (ACEs) are globally associated with higher risks for psychopathology, chronic health diseases, and substance use throughout the life course (Bellis et al., 2019; Felitti et al., 1998; Hughes et al., 2017). Annual health costs associated with ACEs in North America and Europe are estimated to be $748 billion and $581 billion respectively (Bellis et al., 2019). Although a wealth of research has established robust associations between ACEs and poor health, there is not yet a consensus across the field of developmental psychopathology on how ACEs should be operationalised. Specifically, studies use inconsistent approaches to operationalise ACEs, focus on different combinations of ACEs, and tend to follow different definitions of adversity (Lacey & Minnis, 2020).

Most research has followed the pioneering methodology of the CDC-Kaiser ACE Study, which summed 10 ACEs as a cumulative risk score to demonstrate a dose-response relationship between multiple adversities and detrimental health outcomes (Baldwin et al., 2021; Felitti et al., 1998; Hughes et al., 2017). These 10 ACEs included abuse (emotional, physical, sexual), neglect (emotional, physical), and household dysfunction (parental marital discord, domestic violence, substance abuse, mental illness, or criminal behaviour). Subsequent research has incorporated more diverse ACEs; for instance, the World Health Organisation includes parental bereavement and exposure to peer, community, and collective violence (World Health Organisation, 2020). Research has also shown that expanding the original ACE scale to include peer victimisation, community violence, and low socioeconomic status (SES) significantly improved the prediction of mental and physical health problems (Finkelhor et al., 2015; Mersky et al., 2017). Therefore, broadening the definition of adversity beyond the original 10 ACEs could advance our understanding of the relationship between adversity and psychopathology.

While the cumulative risk approach has proven useful in establishing the dose-response relationship, it has two key limitations. First, by summing ACEs together, it implicitly assumes that different ACEs have equal effects on psychopathology; this is unlikely considering how

heterogeneous ACEs are in severity, frequency, and duration. For example, sexual abuse and parental divorce are likely to impact physical and mental health outcomes in differential ways (Westermair et al., 2018). Second, as it lacks specificity in identifying the mechanisms through which ACEs impact development, the cumulative risk approach falls short in explaining how ACEs increase the risk for psychopathology. Recent studies have attempted to overcome these limitations by using dimensional models to operationalise adversity. The Dimensional Model of Adversity and Psychopathology (DMAP) proposes that ACEs reflecting dimensions of threat (e.g., abuse) and deprivation (e.g., neglect) exert differential effects on neurodevelopment via distinct mechanisms (McLaughlin et al., 2014) and that even when threat and deprivation co-occur, they work through dimension-specific pathways to increase risk for psychopathology (Lambert et al., 2017; Machlin et al., 2019). Previous DMAP-informed research largely relied on relatively small cross-sectional samples focused on early childhood, adolescence, or young adulthood (Lambert et al., 2017; Machlin et al., 2019; Sosnowski et al., 2023). Thus, results might not be as generalisable to the rest of the population. Studying longitudinal cohort studies that follow children throughout similar developmental periods would facilitate the identification of naturally occurring dimensions of adversity in the wider population context.

Nevertheless, determining the dimensions of adversity has proven challenging. It is important to clarify that dimensional models can be theoretically driven (i.e., informed by frameworks such as DMAP) or empirically driven (i.e., informed by variable-centred or person-centred statistical methods; Lacey & Minnis, 2020). Theoretically driven studies informed by DMAP have applied confirmatory factor analysis (CFA) to validate two dimensions of threat and deprivation (Awada et al., 2023; Lian et al., 2022; Miller et al., 2021; Ning et al., 2023). However, confirmatory approaches such as CFA rely on *a priori* categorisations of ACEs, which can differ across research and practice even when using the DMAP framework. For example, in a study where mental health clinicians were first instructed to read the DMAP definitions and then categorise ACEs as either threat or deprivation according to their professional opinions, the

majority categorised emotional abuse as deprivation (Henry et al., 2021), contrary to previous DMAP research which categorised emotional abuse as threat (Lambert et al., 2017; Miller et al., 2021). Furthermore, subjective practices in defining ACE measures can lead to inconsistent dimensions of adversity across studies (Wang et al., 2023), even if samples were drawn from the same dataset. Two independent studies which applied CFA on the same US birth cohort derived different numbers of dimensions, despite drawing from the same population and being informed by DMAP (Awada et al., 2023; Sisitsky et al., 2023). This was likely because each study chose different ACEs for each dimension and different measures for the same construct. For instance, Awada et al. (2023) derived two dimensions of threat and deprivation, which included parenting, financial, and neighbourhood measures of deprivation. However, Sisitsky et al. (2023) selected physical, emotional, and cognitive measures of deprivation, and found that a four-dimensional model of home threat, community threat, neglect, and lack of stimulation demonstrated better fit in their study. Altogether, these findings suggest that utilising a data-driven approach to explore whether each measure might load onto different factors would help distinguish dimensions without being influenced by *a priori* categorisations.

Contrary to CFA, exploratory factor analysis (EFA) explores the underlying dimensions of interrelated measures without specifying any predefined structure. Empirically driven studies have used EFA as a variable-centred method to derive varying dimensions, such as child maltreatment and household dysfunction from the original 10 ACEs (Mersky et al., 2017). When using an expanded set of ACEs, EFA studies have identified four to ten dimensions ranging from subtypes of threat and deprivation to caregiver psychopathology, socioeconomic disadvantage, and trauma exposure (Brieant et al., 2023; Mersky et al., 2017; Orendain et al., 2023; Sosnowski et al., 2023). The variability in dimensions of adversity is likely in part due to sample-specific differences in sociodemographic factors, developmental periods, and sample size. Thus, replicating a consistent protocol across two different populations could help distinguish if there are meaningful dimensions of adversity beyond sample-specific artefacts.

Finally, it is also essential that researchers operationalise their measures transparently to improve the reproducibility of research on ACEs, and this can be achieved through open science practices such as preregistration and openly shared code. I preregistered a data-driven exploratory analysis of two longitudinal cohorts: the UK Millennium Cohort Study and the US Adolescent Brain Cognitive Development Study. Using empirically justified measures of ACEs, I aimed to (1) test if there were meaningful dimensions of ACEs across two populations, and (2) investigate whether these dimensions were differentially associated with psychopathology in adolescence.

2.3 Methods

This study was preregistered on the Open Science Framework (https://osf.io/xqy9c). Although I preregistered competing hypotheses about potential dimensions of ACEs that could emerge, this study aimed to be exploratory; details of the rationale can be found in the preregistration. I hypothesised that (1a) ACEs would cluster as one higher-order latent factor (supporting the cumulative risk score approach), or (1b) ACEs would cluster as two latent factors of threat and deprivation (supporting the dimensional approach of DMAP). I also hypothesised that (2a) ACEs operationalised as the dimension of threat (e.g., abuse, violence) would be more strongly associated with psychopathology outcomes than deprivation, or (2b) ACEs operationalised as the dimension of deprivation (e.g., poverty, neglect) would be more strongly associated with psychopathology outcomes than threat.

Participants

The Millennium Cohort Study (MCS) is an ongoing longitudinal cohort study following over 18,000 children born between 2000-2002 in the United Kingdom (England, Scotland, Wales and Northern Ireland). This study analysed data from 18,539 children (48.6% females) after imputation (complete sample reported in **Table 6.1**) from sweeps 1 to 7 (ages 9 months, 3, 5, 7, 11, 14, and 17 years). Sweeps 1-7 were the most recent data sweeps made publicly available at the

time (the upcoming age 23 sweep is expected to be released in early 2026). The MCS collects rich information on their cohort members' physical, emotional, cognitive, and behavioural development over time, as well as their family relationships, socioeconomic circumstances, and social experiences. Further information on the MCS measures can be found on the study website (https://cls.ucl.ac.uk/cls-studies/millennium-cohort-study/). Participants were recruited from a random sample of electoral wards across the UK, and the sample was disproportionately stratified to ensure adequate representation of all four UK countries. The MCS intentionally oversampled children from disadvantaged areas, ethnic minority backgrounds, and the smaller nations of the UK to improve representativeness (for study details, see Connelly & Platt, 2014).

Ethical approval for the MCS was provided by the NHS Medical Research Ethics Committee (MREC), and informed consent was obtained from parents and children (Connelly & Platt, 2014). To use MCS data for this thesis, the University of Oxford Medical Sciences Interdivisional Research Ethics Committee reviewed the proposed secondary data analysis and approved the use of previously collected, anonymised, non-NHS data that cannot be traced back to identifiable individuals. Following approval from the Centre for Longitudinal Studies (CLS) Data Access Committee (DAC), I accessed the MCS phenotypic data from the UK Data Service on 4 February 2022 and accessed the genotypic data from the CLS Research Data Storage Service on 10 September 2024.

The Adolescent Brain Cognitive Development (ABCD) Study is an ongoing longitudinal cohort study following over 11,000 children born between 2006-2008 across 21 sites in the United States. This study analysed data from 11,876 children (47.8% females) after imputation (minimum N in the complete sample = 5,660) from baseline to the next three sweeps of follow-up (ages 9-10, 10-11, 11-12, 12-13 years). These were the most recent sweeps made publicly available at the time of my data application in February 2023 (the next annual Data Release 5.0 was released in June 2023). The ABCD collects multidisciplinary data on their cohort members' physical and

mental health, social and emotional functioning, neurocognition, and culture and environment. Further information on the ABCD measures can be found on the study website (https://abcdstudy.org/). Participants were recruited using stratified random sampling, selecting schools within catchment areas at each study site and then randomly choosing eligible children from those schools to ensure a representative sample of the US population. Relative to national proportions, the ABCD intentionally oversampled children from African-American and ethnic minority groups, as well as children from rural/non-urban school districts to improve representativeness (Garavan et al., 2018).

Ethical approval for the ABCD was provided by the Institutional Review Board (IRB) at the University of California San Diego, and informed consent was obtained from parents and children. To use ABCD data for this thesis, the University of Oxford Tropical Research Ethics Committee reviewed the proposed secondary data analysis and approved it as minimal risk health-related research conducted outside the UK. All data was stripped of individual identifiers, and participants were anonymised with numeric IDs. Following approval from the US National Institute of Mental Health (NIMH) Data Help Desk, I accessed the ABCD data from the NIMH Data Archive on 1 March 2023.

Measures

I systematically searched through both cohorts' data dictionaries and selected ACE measures based on previous MCS studies (Adjei et al., 2021; Bevilacqua et al., 2021; Ning et al., 2023), ABCD studies (Baldwin, Sallis, et al., 2022; Brieant et al., 2023), and DMAP studies (Lambert et al., 2017; Machlin et al., 2019; Miller et al., 2021). I included a broad range of ACEs informed by previous research, such as peer victimisation (Finkelhor et al., 2015; World Health Organisation, 2020). To ensure consistency across measures, ACEs were binarized where a score of 1 represented exposure to the adversity at least once throughout childhood. Within each measure for each time point, ACEs were aggregated at the item level and then binarized as present

if they surpassed a clinical or statistical cut-off. Cut-offs were conservative to represent more severe exposure and based on validated cut-offs from previous studies (see **Table *2.1*** and **Table *2.2*** for full details on how measures were derived). Where possible, I derived equivalent ACEs across both cohorts.

ACEs in MCS. I identified 173 items from the MCS and aggregated them across 9 months to age 14 years to create 18 composite ACE measures: poor parental mental health, frequent parental alcohol use, parental drug use, single parent, unhappy parental relationship, domestic violence, harsh parental discipline, parental smacking, negative home environment, peer victimisation, verbal victimisation, physical victimisation, theft victimisation, sexual victimisation, low cognitive stimulation, neighbourhood deprivation, unsafe home area, and low household income.

ACEs in ABCD. I identified 134 items from the ABCD Study and aggregated them across birth to age 11-12 years to create 18 composite ACE measures: parental psychopathology, parental alcohol abuse, parental drug abuse, parental separation, domestic violence, parental criminality, peer victimisation, cyber victimisation, physical abuse, emotional abuse, sexual abuse, emotional neglect, accident requiring medical attention, natural disaster, community violence, bereavement, unsafe neighbourhood, and low household income.

Psychopathology in MCS. Internalising and externalising symptoms were measured at age 17 using child self-reports from the Strengths and Difficulties Questionnaire (SDQ), a 25-item behavioural questionnaire with high reliability and validity (Goodman, 1997). I derived composite measures of internalising symptoms (emotional problems and peer problems) and externalising symptoms (conduct problems and hyperactivity/inattention) by summing and then standardising scores across the subscales.

Psychopathology in ABCD. Internalising and externalising symptoms were measured at age 12-13 using parent reports from the Child Behaviour Checklist (CBCL), a 119-item behavioural

questionnaire with excellent reliability and validity (Achenbach, 2001). I derived composite measures of internalising symptoms (anxious/depressed, withdrawn/depressed, and somatic complaints) and externalising symptoms (rule-breaking, aggressive behaviour, and attention problems) by summing and then standardising scores across the subscales.

Scores from the SDQ and CBCL have been shown to be highly correlated and equally able to differentiate between high-risk and low-risk children (Goodman & Scott, 1999), ensuring outcome measures were broadly consistent across both cohorts.

Table 2.1 Criteria for deriving exposures and outcome measures in the MCS.

Measure	Informant	Assessment type	Exposure period	Assessment phase	Criteria for coding measure as present
Poor parental mental health	Parent	Rutter Malaise Inventory (RMI); Kessler (K6) Scale	9 months, 3, 5, 7, 11, and 14 years	Sweeps 1-6	At 9 months, the Rutter Malaise Inventory (RMI) scale was used to measure parental mental health in the last 30 days (e.g., "do you often feel miserable or depressed?", "does your heart often race like mad?"). Scores were summed and then dichotomised (cut-off score ≥ 4; Adjei et al., 2022). At 3, 5, 7, 11, and 14 years, the Kessler (K6) scale was used to measure parental mental health in the last 30 days (e.g., "so depressed nothing could cheer you up", "nervous"). Scores were summed and then dichotomised with the cut-off score ≥ 13 (Straatmann et al., 2020). If parents reported poor mental health for at least 1 out of 6 sweeps, poor parental mental health was coded as present.
Frequent parental alcohol use	Parent	Parent interview (alcohol consumption)	9 months, 3, 5, 7, 11, and 14 years	Sweeps 1-6	Parents reported the frequency of their alcohol use which was dichotomised (every day/5-6 times per week = 1 vs 3-4 times per week/1-2 times per week/less than once a month/never = 0; Straatmann et al., 2020). If parents reported frequent alcohol use for at least 1 out of 6 sweeps, frequent parental alcohol use was coded as present.
Parental drug use	Parent	Parent interview (substance abuse)	3, 5, and 14 years	Sweeps 2, 3, 6	Parents reported the frequency of their drug use, which was dichotomised as regularly/occasionally = 1 vs never = 0 (Bevilacqua et al., 2021). If parents reported drug use for at least 1 out of 3 sweeps, parental drug use was coded as present.
Single parent	Parent	Parent interview (marital status)	9 months, 3, 5, 7, 11, and 14 years	Sweeps 1-6	Parents reported their marital status, which was dichotomised (divorced/legally separated/widowed/single = 1 vs married/remarried/civil partnership = 0). If parents reported a single parent status for at least 1 out of 6 sweeps, the single parent measure was coded as present.
Unhappy parental relationship	Parent	Golombok Rust Inventory of Marital State	9 months, 3, 5, 7, 11, and 14 years	Sweeps 1-6	Parents reported how happy they were with their relationship with their partner on a 7-point scale (1 = very unhappy and 7 being very happy), which was dichotomised (very unhappy [1]/2/3 = 1 vs 4/5/6/very happy [7] = 0). If parents reported an unhappy relationship for at least 1 out of 6 sweeps, unhappy parental relationship was coded as present.
Domestic violence	Parent	Golombok Rust Inventory of Marital State	9 months, 3, 5, 7, 11, and 14 years	Sweeps 1-6	Parents reported whether their partner had ever used force in their relationship, which was dichotomised (yes = 1 vs no = 0). If parents reported experiencing this for at least 1 out of 6 sweeps, domestic violence was coded as present.

Measure	Informant	Assessment type	Exposure period	Assessment phase	Criteria for coding measure as present
Harsh parental discipline	Parent	Straus Conflict Tactics scale (CTS)	3, 5, and 7 years	Sweeps 2-4	The Straus Conflict Tactics scale was used to measure parental discipline practices (e.g., "tells child off when naughty"). Scores were summed and then dichotomised (with a cut-off score ≥ 5; Bevilacqua et al., 2021). If parents surpassed the cut-off for at least 1 out of 3 sweeps, harsh parental discipline was coded as present.
Parental smacking	Parent	Straus Conflict Tactics scale (CTS)	3, 5, and 7 years	Sweeps 2-4	Parents reported whether they smacked their child, which was dichotomised (daily/once a week or more/once a month = 1 vs never/rarely = 0; Bevilacqua et al., 2021). If parents smacked their child for at least 1 out of 3 sweeps, parental smacking was coded as present.
Negative home environment	Interviewer	Home Observation for Measurement of the Environment (HOME-SF)	3 years	Sweep 2	An interviewer visited the cohort member's home to observe the physical environment (e.g., "child's in-home play environment safe") and responsiveness of the mother (e.g., "mother's voice positive when speaking to child"). Scores were negatively coded, summed, and then dichotomised. Scores that were 2 standard deviations above the mean were coded as a negative home environment (Totsika & Sylva, 2004).
Peer victimisation	Parent, teacher, child	Strengths and Difficulties Questionnaire (SDQ)	3, 5, 7, 11, and 14 years	Sweeps 2-6	At ages 7, 11, and 14, children self-reported on peer victimisation (e.g., "how often do other children hurt you or pick on you on purpose?"). The victimisation items from the SDQ were used for parent reports at ages 3, 5, 7, and 14, and teacher reports at ages 7 and 11 (e.g., "child picked on or bullied by other children"). Scores were dichotomised (most days/about once a week = 1 vs once a month/every few months/less often/never = 0). If children were reported by at least one informant to have experienced peer victimisation for at least 1 out of 5 sweeps, peer victimisation was coded as present.
Verbal victimisation	Child	Victimisation questionnaire	14 years	Sweep 6	Children self-reported whether they had ever been insulted, threatened, or shouted at by anyone in the past 12 months. Scores were dichotomised (yes = 1 vs no = 0).
Physical victimisation	Child	Victimisation questionnaire	14 years	Sweep 6	Children self-reported whether anyone had ever been physically violent (e.g., "pushed, shoved, hit, slapped or punched you"), or used a weapon against them in the past 12 months. Scores were dichotomised (yes = 1 vs no = 0).
Theft victimisation	Child	Victimisation questionnaire	14 years	Sweep 6	Children self-reported whether anyone had ever stolen something from them (e.g., mobile phone, money) in the past 12 months. Scores were dichotomised (yes = 1 vs no = 0).
Sexual victimisation	Child	Victimisation questionnaire	14 years	Sweep 6	Children self-reported whether anyone had ever sexually assaulted them in the past 12 months. Scores were dichotomised (yes = 1 vs no = 0).

Measure	Informant	Assessment type	Exposure period	Assessment phase	Criteria for coding measure as present
Low cognitive stimulation	Parent	Parenting questionnaire	3, 5, 7, and 11 years	Sweeps 2-5	Cognitive stimulation was measured using several parent-reported items (e.g., "how often do you read to the child?", "how often do you teach child counting?") which were dichotomised (not at all/on special occasions = 1 vs once a week/several times a week/every day = 0). If cognitive stimulation was reported as low for at least 1 out of 4 sweeps, low cognitive stimulation was coded as present.
Neighbourhood deprivation	Parent	Neighbourhood questionnaire	9 months	Sweep 1	Neighbourhood deprivation was measured using several parent-reported items on the neighbourhood (e.g., "noisy neighbours"), cleanliness (e.g., "how common are rubbish/litter in area"), and access (e.g., "poor public transport"). Scores were dichotomised (very dissatisfied/fairly dissatisfied = 1 vs fairly satisfied/very satisfied = 0) and then summed. If more than half of the items were reported as unsatisfactory, neighbourhood deprivation was coded as present.
Unsafe home area	Parent	Housing questionnaire	3, 5, and 11 years	Sweeps 2, 3, 5	Home area safety was measured using several parent-reported items (e.g., "is this a good area to bring up a child?", "how safe is it to walk/play in this area?") which were dichotomised (very unsafe/fairly unsafe = 1 vs fairly safe/very safe = 0). If home area was reported as unsafe for at least 1 out of 3 sweeps, unsafe home area was coded as present.
Low household income	Parent	OECD Income Weighted Quintiles	9 months, 3, 5, 7, 11, and 14 years	Sweeps 1-6	Household equivalised income was measured using the OECD Income Weighted Quintiles. Scores were dichotomised (lowest quintile = 1 vs second/third/fourth/highest quintile = 0). If household income was reported as the lowest quintile for at least 1 out of 6 sweeps, low household income was coded as present.
Internalising symptoms	Child	Strengths and Difficulties Questionnaire (SDQ)	17 years	Sweep 7	Children self-reported on a three-point scale (0 = not true, 1 = somewhat true, 2 = certainly true) if they displayed: emotional problems (e.g., "I am often unhappy, down-hearted or tearful") and peer problems (e.g., "other children pick on me or bully me"). Scores were summed across the internalising subscales and then standardised as a composite measure of internalising symptoms.
Externalising symptoms	Child	Strengths and Difficulties Questionnaire (SDQ)	17 years	Sweep 7	Children self-reported on a three-point scale (0 = not true, 1 = somewhat true, 2 = certainly true) if they displayed: conduct problems (e.g., "I get very angry and often lose my temper") and hyperactivity/inattention (e.g., "I am restless, I cannot sit still for long"). Scores were summed across the externalising subscales and then standardised as a composite measure of externalising symptoms.

Table 2.2 Criteria for deriving exposure and outcome measures in the ABCD.

Measure	Informant	Assessment type	Exposure period	Assessment phase	Criteria for coding measure as present
Parental psychopathology	Parent	Family History Assessment, Adult Self-Report (ASR)	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether they had ever suffered from depression, manic episodes, psychotic experiences for more than 6 months, attempted or committed suicide in the Family History Assessment. If family history of psychopathology was present for either biological father or mother, or if parents scored above the clinical cut-off of ASR > 63 (Achenbach & Rescorla, 2003) for depression, anxiety, or ADHD for at least 1 assessment, parental psychopathology was coded as present.
Parental alcohol abuse	Parent	Family History Assessment	0-9/10y	Baseline	Parents reported whether they ever had any problems due to alcohol (e.g., marital problems, work problems, arrests/DUI, in a treatment programme, isolated self/caused arguments/drunk a lot). If family history of alcohol abuse was present for either biological father or mother, parental alcohol abuse was coded as present.
Parental drug abuse	Parent	Family History Assessment, Adult Self-Report (ASR)	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether they ever had any problems due to drugs (e.g., marital problems, work problems, arrests/DUI, in a treatment programme, isolated self/caused arguments/high a lot). If family history of drug abuse was present for either biological father or mother, or if parents reported using drugs multiple times weekly in the past 6 months in the ASR for at least 1 assessment, parental drug abuse was coded as present.
Parental separation	Parent	Parent Demographics Survey, Longitudinal Parent Demographics Survey, Parent Life Events	0-9/10y, 10/11y, 11/12y	Baseline, 1y follow-up, 2y follow-up	Parents reported whether they had separated or divorced, or if their current partner was not the child's biological or adoptive parent. If any instance of parental separation was reported for at least 1 assessment, parental separation was coded as present.
Domestic violence	Parent	KSADS Traumatic Events	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether their child had ever witnessed the grown-ups in the home push, shove or hit one another. If parents reported any instance of domestic violence for at least 1 assessment, domestic violence was coded as present.
Parental criminality	Parent	Parent Life Events	0-10/11y, 11/12y	1y follow-up, 2y follow-up	Parents reported whether they had ever got into trouble with the law or went to jail, or a family member had been arrested. If any instance of parental criminality was reported for at least 1 assessment, parental criminality was coded as present.

Measure	Informant	Assessment type	Exposure period	Assessment phase	Criteria for coding measure as present
Peer victimisation	Child	Peer Experiences Questionnaire	11/12y	2y follow-up	Children reported whether they had been victimised by peers in the past year (e.g., kids left me out; chased me like trying to hurt me; spread rumours about me; did not invite me to party; left me out; gossiped about me; threatened to hurt/beat me; said mean things about me; hit/kicked/pushed me). Scores were dichotomised (a few times a week /once a week = 1 vs a few times/once or twice/never = 0). If children reported at least 1 type of victimisation, peer victimisation was coded as present.
Cyber victimisation	Child	Cyber Bully Questionnaire	11/12y	2y follow-up	Children reported whether they had experienced cybervictimisation, and if they had, how often they had been cyberbullied in the past year. Scores were dichotomised (≥ 10 times in the past 12 months = 1). If children reported at least 1 experience of cybervictimisation, cybervictimisation was coded as present.
Physical abuse	Parent	KSADS Traumatic Events	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether their child had ever been shot, stabbed, beaten brutally, or beaten to the point of having bruises by a grown-up in the home. If parents reported any instance of physical abuse for at least 1 assessment, physical abuse was coded as present.
Emotional abuse	Parent	KSADS Traumatic Events	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether a non-family member or family member had ever threatened to kill their child. If parents reported any instance of emotional abuse for at least 1 assessment, emotional abuse was coded as present.
Sexual abuse	Parent	KSADS Traumatic Events	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether a grown-up in the home or an adult outside the family had ever touched their child in their privates, had their child touch the adult's privates, or if the adult did other sexual things to their child, or if a peer had ever forced their child to do something sexually. If parents reported any instance of sexual abuse for at least 1 assessment, sexual abuse was coded as present.
Emotional neglect	Child	Children's Report of Parental Behavioural Inventory	0-9/10y, 10/11y	Baseline, 1y follow-up	Children rated their caregiver's behaviour (e.g., believes in showing love for me; makes me feel better when upset; or when talking over worries; is easy to talk to; smiles at me very often). Scores were dichotomised (not like him/her = 1 vs somewhat/a lot like him/her = 0) and then if children reported 2 or more items with the cut-off score ≥ 2 (Baldwin, Sallis, et al., 2022) for at least 1 assessment, emotional neglect was coded as present.
Accident requiring medical attention	Parent	KSADS Traumatic Events	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether their child had ever been in a car accident or another significant accident for which their child or another person needed medical attention. If parents reported any instance of an accident for at least 1 assessment, this was coded as present.

Measure	Informant	Assessment type	Exposure period	Assessment phase	Criteria for coding measure as present
Natural disaster	Parent	KSADS Traumatic Events	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether their child had ever witnessed or been caught in a fire or natural disaster that caused significant property damage or personal injury. If parents reported any instance of a natural disaster for at least 1 assessment, this was coded as present.
Community violence	Parent	KSADS Traumatic Events	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether their child had ever witnessed an act of terrorism, death or mass destruction in a war zone, or someone shot or stabbed in the community. If parents reported any instance of community violence for at least 1 assessment, community violence was coded as present.
Bereavement	Parent	KSADS Traumatic Events	0-9/10y, 11/12y	Baseline, 2y follow-up	Parents reported whether their child had ever learned about the sudden unexpected death of a loved one. If parents reported any instance of bereavement for at least 1 assessment, bereavement was coded as present.
Unsafe neighbourhood	Parent, Child	Parent and Youth Neighbourhood Safety/Crime Survey	9/10y, 10/11y, 11/12y	Baseline, 1y follow-up, 2y follow-up	Parents and children reported neighbourhood safety (e.g., feel safe walking in my neighbourhood; violence is not a problem; my neighbourhood is safe from crime). Scores were dichotomised (strongly disagree = 1 vs disagree/neutral/agree/strongly agree = 0). If either parent or child reported the neighbourhood as unsafe for at least 1 assessment, unsafe neighbourhood was coded as present.
Low household income	Parent	Parent Demographics Survey	9/10y, 10/11y, 11/12y	Baseline, 1y follow-up, 2y follow-up	Parents reported their total combined family income for the past 12 months. Scores were dichotomised according to guidelines from the US Census Bureau, where lowest quintile households had ≤ $28,007 income = 1 (Semega & Kollar, 2022). If household income was reported as the lowest quintile for at least 1 assessment, low household income was coded as present.
Internalising symptoms	Parent	Child Behaviour Checklist (CBCL)	12/13y	3y follow-up	Parents reported on a three-point scale (0 = absent, 1 = occurs sometimes, 2 = occurs often) if their child displayed: anxious/depressed behaviour (e.g., cries a lot), withdrawn/depressed behaviour (e.g., there is very little he/she enjoys), and somatic complaints (e.g., nightmares). Scores were summed across the internalising subscales and then standardised as a composite measure of internalising symptoms.
Externalising symptoms	Parent	Child Behaviour Checklist (CBCL)	12/13y	3y follow-up	Parents reported on a three-point scale (0 = absent, 1 = occurs sometimes, 2 = occurs often) if their child displayed: rule-breaking behaviour (e.g., drinks alcohol without parents' approval), aggressive behaviour (e.g., argues a lot), and attention problems (e.g., fails to finish things he/she starts). Scores were summed across the externalising subscales and then standardised as a composite measure of externalising symptoms.

Statistical Analysis

Analyses for this study were conducted using R (version 4.1.2) and the code is publicly available on GitHub (https://github.com/athena-chow/dimensions-aces).

Dimensions of ACEs. To identify the dimensions underlying ACEs, I conducted exploratory factor analysis (EFA) using the 'psych' package (Revelle, 2015). I chose factor analysis instead of a person-centred approach because the variable-centred approach of factor analysis examines which ACEs cluster together regardless of population characteristics, whereas the person-centred approach (e.g., latent class analysis) identifies subgroups of people who report similar ACE exposure in that particular population. I chose EFA over CFA as I aimed to explore the naturally occurring factor structure in both populations, although I did expect at least one threat-related and one deprivation-related factor based on previous research (McLaughlin et al., 2014). First, I conducted parallel analysis with 1,000 Monte-Carlo simulations to determine the optimal number of factors to extract. EFA was conducted with an oblique rotation on the tetrachoric correlation matrix using weighted least squares estimation. I evaluated model fit using absolute and relative fit indices (RMSEA < 0.06, RMSR < 0.08, and TLI > 0.95 indicated good fit; Hu & Bentler, 1999). I also considered which model had the "cleanest" factor structure, defined as factor loadings equal to or more than 0.30, with no or few item cross-loadings (Costello & Osborne, 2005).

Associations between ACE dimensions and psychopathology. After selecting the best-fitting model, I extracted continuous factor scores for each child where higher scores reflected higher levels of the ACE dimension. I then ran univariate linear regressions to test the associations between each dimension and psychopathology outcomes. Next, I ran adjusted models including sex and ethnicity as covariates, given that previous research has suggested that sex and ethnicity are associated with both the clustering of ACEs and adolescent mental health (Jones et al., 2022; Zhang & Monnat, 2022). Finally, I ran a multivariate multiple regression model including all

dimensions, covariates, and psychopathology outcomes. As preregistered sensitivity analyses, I also tested for interactions between sex and ACE dimensions on psychopathology, given that some previous research found that sex moderated the relationships between ACEs and psychopathology (Houtepen et al., 2018; Jones et al., 2022).

Missing data imputation. I imputed missing data with a random forest algorithm using the 'missForest' package (Stekhoven & Buehlmann, 2012). I trained the random forest on the raw items comprising the exposure and outcome variables, covariates, and auxiliary variables. Auxiliary variables were sociodemographic indicators associated with missingness and ACEs (e.g., birthweight, smoking during pregnancy, home ownership at birth; Houtepen et al., 2018). For both the MCS and ABCD, I re-derived the composite measures of ACEs and psychopathology from the imputed data and then replicated the analyses to ensure results were consistent across complete and imputed samples.

2.4 Results

Prevalence of ACEs in the MCS and ABCD

Descriptive statistics are reported in **Table *2.3***, with information on missingness and sample attrition available in the appendices (MCS **Figure 6.1** and **Table 6.1**; ABCD **Figure 6.2** and **Table 6.2**). The most prevalent ACE in the MCS sample was ever having a single parent (51.30%) by age 14, whereas the least prevalent ACE was sexual victimisation (1.58%). The most prevalent ACE in the ABCD Study was parental psychopathology (39.93%), while the least prevalent ACE was physical abuse (1.03%). Levels of sexual victimisation in the MCS (1.58%) were approximately equivalent to sexual abuse in the ABCD (2.42%). 7.80% of MCS children were from households with domestic violence by age 14, while 9.68% of ABCD children had witnessed domestic violence by age 12.

Table 2.3 Descriptive statistics for the MCS and ABCD.

Millennium Cohort Study (MCS)

ACEs (9 months to 14 years)	**Complete n**	**n exposed**	**% exposed**
Poor parental mental health	18,312	3,721	20.07
Frequent parental alcohol use	18,521	2,385	12.86
Parental drug use	15,574	990	5.34
Single parent	18,521	9,510	51.30
Unhappy parental relationship	16,383	6,117	33.00
Domestic violence	16,233	1,446	7.80
Harsh parental discipline	15,163	7,276	39.25
Parental smacking	15,118	3,201	17.27
Negative home environment	13,863	675	3.64
Peer victimisation	16,420	4,477	24.15
Verbal victimisation	10,787	4,634	25.00
Physical victimisation	10,786	2,386	12.87
Theft victimisation	10,782	770	4.15
Sexual victimisation	10,781	293	1.58
Low cognitive stimulation	16,377	1,484	8.00
Neighbourhood deprivation	17,844	2,100	11.33
Unsafe home area	16,351	3,472	18.73
Low household income	18,513	7,586	40.92

Sociodemographic characteristics (baseline)		**Complete n**	**%**
Sex	Male	9,526	51.38
	Female	9,013	48.62
Ethnicity	White	15,277	82.40
	Black/Black British	666	3.59
	Pakistani/Bangladeshi	1,265	6.82
	Indian	465	2.51
	Mixed	552	2.98
	Other (inc. Chinese)	266	1.43
Maternal education	Higher degree	635	3.44
	First degree/diploma in higher educ.	3813	20.65
	A/AS/S levels	1732	9.38
	GCSE A*–C	6167	33.40
	GCSE D–G/no qualifications	5600	30.33
	Other (inc. overseas)	515	2.79

Psychopathology (17 years)	**Complete n**	**M (SD)**	**Range**
Internalising symptoms	9,398	5.62 (3.47)	0 – 20
Externalising symptoms	9,399	5.61 (3.29)	0 – 20

Adolescent Brain Cognitive Development (ABCD) Study

ACEs (0–11/12 years)	Complete n	n exposed	% exposed
Parental psychopathology	11,784	4,742	39.93
Parental alcohol abuse	11,876	1,720	14.48
Parental drug abuse	11,607	1,366	11.50
Parental separation	11,409	2,750	23.16
Domestic violence	11,836	1,150	9.68
Parental criminality	11,446	1,146	9.65
Peer victimisation	10,392	829	6.98
Cyber victimisation	10,361	930	7.83
Physical abuse	11,836	122	1.03
Emotional abuse	11,836	189	1.59
Sexual abuse	11,836	287	2.42
Emotional neglect	11,876	433	3.65
Accident requiring medical attention	11,836	1,347	11.34
Natural disaster	11,836	754	6.35
Community violence	11,836	187	1.57
Bereavement	11,836	3,876	32.64
Unsafe neighbourhood	11,441	2,056	17.31
Low household income	10,607	1,901	16.01

Sociodemographic characteristics (baseline)		Complete n	%
Sex	Male	6,196	52.17
	Female	5,680	47.83
Ethnicity	White	7,522	63.34
	Black/African American	2,269	19.11
	Other Race	800	6.74
	Asian	716	6.03
	American Indian/Alaska Native	346	2.91
	Native Hawaiian/Pacific Islander	50	0.42
Parental education	Postgraduate degree	4,043	34.04
	Bachelor's degree	3,015	25.39
	Some college degree	3,079	25.93
	HS Diploma/GED	1,131	9.52
	< HS Diploma	592	4.98

Psychopathology (12/13 years)	Complete n	M (SD)	Range
Internalising symptoms	6,169	5.13 (5.78)	0 – 44
Externalising symptoms	6,169	6.69 (7.89)	0 – 64

Dimensions of Adverse Childhood Experiences in the MCS and ABCD

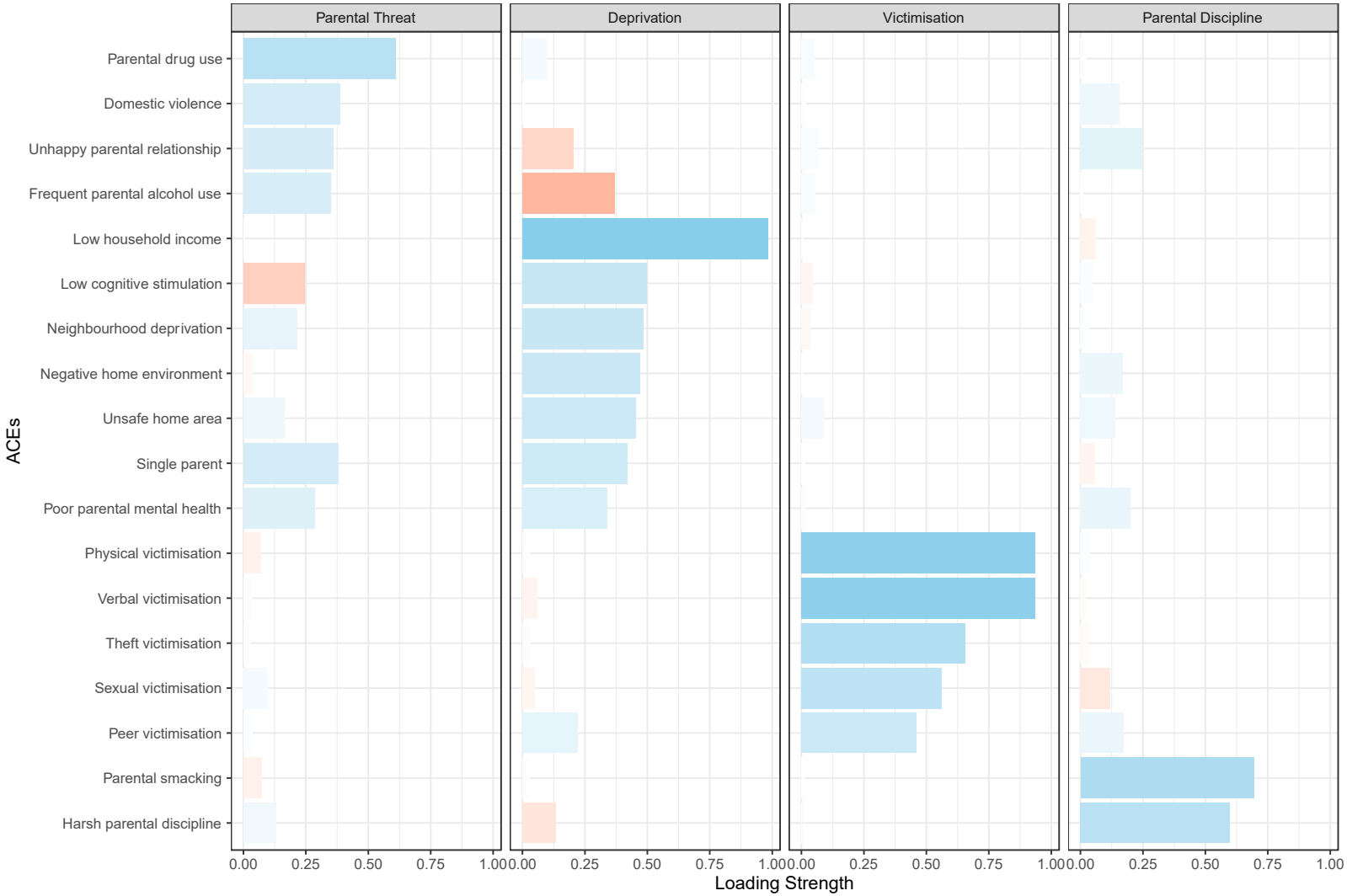
My data-driven exploratory factor analysis revealed the four-factor model as the best-fitting according to model fit indices in the MCS (RMSEA = 0.09, RMSR = 0.03, TLI = 0.80) and ABCD (RMSEA = 0.09, RMSR = 0.04, TLI = 0.79). Three of the four factors emerged as consistent dimensions across both populations: parental threat, deprivation, and victimisation. Full details of how the four-factor model holistically met the criteria as the best-fitting model are available in the appendices (MCS **Appendix 6.1.1** & **6.1.2**; ABCD **Appendix 6.1.3** & **6.1.4**).

In the MCS, the one-factor model (**Figure 6.5**) indicated poor fit indices compared to the rest of the models (**Table *6.3***), and two ACE measures (low cognitive stimulation and sexual victimisation) had low loadings of 0.20. Parental smacking, frequent parental alcohol use, harsh parental discipline, and unhappy parental relationship did not load onto the one-factor model. The two-factor model (**Figure 6.6**) had better fit indices than the one-factor model. Harsh parental discipline, parental smacking, and unhappy parental relationship did not load onto the two-factor model. Although there appeared to be two factors of threat/deprivation-related events and victimisation, there was no distinction between threat and deprivation ACEs to support DMAP. The three-factor model (**Figure 6.7**) had better fit indices than the two-factor model, with all items loading onto three factors. The second and third factor were moderately correlated (r = 0.30) but their respective ACE measures loaded onto distinct dimensions. The four-factor model (**Figure 6.8**) was the second-best fitting model in terms of fit indices, with all loadings equal to or above 0.30. The first three factors were moderately correlated with each other (r = 0.20), but their respective ACE measures loaded onto distinct dimensions. The five-factor model (**Figure 6.9**) demonstrated the best fit indices, but the third factor consisted of only one item (parental drug use), indicating model instability. All five factors were correlated with each other (r = 0.20-0.30). Overall consideration of the fit indices and factor structure suggested the four-factor model fit the MCS data optimally, and these findings were replicated in the imputed sample (**Appendix 6.1.2**).

In the MCS, ACEs loaded onto four factors of parental threat, deprivation, victimisation, and parental discipline (**Figure 2.1**). The parental threat dimension included parental drug use, domestic violence, unhappy parental relationship, and frequent parental alcohol use. The deprivation dimension included low household income, low cognitive stimulation, neighbourhood deprivation, negative home environment, unsafe home area, single parent, and poor parental mental health. The victimisation dimension consisted of physical, verbal, theft, sexual, and peer victimisation. The parental discipline dimension consisted of parental smacking and harsh parental discipline.

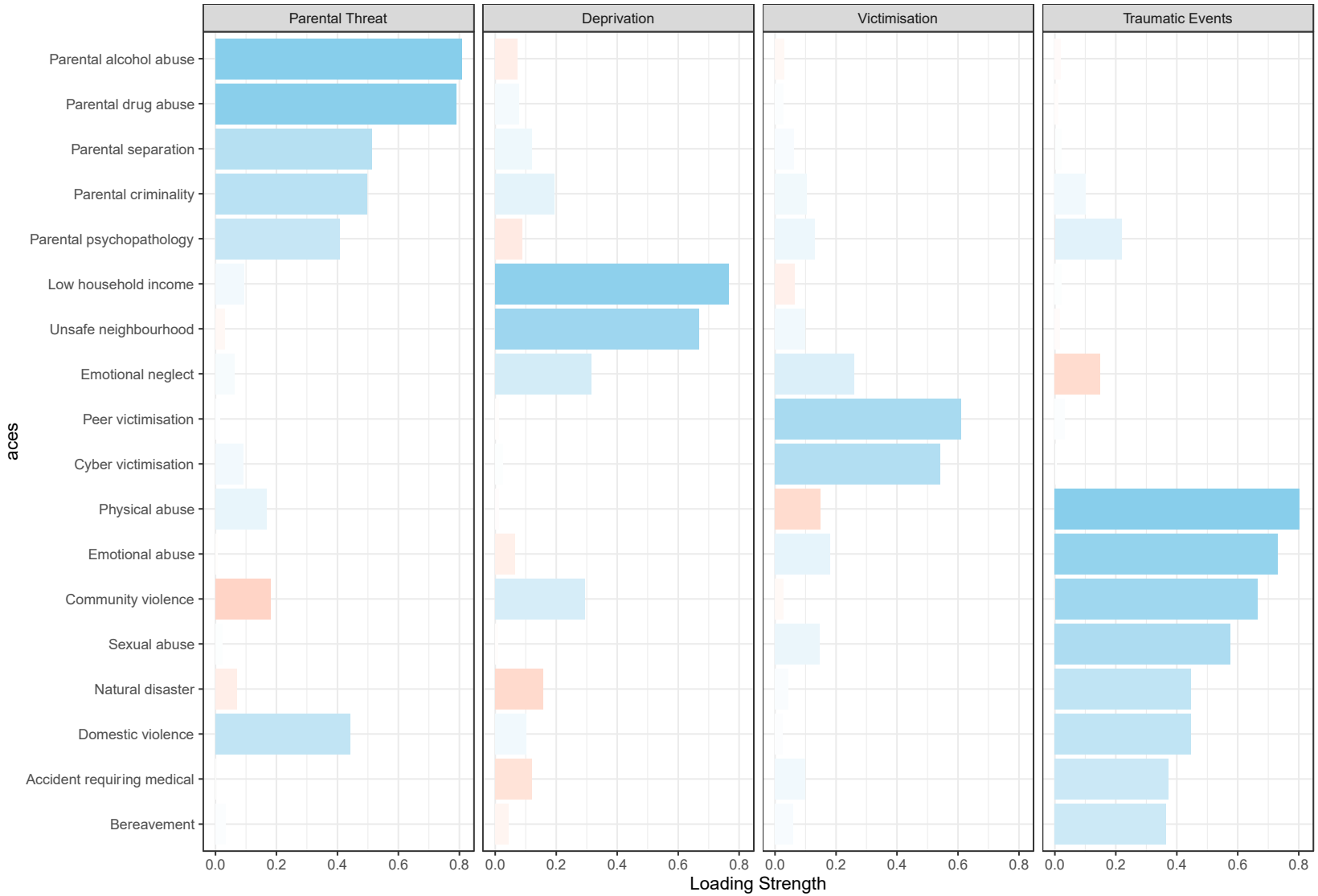
In the ABCD, the one-factor model (**Figure 6.13**) indicated poor fit indices compared to the rest of the models (**Table 6.5**), and one ACE measure (peer victimisation) had a low loading of 0.20. Emotional neglect did not load onto the one-factor model. The two-factor model (**Figure 6.14**) had better fit indices than the one-factor model. Peer victimisation did not load onto the two-factor model. The first and second factors were correlated ($r = 0.50$) but their respective ACE measures loaded onto distinct dimensions. Although there appeared to be two factors of threat/deprivation-related events and traumatic events, there was no distinction between threat and deprivation ACEs to support DMAP. The three-factor model (**Figure 6.15**) had better fit indices than the two-factor model, with all items loading onto three factors. The first and second factors were identical to the two-factor model, except that emotional neglect, peer victimisation and cyber victimisation loaded onto the third factor. The four-factor model (**Figure 6.16**) demonstrated the best fit indices, with all loadings equal to or above 0.30. The first three factors were moderately correlated with each other (r = 0.30-0.40) but their respective ACE measures loaded onto distinct dimensions. Overall consideration of the fit indices and factor structure criteria suggested the four-factor model fit the ABCD data optimally, and these findings were replicated in the imputed sample (**Appendix 6.1.4**).

Figure 2.1 MCS factor loadings onto each dimension.



Note. Blue bars represent positive loadings of ACEs onto each dimension, while red bars represent negative loadings.

Figure 2.2 ABCD factor loadings onto each dimension.



In the ABCD, ACEs loaded onto four factors of parental threat, deprivation, victimisation, and traumatic events (**Figure 2.2**). The parental threat dimension included parental alcohol abuse, parental drug abuse, parental separation, parental criminality, and parental psychopathology. The deprivation dimension included low household income, unsafe neighbourhood, and emotional neglect. The victimisation dimension consisted of peer and cyber victimisation. The traumatic events dimension consisted of physical abuse, emotional abuse, community violence, sexual abuse, natural disaster, domestic violence, accident requiring medical attention, and bereavement.

Associations Between Adversity Dimensions and Adolescent Psychopathology

Within both cohorts, dimensions of adversity were differentially associated with adolescent psychopathology (**Table 2.4** & **Table 2.5**). In the MCS, univariate analyses revealed that parental threat was associated with internalising symptoms (β = .17, 95% CI [0.16, 0.18], p < .001), as well as externalising symptoms (β = .21, 95% CI [0.20, 0.23], p < .001). These associations remained after adjusting for covariates. There was no significant association between deprivation and internalising symptoms (β = –.01, 95% CI [–0.03, 0.00004], p = .051), or externalising symptoms (β = –.003, 95% CI [–0.02, 0.01], p = .661). After adjusting for sex and race, deprivation remained unassociated with internalising and externalising symptoms. Victimisation was associated with internalising symptoms (β = .37, 95% CI [0.36, 0.39], p < .001) and externalising symptoms (β = .38, 95% CI [0.37, 0.40], p < .001), and these associations remained after adjusting for covariates. Parental discipline showed a small association with internalising symptoms (β = .16, 95% CI [0.15, 0.18], p < .001), and a stronger association with externalising symptoms (β = .31, 95% CI [0.29, 0.32], p < .001). After covariate adjustment, parental discipline remained associated with both internalising and externalising symptoms. In the multivariate adjusted model, victimisation appeared to be the most strongly associated with internalising and externalising symptoms, followed by parental discipline and parental threat. Deprivation remained unassociated with psychopathology after accounting for the other three dimensions.

Table 2.4 Adjusted associations between ACE dimensions and internalising symptoms.

Millennium Cohort Study (MCS)		
ACE Dimension	Internalising symptoms **β (95% CI)**	Multivariate model **β (95% CI)**
Parental Threat	0.17*** (0.15, 0.18)	0.06*** (0.05, 0.08)
Deprivation	-0.002 (-0.02, 0.01)	0.003 (-0.01, 0.02)
Victimisation	0.38*** (0.36, 0.39)	0.34*** (0.33, 0.36)
Parental Discipline	0.18*** (0.16, 0.19)	0.08*** (0.07, 0.10)
Adolescent Brain Cognitive Development (ABCD) Study		
ACE Dimension	Internalising symptoms **β (95% CI)**	Multivariate model **β (95% CI)**
Parental Threat	0.10*** (0.08, 0.12)	0.07*** (0.05, 0.09)
Deprivation	-0.01 (-0.03, 0.01)	-0.05*** (-0.07, -0.03)
Victimisation	0.13*** (0.11, 0.15)	0.11*** (0.10, 0.13)
Traumatic Events	0.08*** (0.07, 0.10)	0.05*** (0.03, 0.07)

Table 2.5 Adjusted associations between ACE dimensions and externalising symptoms.

Millennium Cohort Study (MCS)		
ACE Dimension	Externalising symptoms **β (95% CI)**	Multivariate model **β (95% CI)**
Parental Threat	0.22*** (0.20, 0.23)	0.08*** (0.07, 0.10)
Deprivation	0.01 (-0.01, 0.02)	0.01 (-0.002, 0.03)
Victimisation	0.38*** (0.37, 0.39)	0.31*** (0.30, 0.33)
Parental Discipline	0.30*** (0.29, 0.32)	0.21*** (0.20, 0.23)
Adolescent Brain Cognitive Development (ABCD) Study		
ACE Dimension	Externalising symptoms **β (95% CI)**	Multivariate model **β (95% CI)**
Parental Threat	0.11*** (0.10, 0.13)	0.08*** (0.06, 0.10)
Deprivation	0.02 (-0.001, 0.04)	-0.02** (-0.04, -0.004)
Victimisation	0.15*** (0.13, 0.17)	0.13*** (0.11, 0.15)
Traumatic Events	0.09*** (0.07, 0.11)	0.04*** (0.02, 0.06)

Note. All regression models were adjusted for sex and ethnicity. ACE dimensions, internalising and externalising symptoms were standardised.

β = standardised regression coefficient, CI = confidence interval. *p <.05; **p <.01; ***p <.001

In the ABCD, univariate analyses revealed that parental threat was also associated with internalising symptoms (β = .09, 95% CI [0.07, 0.11], p < .001) and externalising symptoms (β = .11, 95% CI [0.09, 0.13], p < .001), and remained associated after covariate adjustment (**Table 2.4** & **Table 2.5**). Deprivation was not associated with externalising symptoms (β = –.004, 95% CI [–0.02, 0.01], p = .633). While a very small negative association with internalising symptoms was found in univariate analyses (β = –.05, 95% CI [–0.07, –0.03], p < .001), this was not the case after adjusting for sex and race. Victimisation was associated with internalising symptoms (β = .13, 95% CI [0.11, 0.15], p < .001) and externalising symptoms (β = .15, 95% CI [0.13, 0.17], p < .001), and remained associated with these outcomes after adjusting for covariates. There were small associations between traumatic events and internalising symptoms (β = .07, 95% CI [0.06, 0.09], p < .001), as well as externalising symptoms (β = .09, 95% CI [0.07, 0.11], p < .001). Traumatic events remained associated with psychopathology after adjusting for covariates. Similar to the MCS, in the multivariate adjusted model, victimisation was the most strongly associated with internalising and externalising symptoms, followed by parental threat and traumatic events. After accounting for the other dimensions, deprivation had very small negative associations with internalising symptoms (β = –.05, 95% CI [–0.07, –0.03], p < .001) and externalising symptoms (β = –.02, 95% CI [–0.04, –0.004], p < .001). However, these associations were extremely small and not found in the complete case sample (**Appendix 6.1.7**, **Table *6.11*** & **Table 6.12**).

In preregistered sensitivity analyses, I also investigated whether sex interacted with adversity to influence psychopathology. I found small, statistically significant interactions between sex and specific adversity dimensions; specifically, girls in the MCS who experienced victimisation were at slightly higher risk for internalising symptoms than boys, while boys in the ABCD who experienced parental threat were at slightly higher risk for externalising symptoms than girls (MCS **Appendix 6.1.6**; ABCD **Appendix 6.1.8**). However, these results were not replicated across cohorts, and I did not find sex by adversity interactions for the majority of adversity dimensions and psychopathology outcomes.

Associations between adversity dimensions and psychopathology were broadly consistent across the complete and imputed samples, with detailed results available in the appendices (MCS **Appendix 6.1.5**, **Table 6.7** and **Table 6.8**; ABCD **Appendix 6.1.7**, **Table *6.11*** and **Table 6.12**). For both populations, I established that multicollinearity between ACE dimensions was very unlikely due to low variance inflation factors (<1.30), high tolerance values (>.80), and dimension intercorrelations (mean r = .17) (MCS **Table *6.9*** and **Table *6.10***; ABCD **Table 6.13** and **Table *6.14***).

2.5 Discussion

To my knowledge, this is the largest preregistered data-driven analysis of adversity dimensions using two contemporary longitudinal cohorts from the UK and US. I identified four dimensions of parental threat, deprivation, victimisation, and parental discipline in the MCS, and four dimensions of parental threat, deprivation, victimisation, and traumatic events in the ABCD. The parental threat and deprivation dimensions partially support my hypothesis that ACEs would cluster as threat and deprivation. Three of the four dimensions of adversity emerged consistently across both populations: parental threat, deprivation, and victimisation. The consistency of these dimensions is striking given the sociodemographic differences between the UK and US populations. This suggests that these dimensions are meaningful and not sample-specific, as they were identified despite the different instruments and informants used. In both populations, low household income and lack of neighbourhood safety loaded onto the deprivation dimension, peer victimisation clustered with other forms of interpersonal victimisation, and parental drug and alcohol use clustered with other parental threat-related ACEs. Of note, the dimensions of parental threat and deprivation converged with equivalent dimensions from recent ABCD studies which also applied EFA, demonstrating the advantage of exploratory data-driven methods (Brieant et al., 2023; Orendain et al., 2023).

Two dimensions of childhood adversity were unique to each cohort: parental discipline in the MCS, and traumatic events in the ABCD. In the MCS, the parental discipline dimension comprised of parental smacking and harsh parental discipline. Contrary to a recent MCS study that constructed the threat dimension *a priori* from interparental violence and parental discipline in a CFA (Ning et al., 2023), my data-driven EFA demonstrated that parental discipline emerged as a distinct dimension from parental threat. In the ABCD, the traumatic events dimension included ACEs such as physical, emotional, and sexual abuse but also bereavement and natural disasters. The traumatic events dimension in my study was identical to the trauma exposure dimension identified by a recent EFA of cross-sectional data from the ABCD (Brieant et al., 2023). It appears that the parental discipline and traumatic events dimensions did not replicate across populations because they each consisted of ACEs from measuring instruments specific to each cohort, i.e., the MCS parental discipline dimension from the Conflict Tactics Scale (Straus, 1979), and the ABCD traumatic events dimension from the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997). The convergence of these instrument-specific dimensions highlights how data-driven dimensions of adversity might be partly driven by shared method variance. For researchers analysing secondary datasets, dimensions of adversity are ultimately constrained by the measuring instruments used, which vary considerably across studies (e.g., differences in adversity type measured, informant, timing, and phrasing of questions to measure the same construct). These cumulative differences present a sizeable challenge in operationalising a universal model for adversity that transcends divergent measures across studies, and likely account for the discrepant dimensions identified across cohorts (e.g., parental discipline in MCS and traumatic events in ABCD) despite the three common dimensions.

I found that dimensions of adversity in the MCS and ABCD Study were associated with adolescent psychopathology in distinct ways. Parental threat was consistently associated with internalising and externalising symptoms across both cohorts, in line with previous DMAP-informed research (Awada et al., 2023; Miller et al., 2021; Sosnowski et al., 2023). However, there

was no association between deprivation and adolescent psychopathology in the MCS, and very small associations between deprivation and adolescent psychopathology in the ABCD. These findings support my hypothesis that the dimension of threat would be more strongly associated with psychopathology than deprivation. Similarly, recent ABCD studies which operationalised deprivation as a dimension of socioeconomic disadvantage or scarcity did not find associations with internalising and externalising symptoms (Brieant et al., 2023), or only with internalising symptoms (Orendain et al., 2023). Whilst it seems that deprivation does emerge as a meaningful dimension, its impact on adolescent psychopathology appears to be inconsistent in these samples, and this is likely due to the complexity of measuring deprivation as a multi-dimensional construct. Research has shown that the strength and consistency of the association between deprivation and psychopathology varies according to the dimension of deprivation used (Díaz et al., 2022; Lund et al., 2010). For example, there is evidence for individual deprivation (e.g., educational non-attendance) being more strongly associated with adolescent psychopathology than material deprivation (e.g., household overcrowding) (Díaz et al., 2022), as well as more consistent associations found between subjective social status and adolescent mental disorders compared to objective socioeconomic indicators (McLaughlin et al., 2012). As the deprivation dimensions I derived in the MCS and ABCD cohorts included a broad range of measures of deprivation, this might have contributed to the inconsistent associations with adolescent psychopathology. Thus, future research could clarify which dimensions of deprivation influence adolescent psychopathology within the context of co-occurring ACEs.

Notably, I found stable associations between victimisation and internalising and externalising symptoms, which displayed the strongest effect sizes over and above the other ACE dimensions for both populations. In the MCS, associations were particularly strong and might have been inflated by shared method variance, as victimisation ACEs and adolescent psychopathology were self-reported. However, shared method variance cannot completely explain the associations in the ABCD as adolescent psychopathology was parent-reported. Moreover, the

ABCD victimisation dimension consisted of only peer and cyber victimisation, yet victimisation persisted in being more strongly associated with adolescent psychopathology compared to the traumatic events dimension, which consisted of maltreatment-related ACEs such as physical, emotional, and sexual abuse. My findings align with quasi-experimental meta-analytic evidence suggesting a causal relationship between bullying victimisation and mental health problems (Schoeler et al., 2018), and suggest that when operationalising ACEs as dimensions, future research should investigate whether victimisation ACEs impact adolescent psychopathology via different mechanisms than other dimensions (e.g., threat and deprivation). For example, the interpersonal nature of victimisation, particularly when the perpetrator is a peer, might impair adolescent mental health in a targeted way unlike other less relational ACEs. Thus, I strongly recommend the inclusion of peer victimisation as an ACE in future studies, as many recent studies which derived adversity dimensions did not include peer victimisation as a measure of childhood adversity (e.g., Awada et al., 2023; Brieant et al., 2023; Lambert et al., 2017; Machlin et al., 2019; Miller et al., 2021; Ning et al., 2023; Orendain et al., 2023; Sosnowski et al., 2023).

Regarding the unique dimensions within each cohort, parental discipline and traumatic events demonstrated small consistent associations with adolescent psychopathology. In the MCS, parental discipline showed larger associations with externalising symptoms compared to internalising symptoms, supporting previous longitudinal evidence for the reciprocal relationship between parents' use of harsh discipline and children's externalising behaviour (Lansford et al., 2011). In the ABCD, traumatic events showed stable associations with both internalising and externalising symptoms. As this relationship has so far been demonstrated by cross-sectional evidence from the ABCD (Brieant et al., 2023; Orendain et al., 2023), the longitudinal findings from my study extend the literature by reducing the possibility of reverse causality.

The findings of this study should be interpreted in the context of several limitations. First, most of the ACE measures were parent-reported, which might lead to underreporting due to social

desirability bias. Second, although I attempted to derive equivalent ACEs across both populations, these were still limited by the available measures which tended to vary in severity across cohorts. I minimised these differences by applying conservative cut-offs and clarifying if the ACE measure was relative or absolute. Third, both longitudinal cohorts are affected by selective attrition with less affluent families and more marginalised groups being more likely to drop out of both cohorts (Connelly & Platt, 2014; Feldstein Ewing et al., 2022). However, I imputed missing data with a random forest algorithm trained on sociodemographic variables associated with missingness to mitigate this selection bias. Fourth, I note that the dimension labels are broad categorisations. It is important to acknowledge the duality in the nature of some adversities (e.g., parent psychopathology could be labelled as threat or deprivation, as indicated by cross-loadings between factors), and this highlights a broader limitation of DMAP: there is no clear delineation of either threat or deprivation experiences due to the duality and frequent co-occurrence of ACEs (Lian et al., 2022). Lastly, this study cannot infer that different dimensions of ACEs caused internalising and externalising symptoms in adolescence as there might have been unmeasured confounding (e.g., from genetic influences; Baldwin, Sallis, et al., 2023).

Nevertheless, my findings advance the literature with implications for how we should best operationalise ACEs. First, I provide an open science resource of ACE measures in the MCS and ABCD, many of which have not been derived before. My code can be replicated by future researchers and will hopefully contribute to facilitating the reproducibility of ACE-related research in both the MCS and ABCD datasets. My findings provide empirical support for the utility of the dimensional approach of operationalising ACEs, which may have advantages over the cumulative risk approach by showcasing how different dimensions of ACEs were differentially associated with adolescent psychopathology. I demonstrated that applying a data-driven exploratory factor analysis without *a priori* categorisations successfully captured common underlying dimensions of parental threat, deprivation, and victimisation across two distinct populations. These dimensions are meaningful as they converged despite the sociodemographic and measurement differences

between the UK MCS and US ABCD Study. Whilst these dimensions of parental threat and deprivation provide partial support for DMAP, my findings also suggest that existing conceptual frameworks of ACEs should be expanded to include victimisation as a distinct dimension, as victimisation demonstrated the strongest associations with adolescent psychopathology over and above the other dimensions. This offers potential avenues for future research regarding mechanisms, as ACEs within the victimisation dimension might impact adolescent psychopathology via different pathways than threat and deprivation. Given that the dimensions of ACEs were differentially associated with adolescent psychopathology, it is important to identify the specific adversities which may be driving these associations. In the next chapter, I shift the focus from operationalising ACEs to inferring their potentially causal effects. Specifically, I apply propensity score matching to examine how individual ACEs influence adolescent mental health outcomes, providing robust estimates of their unique contributions within a quasi-experimental framework.

3 Propensity score matched estimates of adversity

3.1 Abstract

Background: Adverse childhood experiences (ACEs) are consistently associated with increased risks for psychopathology, but the extent to which these associations are confounded by individual, family, and sociodemographic vulnerabilities remains unclear.

Methods: Using prospective longitudinal data from 18,539 children in the Millennium Cohort Study, I applied propensity score matching to examine whether ten individual ACEs (experienced between ages 5 and 17) remained associated with depression and anxiety symptoms, psychological distress, self-harm, and suicide attempt at age 17, after adjusting for a comprehensive set of pre-exposure confounders measured during the prenatal period, infancy, and early childhood.

Results: In unadjusted analyses, adolescents exposed to ACEs showed substantially elevated risks for psychopathology, with effect sizes ranging from β = .08–.68 for depression and anxiety, and ORs = 1.46–15.77 for high distress, self-harm, and suicide attempt. After matching and adjustment, associations for significant ACEs were attenuated by approximately 30–80% (adjusted effect sizes ranging from β = .08–.34 and ORs = 1.18–5.02). Emotional victimisation showed the strongest associations with psychopathology (β = .34; ORs up to 5.02), followed by sexual victimisation (β = .27; ORs up to 2.34), emotional neglect (β = .18; ORs up to 2.36), parental mental health problems (β = .17; ORs up to 1.55), peer victimisation (β = .10; ORs up to 2.61), and physical victimisation (β = .08; ORs up to 1.45). In contrast, divorce, bereavement, domestic violence, and parent substance use were no longer associated with psychopathology after adjustment, suggesting their associations were largely explained by pre-existing confounding.

Conclusions: Victimisation and emotional forms of adversity remained robustly associated with psychopathology after comprehensively accounting for contextual confounding, supporting their likely causal impact on adolescent mental health. The associations between most ACEs and psychopathology outcomes were attenuated but remained significant after adjustment, indicating partial confounding. However, associations for certain ACEs (e.g., divorce, parent substance use) were non-significant after adjustment, suggesting they were explained by pre-existing vulnerabilities. My findings highlight the importance of considering ACEs with the most robust associations in prevention and policy efforts, while also addressing the broader contextual risks that may underlie more confounded adversities.

3.2 Introduction

Despite the substantial body of research that has established associations between adverse childhood experiences (ACEs) and psychopathology, the extent to which these associations are confounded by pre-existing vulnerabilities remains unclear. ACEs are not randomly distributed across the global population (Madigan et al., 2023), and children exposed to ACEs often differ systematically from those with low or no exposure across a range of sociodemographic, familial, and individual risk factors for mental health problems. Thus, isolating the potentially causal effects of ACEs on psychopathology in real-world observational studies poses a challenge, as pre-existing confounding may inflate the observed associations between ACE exposure and psychopathology.

ACE-exposed children are more likely to have experienced concurrent adversities such as poverty, bullying victimisation, and the clustering of other co-occurring ACEs (Baldwin et al., 2016; Chow et al., 2025; Lacey et al., 2022; Lewer et al., 2020). Pre-existing vulnerabilities associated with childhood adversity can occur as early as the prenatal period, ranging from risk factors such as prenatal substance exposure (Austin et al., 2022), low birthweight (Sidebotham et al., 2006), and limited breastfeeding duration (Strathearn et al., 2009). It is also vital to acknowledge the broader, structural drivers that shape children's exposure to adversity. Globally, socioeconomic deprivation (e.g., low household income) consistently predicts an elevated risk of ACEs (Madigan et al., 2023; Walsh et al., 2019), and is independently associated with child and adolescent mental health problems (Reiss, 2013). Outside of the household, neighbourhood and community factors also play a significant role. Numerous studies have shown that rates of child maltreatment, domestic violence, and family substance abuse are disproportionately concentrated in disadvantaged neighbourhoods (Benson et al., 2003; Boardman et al., 2001; Walsh et al., 2019). Neighbourhood disparities typically reflect broader structural conditions such as systemic poverty, racial segregation, and housing instability, which may collectively generate chronic stress (i.e., allostatic load) and constrain families' capacity to provide safe, nurturing environments (McEwen & McEwen, 2017; Warner et al., 2023). These structural drivers not only co-occur with but also shape

household-level ACEs by amplifying parental stress, limiting access to resources, and undermining community social cohesion (Warner et al., 2023). Consequently, researchers have emphasised the importance of situating individual and family-level ACEs within neighbourhood and community contexts, recognising that many ACEs are often embedded in, and shaped by, structural disadvantage (Schroeder et al., 2022; Warner et al., 2023). Accordingly, contextual risk factors for childhood adversity can be holistically conceptualised within the socioecological systems model (Bronfenbrenner, 2000), which frames child development as a dynamic interaction between the individual and a series of nested systems, whereby individual characteristics (e.g., ADHD, autism), interpersonal relations (e.g., parent-child relationship), and broader community conditions (e.g., neighbourhood deprivation) collectively contribute towards the likelihood of ACE exposure (Austin et al., 2020; Hartley et al., 2024; Lugo-Candelas et al., 2021; Morris et al., 2019).

However, the majority of previous research on childhood adversity has predominantly relied on classical epidemiological methods (e.g., multiple regression), which have limited capacity to account for pre-existing confounding (Baldwin, Wang, et al., 2023; Martens et al., 2008). Thus, previous studies employing classical epidemiological approaches may have overestimated the effects of childhood adversity on psychopathology. To better understand the true causal impact of ACEs on psychopathology, it is crucial that researchers strengthen causal inference beyond classical epidemiological approaches. While causal inference methods cannot fully eliminate residual confounding nor establish definitive causality, they enable the derivation of more causally informative estimates. Causal inference methods enhance estimates of the causal relationship by approximating the counterfactual scenario (i.e., where the same individual is both exposed and unexposed to the adverse experience), thereby inferring – but not establishing – causality under reasonable assumptions (Pingault et al., 2018). Indeed, a recent systematic review by Baldwin, Wang, et al. (2023) revealed that the association between childhood maltreatment and mental health problems was approximately 45% smaller after quasi-experimental adjustment for

confounding, supporting the notion that a substantial proportion of the observed psychopathology risk is confounded by pre-existing and co-occurring risk factors.

Within the counterfactual framework of causal inference, propensity score matching provides a quasi-experimental strategy to strengthen causal inference about the effects of childhood adversity on psychopathology. This is achieved by comparing outcomes between exposed and unexposed individuals with similar estimated probabilities of experiencing ACEs, thereby balancing observed confounders (Baldwin, Wang, et al., 2023; Muniz et al., 2019; Thornberry et al., 2010). The propensity score represents the probability of treatment assignment (e.g., exposure to ACEs) conditional on observed baseline characteristics (e.g., individual, family, and sociodemographic confounders), serving as a balancing score between exposed and unexposed groups (Austin, 2011).

Propensity score matching has several key advantages over conventional regression techniques. First, it effectively balances numerous confounders to create groups that are conditionally exchangeable, approximating a randomised controlled trial design where all pre-exposure characteristics are independent of exposure assignment, thereby strengthening causal inference (Kainz et al., 2017). Second, it separates the design phase from the outcome analysis by estimating propensity scores without reference to the outcome, reducing the risk of outcome-driven model specification (Austin, 2011). Third, propensity score matching enables researchers to explicitly assess if the matching process has successfully balanced covariates across exposed and unexposed groups, providing more transparent diagnostics than conventional regression approaches, which tend to rely on overall model fit (Austin, 2011; Kainz et al., 2017). Fourth, in comparison to conventional multivariate regression adjustment, the pseudo-randomisation of propensity score matching has been shown to be superior in reducing measured confounding (Martens et al., 2008).

Propensity score matching is particularly well-suited for studying childhood adversity in observational settings, where random assignment to adverse experiences is both unethical and infeasible. By matching ACE-exposed children with demographically similar, non-exposed peers, this method provides a feasible approach to strengthen causal inference about the effects of ACEs on psychopathology risk. For instance, Thornberry et al. (2010) demonstrated that maltreated youth were significantly more likely to experience depressive symptoms, suicidal thoughts, substance use problems, and criminal behaviours in young adulthood compared to non-maltreated youth who were matched on pre-existing sociodemographic and familial risk factors for maltreatment. Similarly, Muniz et al. (2019) applied propensity score matching to a sample of delinquent youth and found that emotional abuse emerged as the strongest predictor of externalising problems, followed by physical abuse, household violence, household substance use, emotional neglect, and parental incarceration. In contrast, sexual abuse more strongly predicted the risk of internalising problems over externalising problems, suggesting a specific pathway of psychological trauma for sexually abused victims. Bentivegna & Patalay (2022) extended this work using the Millennium Cohort Study, showing that adolescents who experienced sexual violence had higher risks of psychological distress, self-harm, and attempted suicide than their non-exposed, propensity score matched counterparts. Strikingly, this study's population attributable fractions also estimated that eliminating sexual violence could reduce the prevalence of mental health problems by 3.7-10.5% in boys and 14.0-18.7% in girls, potentially narrowing the gender gap in adolescent mental health. Together, these findings highlight the public health burden of specific ACEs and demonstrate the potential of propensity score matching in deriving meaningful, policy-relevant estimates.

Evidently, applying propensity score matching to the study of childhood adversity enables researchers to draw more credible causal inferences about the impact of ACEs on psychopathology using real-world observational data. However, despite increasing interest in quasi-experimental methods, few studies have applied propensity score matching to study the

impact of ACEs on psychopathology outcomes (Baldwin, Wang, et al., 2023). Amongst this small but growing body of evidence, most studies have either focused on a single type of adversity (Bentivegna & Patalay, 2022) or a broad measure of maltreatment (Gerin et al., 2019; Thornberry et al., 2010), or relied on high-risk, cross-sectional samples that limit temporal and population generalisability (Díaz-Faes et al., 2024; Muniz et al., 2019).

The present study advances existing knowledge by applying propensity score matching to strengthen causal inference about the effects of individual ACEs on psychopathology within a large, nationally representative longitudinal cohort, the UK Millennium Cohort Study (MCS). Specifically, I investigated whether individuals who were exposed to ten distinct ACEs might be at higher risk of depression and anxiety symptoms, psychological distress, self-harm, and suicide attempt during late adolescence, compared to matched counterparts without a history of these ACEs. This design not only strengthens causal inference about the effects of ACEs on psychopathology, but also isolates the potentially distinct impacts of individual ACEs by using the specificity approach. This can help to provide granular insights into which ACEs are most likely to yield meaningful change if directly targeted, thereby informing the development of tailored, evidence-based policy and intervention. I hypothesised that children exposed to ACEs would be at higher risk of developing psychopathology in adolescence compared to matched counterparts without a history of ACEs, after statistically controlling for measured pre-exposure confounding (e.g., prenatal, infancy, and early childhood risk factors).

3.3 Methods

Participants

I analysed data from the first seven sweeps of the UK Millennium Cohort Study (MCS), corresponding to when participants were aged 9 months, 3, 5, 7, 11, 14, and 17 years old. Details of the MCS data collection and ethics procedures are reported in the previous chapter **Methods**

2.3. This study analysed data from 18,539 children (48.6% females) after imputation (complete sample reported in **Table *6.15***; missing data imputation procedure described below).

Measures

Details of how I derived measures for the propensity score analysis are reported in **Table *3.1*** and **Appendix 6.2.1**. Unlike my dimensional analysis in **Chapter 2** which included a broader range of ACEs, I chose to focus on fewer 'core' ACEs in the present analysis as I wanted to focus on the available measures in the MCS which mapped onto the original 10 ACEs. As most of the literature has replicated the original ACEs from the CDC-Kaiser ACE Study, focusing on similar ACEs would facilitate a critical evaluation of whether previous research has overestimated - or underestimated - the causal effects of ACEs on psychopathology.

ACE exposures. I derived ten composite ACE measures across the ages 5 to 17 years: parent mental health problems, parent substance use, parent divorce, bereavement, domestic violence, emotional neglect, physical victimisation, emotional victimisation, sexual victimisation, and peer victimisation. ACEs were binarized as present if they surpassed a clinical or statistical cut-off, then aggregated across time points. As the MCS does not have a specific ACE questionnaire, all ACE measures were derived from the available raw items (see **Table *3.1*** for details on how I derived each ACE measure). The MCS does not provide available measures for two of the original ACEs: physical neglect and parental criminal behaviour, so I chose to include bereavement and peer victimisation instead. Parental bereavement is included in the ACE International Questionnaire by the World Health Organisation (World Health Organisation, 2020). Although peer victimisation was not in the original ACE scale, I included peer victimisation as the victimisation dimension showed the largest effect sizes in my dimensional analysis (**Table 2.4**, **Table 2.5**, **Table 6.7**, **Table 6.8**), demonstrating its significant impact on adolescent psychopathology in comparison to other ACEs.

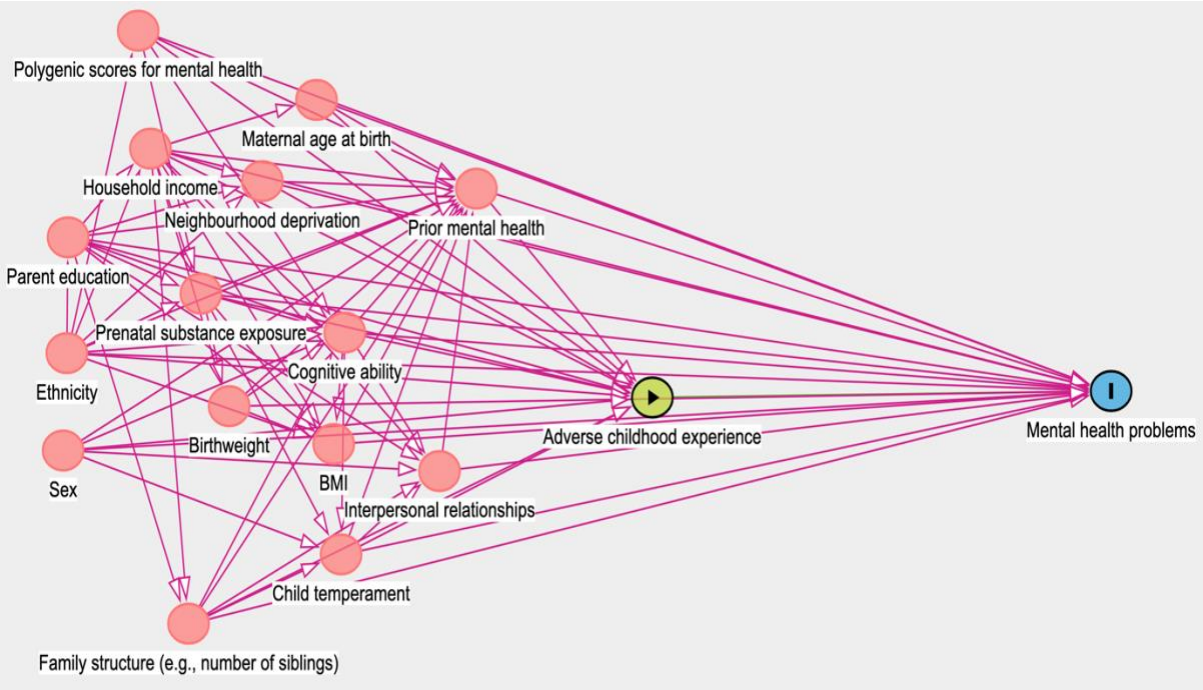
Psychopathology outcomes. I assessed four psychopathology outcomes at age 17: depression and anxiety symptoms, high psychological distress, self-harm, and suicide attempt. Depression and anxiety symptoms were measured using child self-reports from the Kessler Psychological Distress (K6) Scale, a well validated six-item screening scale with high population validity (Kessler et al., 2002). For each participant, I derived a continuous score of depression and anxiety by summing and standardising their total K6 score. I also derived a binary score of high psychological distress, which I coded as present if participants met the clinical cut-off (K6 score ≥ 13). I derived binary scores of self-harm and suicide attempt using the available measures from the MCS Young Person Self-Completion Questionnaire. For self-harm, participants reported if they had ever self-harmed (e.g., 'cut or stabbed yourself', 'taken an overdose of tablets'). For suicide attempt, participants self-reported whether they had ever attempted suicide ('Have you ever hurt yourself on purpose in an attempt to end your life?'). Details on how I derived these psychopathology outcomes are also reported in **Table *3.1***.

Matching variables. I derived 36 matching variables (i.e., covariates) across the prenatal (e.g., gestation time, pregnancy illness), birth (e.g., labour/birth complications, birthweight), postnatal (e.g., breastfeeding), and infancy (e.g., infant temperament) periods, as well as early childhood up to age 5 (e.g., household income, parent-child relationship, child emotion dysregulation). I chose these matching variables through a systematic search of the MCS data dictionary, while being guided by my epidemiological training and causal assumptions informed by prior literature and the socioecological systems framework (Austin et al., 2020), along with the recommendation that measured baseline covariates which affect both treatment assignment and outcome (i.e., true confounders) should be included in the propensity score model (Austin, 2011; Kainz et al., 2017). This resulted in a comprehensive range of phenotypic matching variables which were likely to be confounders of ACEs and adolescent psychopathology. The detailed rationale of how I derived these phenotypic matching variables, justified by previous literature, is provided in **Appendix 6.2.1**.

Directed Acyclic Graph (DAG)

As the first step in planning the propensity score analysis, I drew a DAG (**Figure 3.1**) of the potential causal pathways between the matching variables (e.g., pre-exposure confounders), ACE exposures, and adolescent psychopathology outcomes. It also depicts potential causal pathways between the matching variables (e.g., parent education → household income → neighbourhood deprivation). The lime green node in the centre represents the ACE (e.g., emotional neglect). The blue node on the far right, mental health problems, represents the psychopathology outcome in adolescence (e.g., self-harm). The pink nodes on the left represent a variety of biological, environmental, familial, and sociodemographic factors that are assumed to influence both exposure to the ACE and the outcome of mental health problems. Thus, the pink nodes are considered confounders (i.e., a common cause of both exposure and outcome, as explained in **Figure *1.1***) which need to be statistically adjusted for. For example, low household income could be a confounder of the relationship between emotional neglect and self-harm in adolescence, represented in the DAG as follows (ACE ← household income → mental health problems). By matching participants on the propensity score, this blocks all backdoor paths from ACEs to mental health problems and ensures that the only open path remaining is the direct causal path (ACE → mental health problems). Polygenic scores were examined in the next chapter.

Figure 3.1 DAG for planning the propensity score analysis.



Preregistration

This study was preregistered on the Open Science Framework (https://osf.io/hb82q). As the CLS delayed the release of MCS polygenic scores until mid-2025 (instead of the fourth quarter of 2024 as originally planned), I initially proceeded with the analysis for the phenotypic data only, the findings of which are discussed in the present chapter. I later derived my own polygenic scores for depression, anxiety, and suicide attempt in **Chapter 4** (described in the next chapter **Methods 4.3**). I chose to separate the phenotypic and genetically adjusted analyses to allow a more in-depth analysis of the role of genetic confounding.

Table 3.1 Exposure and outcome measures for the PSM analysis in the MCS.

Measure	Informant	Assessment type	Exposure period	Assessment phase	Criteria for coding measure as present
ACE measures					
Parent mental health problems	Parent	Kessler (K6) Scale	5, 7, 11, 14, and 17 years	Sweeps 3-7	The Kessler (K6) scale was used to measure parental mental health in the last 30 days (e.g., "so depressed nothing could cheer you up", "nervous"). Within each sweep, scores were summed and then dichotomised (clinical cut-off score ≥ 13). If parents reported poor mental health for at least 1 out of 5 sweeps, poor parental mental health was coded as present.
Parent substance use	Parent	Parent interview (alcohol and drug use)	5, 7, 11, and 14 years	Sweeps 3-6	Parents reported the frequency of their alcohol use which was dichotomised (every day/5-6 times per week = 1 vs 3-4 times per week/1-2 times per week/less than once a month/never = 0). Parents also reported if they had anyone concerned about their drinking habits (yes = 1 vs no = 0), not been able to stop drinking, or failed to do as expected because of drinking (monthly/weekly/daily = 1 vs less than monthly/never = 0). For drug use, the frequency was also dichotomised (regularly/occasionally = 1 vs never = 0). If parents reported alcohol or drug use for at least 1 out of 4 sweeps, parent substance use was coded as present.
Parent divorce	Parent	Parent interview (marital status)	5, 7, 11, 14, and 17 years	Sweeps 3-7	Parents reported if they had ever been divorced or separated, which was dichotomised (divorced/legally separated/civil partnership legally dissolved = 1 vs married/remarried/civil partnership/single = 0). If parents reported being divorced/separated for at least 1 out of 5 sweeps, parent divorce was coded as present.
Bereavement	Parent	Family questionnaire	5, 7, 11, and 14 years	Sweeps 3-6	If either the natural mother or natural father of the cohort member had died between the ages of 5 and 14, bereavement was coded as present.
Domestic violence	Parent	Golombok Rust Inventory of Marital State	5, 7, 11, and 14 years	Sweeps 3-6	Parents reported whether their partner had ever used force in their relationship, which was dichotomised (yes = 1 vs no = 0). If parents reported experiencing this for at least 1 out of 4 sweeps, domestic violence was coded as present.
Emotional neglect	Parent & child	Parenting questionnaire	5, 7, 11, 14, and 17 years	Sweeps 3-7	Parents reported how close they were to their child (not very close = 1 vs fairly close/very close/extremely close = 0), how often they enjoyed doing things with their child and how often they expressed affection (never/rarely = 1 vs sometimes/often/always = 0), and the frequency that parents talked to their child about things important to them (not at all/less than once a month = 1 vs monthly/weekly/every day = 0). Children also self-reported how close they were to their parents and the frequency they talked to their parents about important things. If either parent or child reported emotional neglect for at least 1 out of 5 sweeps, emotional neglect was coded as present.

Measure	Informant	Assessment type	Exposure period	Assessment phase	Criteria for coding measure as present
Physical victimisation	Child	Victimisation questionnaire	14 and 17 years	Sweeps 6-7	Children self-reported whether anyone had ever been physically violent (e.g., "pushed, shoved, hit, slapped or punched you"), or used a weapon against them in the past 12 months. Scores were dichotomised (yes = 1 vs no = 0). If children reported experiencing this for at least 1 out of 2 sweeps, physical victimisation was coded as present.
Emotional victimisation	Child	Victimisation questionnaire	14 and 17 years	Sweeps 6-7	Children self-reported whether they had ever been insulted, threatened, or shouted at by anyone in the past 12 months. Scores were dichotomised (yes = 1 vs no = 0). If children reported experiencing this for at least 1 out of 2 sweeps, emotional victimisation was coded as present.
Sexual victimisation	Child	Victimisation questionnaire	14 and 17 years	Sweeps 6-7	Children self-reported whether anyone had ever sexually assaulted them in the past 12 months. Scores were dichotomised (yes = 1 vs no = 0). If children reported experiencing this for at least 1 out of 2 sweeps, sexual victimisation was coded as present.
Peer victimisation	Parent, teacher, child	Strengths and Difficulties Questionnaire (SDQ)	5, 7, 11, 14, and 17 years	Sweeps 3-7	At ages 7, 11, 14, and 17, children self-reported on peer victimisation (e.g., "how often do other children hurt you or pick on you on purpose?"). The victimisation items from the SDQ were used for parent reports at ages 5, 7, 11, 14, and 17, and teacher reports at ages 7 and 11 (e.g., "child picked on or bullied by other children"). Scores were dichotomised (most days/about once a week = 1 vs once a month/every few months/less often/never = 0). If children were reported by at least one informant to have experienced peer victimisation for at least 1 out of 5 sweeps, peer victimisation was coded as present.
Psychopathology outcomes					
Depression / anxiety, high psychological distress	Child	Kessler (K6) Scale	17 years	Sweep 7	At age 17, cohort members self-reported their depression and anxiety symptoms in the last 30 days (e.g., "so depressed nothing could cheer you up", "nervous"). Scores were summed as a continuous score, then standardised. If participants met the clinical cut-off (K6 score ≥ 13), high psychological distress was coded as present.
Self-harm	Child	Young Person Self-Completion Questionnaire	17 years	Sweep 7	At age 17, cohort members self-reported if they had ever self-harmed (e.g., "cut or stabbed yourself", "taken an overdose of tablets"). Scores were dichotomised (yes = 1 vs no = 0). If cohort members reported self-harming in at least one way, self-harm was coded as present.
Suicide attempt	Child	Young Person Self-Completion Questionnaire	17 years	Sweep 7	At age 17, cohort members self-reported whether they had ever attempted suicide ("Have you ever hurt yourself on purpose in an attempt to end your life?"). Scores were dichotomised (yes = 1 vs no = 0).

Statistical Analysis

All analyses for this study were conducted using R (version 4.4.1) and the code will be made publicly available on GitHub upon publication.

Propensity score matching. I conducted propensity score matching (PSM) using the 'MatchIt' package (Ho et al., 2011). PSM aims to address the causal inference assumption of exchangeability by ensuring that the ACE-exposed and unexposed groups are balanced (i.e., conditionally exchangeable) with respect to the observed confounders (Austin, 2011; Hernán & Robins, 2024). Conditional exchangeability means that, given the observed confounders, the psychopathology outcomes of individuals in the ACE-exposed and unexposed groups would be the same if they had received the same exposure status (or 'treatment'). Since random assignment of ACE exposure is not possible in observational studies, PSM achieves conditional exchangeability by matching individuals with similar likelihoods of being exposed to an ACE.

I estimated propensity scores using a probit regression, modelling the probability of each ACE exposure (e.g., parent mental health problems) as a function of the observed covariates, i.e., the matching variables (**Appendix 6.2.1**). The resulting propensity scores were used for matching 'treated' and 'control' individuals. I then applied full matching to group participants into subclasses based on their likelihood of ACE exposure. Each subclass contains either one exposed (treated) individual matched to one or more unexposed (control) individuals, or one control individual matched to one or more treated individuals (Ho et al., 2011). This allows for one-to-many or many-to-one matches, maximising sample retention while minimising covariate imbalance. Full matching minimises differences between matched participants by balancing them on key confounding variables (e.g., sociodemographic and early-life risk factors), reducing bias while retaining as much data as possible (unlike nearest neighbour matching, which may discard unmatched units).

This matching process mimics randomisation, conditional on the observed confounders, thereby strengthening the causal inference of ACEs on adolescent psychopathology. The resulting matched dataset included weights based on subclass membership, which were used to estimate a weighted treatment effect in the subsequent regression analyses. I assessed pre- and post-matching covariate balance by examining the standardised mean differences (SMD) between exposed and unexposed groups. The SMD compares the difference in means in units of pooled standard deviation, thus allowing for the comparison of balance between variables measured in different units; generally, SMD < 0.1 is interpreted as good covariate balance having been achieved (Austin, 2011; Greifer, 2025). Assessing covariate balance in this way provides transparent verification on whether observed confounding has been sufficiently eliminated, unlike conventional regression methods where it is more difficult to assess the degree of overlap in the distribution of baseline covariates between the exposed and unexposed groups (Austin, 2011).

Amongst the matching variables (**Appendix 6.2.1)**, I also included pre-exposure ACEs (measured at age 3) as potential confounders that could influence both later ACE exposure (ages 5-17) and adolescent psychopathology (at age 17). The MCS had available pre-exposure measures for six of the ten core ACEs: parent mental health problems, parent substance use, parent divorce, bereavement, domestic violence, and peer victimisation. To assess the risk of overadjustment, I examined the correlations between each pre-exposure ACE and its later counterpart. Correlations were mostly moderate (e.g., divorce: $r = .41$; parent mental health: $r = .40$; domestic violence: $r = .34$; bereavement: $r = .32$, substance use: $r = .31$), except for peer victimisation: $r = .02$. Given the potential for overadjustment (particularly where correlations were moderate), I selectively excluded each ACE's own pre-exposure counterpart from its corresponding propensity score model, while retaining the other pre-exposure ACEs (**Table *3.2***). For the four ACEs without pre-exposure data, I adjusted for the full set of matching variables (i.e., all the pre-exposure ACEs).

Table 3.2 Strategy for including or excluding pre-exposure ACEs to avoid overadjustment.

Propensity score model	Matching variables included other pre-exposure ACEs (age 3)	Excluded pre-exposure ACE (age 3)
Parent mental health problems (ages 5-17)	Parent substance use, parent divorce, bereavement, domestic violence, peer victimisation	Parent mental health problems
Parent substance use (ages 5-17)	Parent mental health problems, parent divorce, bereavement, domestic violence, peer victimisation	Parent substance use
Parent divorce (ages 5-17)	Parent mental health problems, parent substance use, bereavement, domestic violence, peer victimisation	Parent divorce
Bereavement (ages 5-17)	Parent mental health problems, parent substance use, parent divorce, domestic violence peer victimisation	Bereavement
Domestic violence (ages 5-17)	Parent mental health problems, parent substance use, parent divorce, bereavement, peer victimisation	Domestic violence
Peer victimisation (ages 5-17)	Parent mental health problems, parent substance use, parent divorce, bereavement, domestic violence	Peer victimisation

Propensity score matched estimates of ACEs on psychopathology. To derive the PSM estimates between each of the 10 ACEs and the four psychopathology outcomes, I fit weighted regression models on the matched sample. For the continuous outcome (depression and anxiety symptoms), I ran linear regressions and reported standardised regression coefficients (β). For the binary outcomes (high psychological distress, self-harm, and suicide attempt), I fit logistic regression models and exponentiated the coefficients to obtain odds ratios (OR).

For each ACE, the remaining nine ACEs were included as covariates in the outcome regression models to account for co-occurring adversities across the exposure period (ages 5-17). They were not incorporated into the propensity scores because they occurred concurrently with the focal ACE, and thus were not grouped with the other pre-exposure confounders used for matching. In this way, propensity score matching addressed confounding from pre-exposure vulnerabilities, while the adjusted regression models accounted for co-occurring adversities.

For all outcome models in this chapter, multiple comparisons were corrected for using the False Discovery Rate (FDR) (Benjamini & Hochberg, 1995). I ran the models with increasing levels of adjustment in the following order: unadjusted models on the unmatched sample, adjusted models on the unmatched sample, unadjusted models on the matched sample, and adjusted models on the matched sample (**Table *3.3***). I calculated the percentage in attenuation for the effect sizes of the unadjusted unmatched model versus the adjusted matched model to examine how PSM influenced the associations between ACEs and psychopathology.

Table 3.3 Levels of increasing adjustment in PSM regression models.

Level	Regression Model	Purpose
1	Unadjusted and unmatched, Outcome ~ ACE.	Estimates the raw association between ACE and outcome (baseline model).
2	Adjusted and unmatched, Outcome ~ ACE + other 9 ACEs.	Adjusts for all other ACEs to control for childhood adversity overlap.
3	Unadjusted and matched, Outcome ~ ACE (with PSM weights).	Uses PSM to reduce confounding by balancing groups, but no further covariates.
4	Adjusted and matched, Outcome ~ ACE + other 9 ACEs (with PSM weights).	Fully adjusted model on a balanced sample (most rigorous).

Missing data imputation. I imputed missing data using a random forest algorithm with the 'missForest' package (Stekhoven & Buehlmann, 2012). Following the transform-then-impute approach (Von Hippel, 2009), I first created the derived variables (e.g., ACE exposures, psychopathology outcomes, and matching variables) before performing imputation to ensure that relationships between variables in the regression model were preserved. These derived variables were then included in the imputation model along with the raw items comprising the exposures, outcomes, and matching variables. The random forest algorithm was trained on both the derived and raw variables to enhance the accuracy of imputed values. I then replicated the analyses to check that results were consistent across both the complete and imputed samples.

3.4 Results

The prevalences of ACEs (across ages 5 to 17) and adolescent psychopathology (at age 17) in the MCS are reported in **Table *3.4*.** Sociodemographic characteristics at baseline were reported in **Table *2.3***, with information on missingness available in the appendix (**Table *6.15***). Across the exposure period of 5 to 17 years, the most prevalent ACE was emotional victimisation (37.27%), whereas the least prevalent ACE was bereavement (1.46%). The second most prevalent ACE was peer victimisation, with 31.01% of MCS children having experienced being bullied by peers.

Table 3.4 Prevalences of ACEs and adolescent psychopathology in the MCS (N = 18,539).

Millennium Cohort Study (MCS)			
ACEs (5 to 17 years)	**Complete n**	**n exposed**	**% exposed**
Parent mental health problems	15,133	1,747	9.42
Parent substance use	15,424	4,146	22.36
Parent divorce	15,472	3,293	17.76
Bereavement	15,741	271	1.46
Domestic violence	12,882	905	4.88
Emotional neglect	15,567	3,226	17.40
Physical victimisation	11,703	3,363	18.14
Emotional victimisation	11,703	6,910	37.27
Sexual victimisation	11,701	1,426	7.69
Peer victimisation	15,631	5,749	31.01
Psychopathology (17 years)	**Complete n**	**M(SD)/n**	**Range/%**
Depression and anxiety symptoms	9,637	7.26 (4.92)	0 – 24
High psychological distress	9,637	1,552	8.37
Self-harm	9,386	2,183	11.78
Suicide attempt	9,381	698	3.77

Regarding psychopathology, adolescents displayed moderate levels of depression and anxiety on average (M = 7.26, SD = 4.92). 8.37% of adolescents met the clinical cut-off for high psychological distress (Kessler K6 score ≥ 13). Generally, a score between 5 and 12 on the K6 is considered moderate psychological distress, while ≥ 13 is defined as the cut-off point for severe

psychological distress (Kessler et al., 2002). By age 17, 11.78% of adolescents had self-harmed in at least one way, and 3.77% of adolescents had hurt themselves in an attempted suicide.

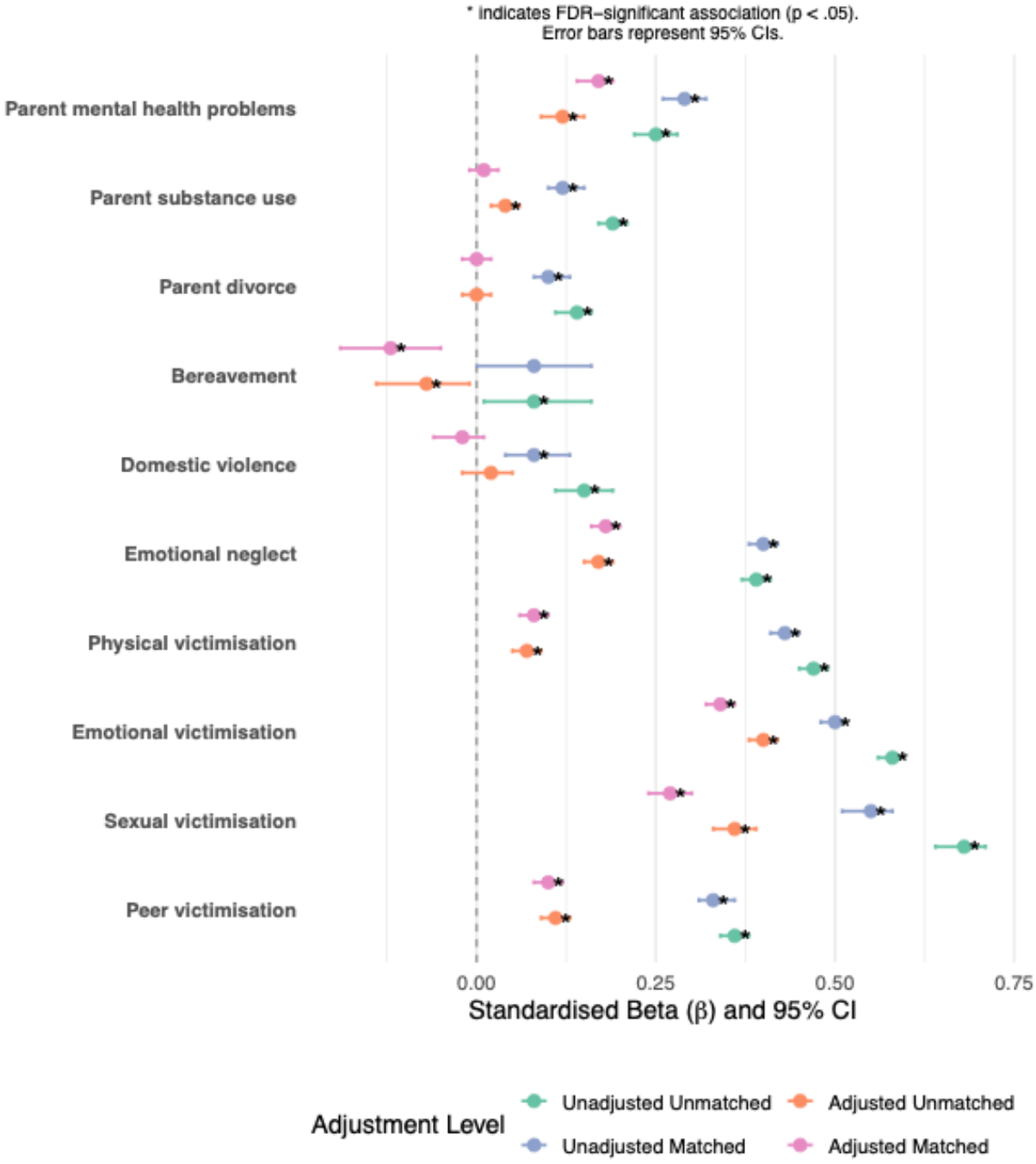
In **Appendix 6.2.2,** I presented pre- and post-matching covariate balance for each ACE using love plots, all of which demonstrated good balance according to the recommended threshold of SMD < 0.1 (Austin, 2011; Greifer, 2025).

In the following sections, I first present an overview of the results by outcome: depression and anxiety symptoms, high psychological distress, self-harm, and suicide attempt. These results are displayed in **Figure 3.2–Figure 3.*5***, which summarise the propensity score matched (PSM) estimates for each outcome. Then, leveraging the specificity approach of this analysis, I discuss the results organised by each individual ACE, providing more granular insights into the distinct contribution of each adversity across outcomes.

PSM Estimates of ACEs on Depression and Anxiety Symptoms

The propensity score matched estimates of ACEs on depression and anxiety symptoms are presented in **Figure 3.2**, with detailed results available in the appendix (**Table *6.16***). Results were broadly consistent with the complete case sample (**Table *6.20***). My findings revealed that emotional victimisation, sexual victimisation, and emotional neglect displayed the strongest associations with depression and anxiety symptoms at age 17 across all models. Other ACEs, such as parent mental health problems, physical victimisation, and peer victimisation were also strong predictors but showed attenuated estimates after matching and adjustment. In contrast, ACEs such as parent substance use, parent divorce, and domestic violence were no longer significantly associated with depression and anxiety symptoms after matching and adjustment.

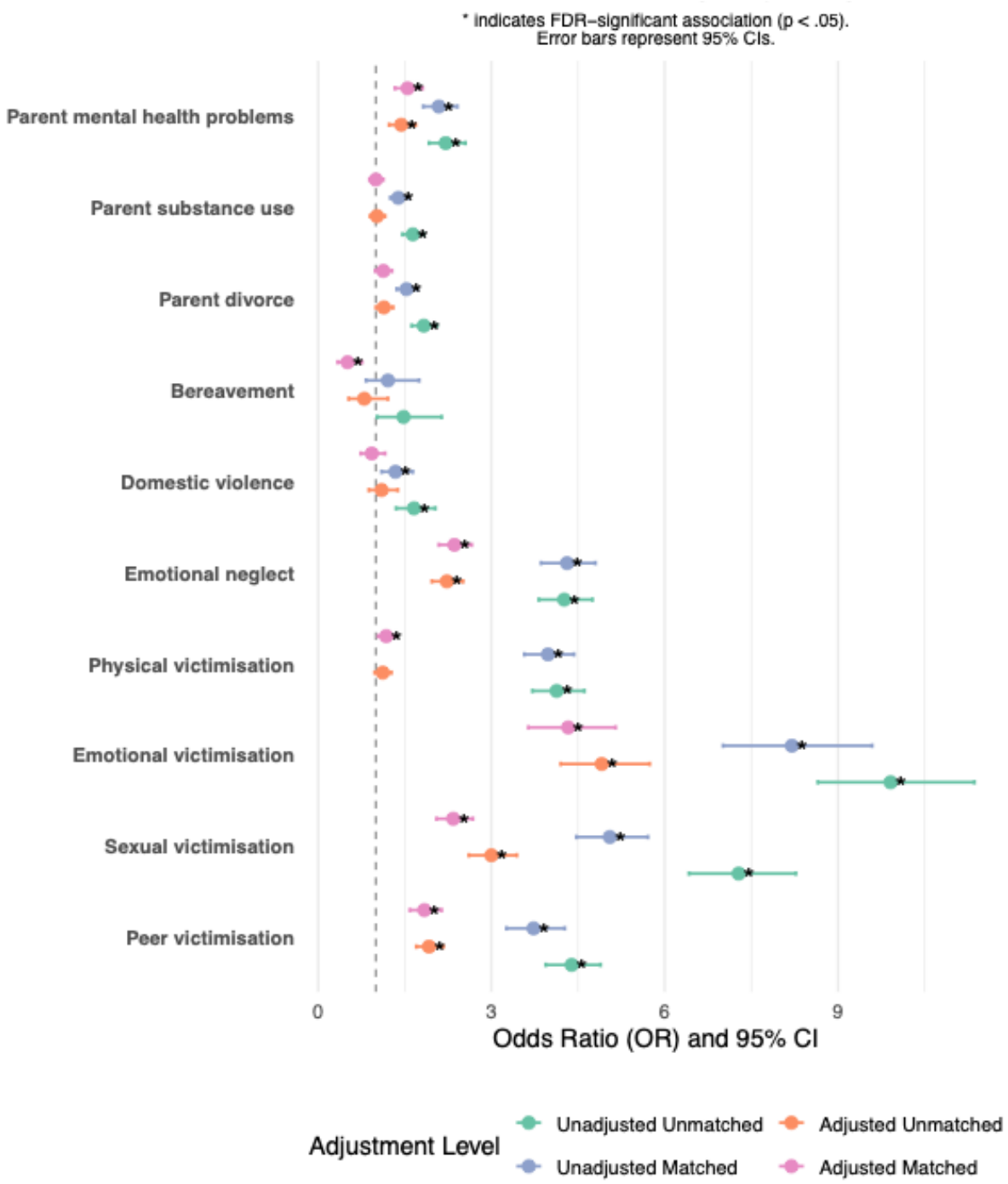
Figure 3.2 PSM estimates of ACEs on depression and anxiety symptoms.



PSM Estimates of ACEs on High Psychological Distress

The propensity score matched estimates of ACEs on high psychological distress are presented in **Figure 3.3**, with detailed results available in the appendix (**Table *6.17***). Results were broadly consistent with the complete case sample (**Table *6.21***). In line with my results regarding depression and anxiety symptoms, I found that emotional victimisation, sexual victimisation, and emotional neglect displayed the strongest associations with high psychological distress at age 17, even after adjusting for co-occurring ACEs and measured confounding through PSM. Parent mental health problems, physical victimisation, and peer victimisation were also significant predictors of high distress which showed attenuated estimates after matching and adjustment. Parent substance use, parent divorce, bereavement, and domestic violence displayed non-significant associations after matching and adjustment.

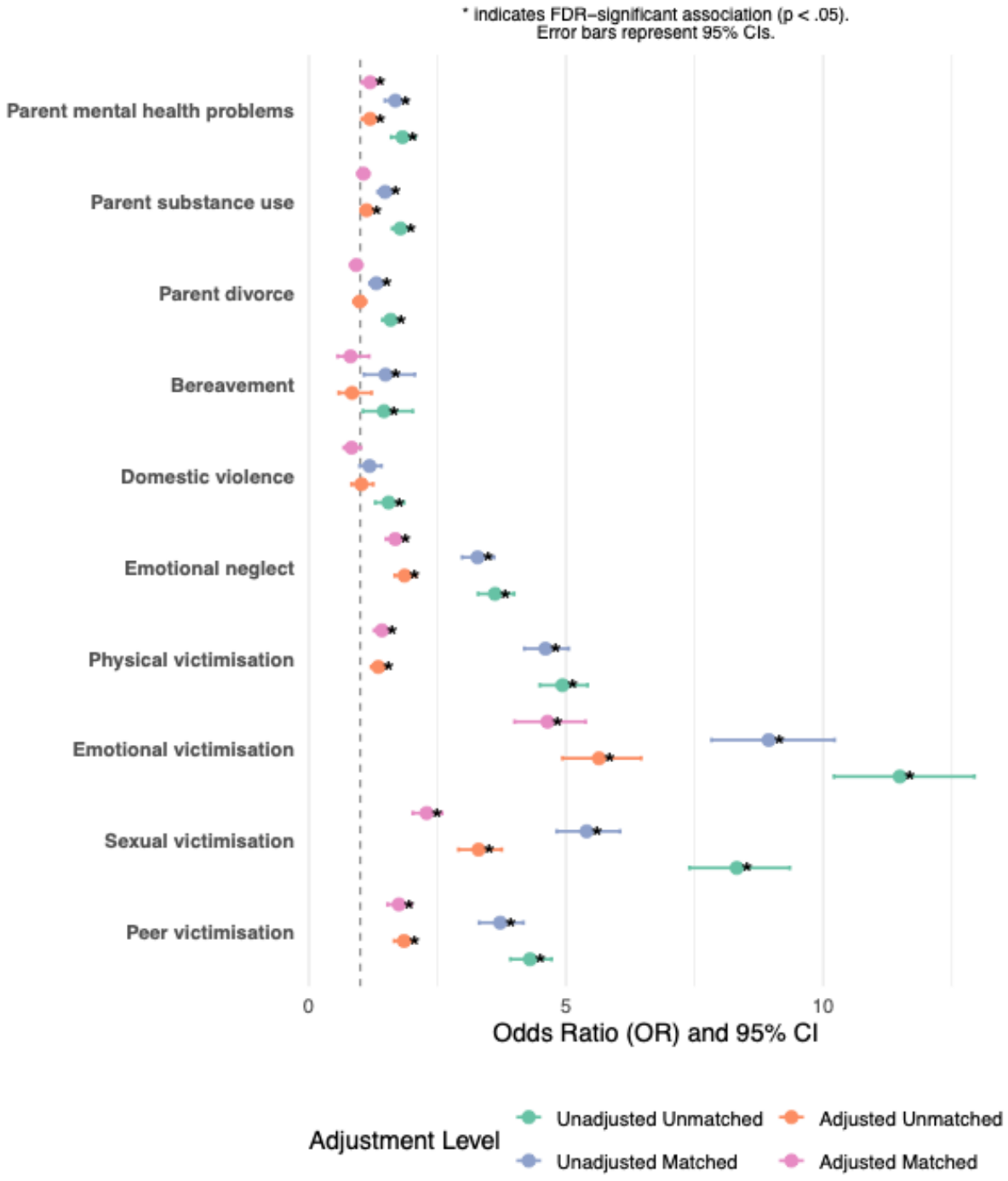
Figure 3.3 PSM estimates of ACEs on high psychological distress.



PSM Estimates of ACEs on Self-Harm

The propensity score matched estimates of ACEs on self-harm are presented in **Figure 3.4**, with detailed results available in the appendix (**Table *6.18***). Results were broadly consistent with the complete case sample (**Table *6.22***). Emotional victimisation and sexual victimisation displayed the strongest associations with self-harm at age 17, after conducting PSM and adjusting for co-occurring ACEs. Emotional neglect, physical victimisation, and peer victimisation were also significant predictors of self-harm, though their associations were attenuated after matching and adjustment. Parent mental health problems consistently predicted self-harm in all models. Parent substance use, parent divorce, bereavement, and domestic violence showed non-significant associations after matching and adjustment.

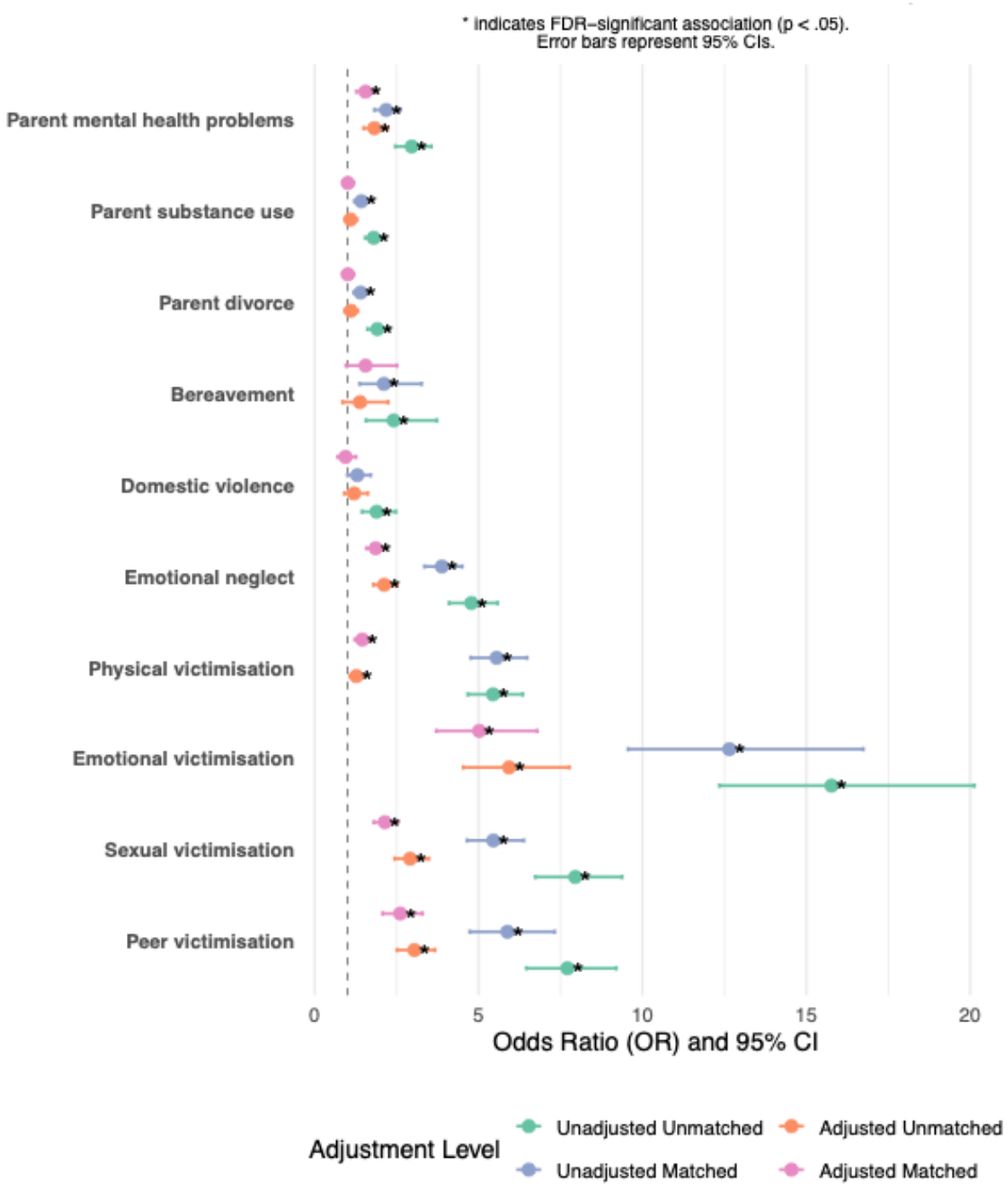
Figure 3.4 PSM estimates of ACEs on self-harm.



PSM Estimates of ACEs on Suicide Attempt

The propensity score matched estimates of ACEs on suicide attempt are presented in **Figure 3.5**, with detailed results available in the appendix (**Table *6.19***). Results were broadly consistent with the complete case sample (**Table *6.23***). My findings revealed that emotional victimisation, peer victimisation, and sexual victimisation displayed the strongest associations with suicide attempt at age 17, after adjusting for co-occurring ACEs and measured confounding through propensity score matching. Physical victimisation, emotional neglect, and parent mental health problems were also significant predictors of suicide attempt, although their associations were attenuated after matching and adjustment. The remaining ACEs, parent substance use, parent divorce, bereavement, and domestic violence showed non-significant associations after matching and adjustment.

Figure 3.5 PSM estimates of ACEs on suicide attempt.



ACE-Specific Results Across Psychopathology Outcomes

Having presented a summary of the PSM estimates by outcome, I now turn to a detailed examination of the differential impacts of each individual ACE across the psychopathology outcomes. In this section, I present results from the imputed sample PSM models (full tables in **Appendix 6.2.3**), and complete sample PSM results are also available in **Appendix 6.2.4**.

Parent mental health problems were consistently associated with elevated risk across all psychopathology outcomes. In the unadjusted unmatched models, adolescents exposed to parental mental health problems reported higher depression and anxiety symptoms (β = .25, 95% CI [0.22, 0.28], $p < .001$), and had increased odds of high psychological distress (OR = 2.21, 95% CI [1.92, 2.55], $p < .001$), self-harm (OR = 1.82, 95% CI [1.60, 2.07], $p < .001$), and suicide attempt (OR = 2.96, 95% CI [2.46, 3.56], $p < .001$). After adjustment and matching on confounders, estimates were attenuated but remained robust: associations with depression and anxiety (β = .17, 95% CI [0.14, 0.19], $p < .001$), high distress (OR = 1.55, 95% CI [1.33, 1.81], $p < .001$), and self-harm (OR = 1.19, 95% CI [1.03, 1.38], $p = .026$) were reduced by approximately 30–35%, while the association with suicide attempt (OR = 1.55, 95% CI [1.27, 1.89], $p < .001$) was attenuated by around 48% but remained significant.

Parent substance use was initially significantly associated with all outcomes in the unadjusted unmatched models: depression and anxiety (β = .19, 95% CI [0.17, 0.21], $p < .001$), high psychological distress (OR = 1.64, 95% CI [1.46, 1.83], $p < .001$), self-harm (OR = 1.78, 95% CI [1.62, 1.96], $p < .001$), and suicide attempt (OR = 1.80, 95% CI [1.54, 2.12], $p < .001$). However, after matching and adjustment, these associations were fully attenuated to non-significance for depression and anxiety (β = .01, 95% CI [-0.01, 0.03], $p = .192$), high distress (OR = 1.00, 95% CI [0.89, 1.13], $p = .977$), self-harm (OR = 1.06, 95% CI [0.95, 1.17], $p = .350$), and suicide attempt (OR = 1.01, 95% CI [0.85, 1.19], $p = .954$).

Parent divorce was also initially associated with higher risk across outcomes in the unadjusted unmatched models, including depression and anxiety (β = .14, 95% CI [0.11, 0.16], p < .001), high distress (OR = 1.83, 95% CI [1.62, 2.06], p < .001), self-harm (OR = 1.59, 95% CI [1.43, 1.77], p < .001), and suicide attempt (OR = 1.91, 95% CI [1.61, 2.26], p < .001). However, after matching and adjustment, none of these associations remained significant for depression and anxiety (β = 0.00, 95% CI [-0.02, 0.02], p = .803), high distress (OR = 1.13, 95% CI [0.99, 1.28], p = .085), self-harm (OR = 0.92, 95% CI [0.81, 1.03], p = .171), and suicide attempt (OR = 1.01, 95% CI [0.84, 1.20], p = .954).

Bereavement displayed mixed results, but its associations with psychopathology were mostly attenuated after matching and adjustment. While unadjusted unmatched models suggested small positive associations with depression and anxiety (β = .08, 95% CI [0.01, 0.16], p = .035), high distress (OR = 1.48, 95% CI [1.02, 2.14], p = .051), self-harm (OR = 1.46, 95% CI [1.05, 2.02], p = .030), and suicide attempt (OR = 2.41, 95% CI [1.56, 3.73], p < .001), these associations were attenuated or reversed after adjustment. In the adjusted matched models, bereavement was linked to lower depression and anxiety symptoms (β = –.12, 95% CI [-0.19, -0.05], p < .001) and reduced odds of high distress (OR = 0.51, 95% CI [0.34, 0.76], p = .002), while associations with self-harm (OR = 0.81, 95% CI [0.56, 1.17], p = .291) and suicide attempt (OR = 1.55, 95% CI [0.95, 2.51], p = .093) were non-significant.

Domestic violence was initially significantly associated with all outcomes in the unadjusted unmatched models: depression and anxiety (β = .15, 95% CI [0.11, 0.19], p < .001), high distress (OR = 1.66, 95% CI [1.35, 2.03], p < .001), self-harm (OR = 1.55, 95% CI [1.29, 1.85], p < .001), and suicide attempt (OR = 1.89, 95% CI [1.44, 2.48], p < .001). However, these were fully attenuated in the adjusted matched models, showing null associations across depression and anxiety (β = –.02, 95% CI [-0.06, 0.01], p = .254), high distress (OR = 0.93, 95% CI [0.74,

1.16], p = .540), self-harm (OR = 0.83, 95% CI [0.68, 1.01], p = .072), and suicide attempt (OR = 0.94, 95% CI [0.70, 1.26], p = .695).

Emotional neglect showed robust associations across all psychopathology outcomes. In unadjusted unmatched models, it was strongly linked to depression and anxiety (β = .39, 95% CI [0.37, 0.41], p < .001), high distress (OR = 4.26, 95% CI [3.82, 4.75], p < .001), self-harm (OR = 3.62, 95% CI [3.29, 3.99], p < .001), and suicide attempt (OR = 4.78, 95% CI [4.10, 5.58], p < .001). Although attenuated by approximately 45–60% after matching and adjustment, associations remained robust for depression and anxiety (β = .18, 95% CI [0.16, 0.20], p < .001), along with a twofold increase in odds of high distress (OR = 2.36, 95% CI [2.09, 2.66], p < .001), and over 1.5 times the odds of self-harm (OR = 1.68, 95% CI [1.50, 1.87], p < .001) and suicide attempt (OR = 1.86, 95% CI [1.58, 2.18], p < .001).

Physical victimisation was strongly associated with all outcomes in the unadjusted unmatched models, including depression and anxiety (β = .47, 95% CI [0.45, 0.49], p < .001), high distress (OR = 4.13, 95% CI [3.71, 4.61], p < .001), self-harm (OR = 4.93, 95% CI [4.49, 5.42], p < .001), and suicide attempt (OR = 5.44, 95% CI [4.67, 6.35], p < .001). After matching and adjustment, associations were substantially attenuated by approximately 70–80% but remained consistently significant for depression and anxiety (β = .08, 95% CI [0.06, 0.10], p < .001), high distress (OR = 1.18, 95% CI [1.04, 1.34], p = .014), self-harm (OR = 1.42, 95% CI [1.27, 1.58], p < .001), and suicide attempt (OR = 1.45, 95% CI [1.22, 1.73], p < .001).

Emotional victimisation emerged as the strongest predictor of psychopathology across all outcomes. Unadjusted unmatched associations were very large for depression and anxiety (β = .58, 95% CI [0.56, 0.59], p < .001), high distress (OR = 9.91, 95% CI [8.65, 11.36], p < .001), self-harm (OR = 11.49, 95% CI [10.21, 12.94], p < .001), and suicide attempt (OR = 15.77, 95% CI [12.35, 20.13], p < .001). Although attenuated by approximately 40–68% in the adjusted matched models, associations remained substantial for depression and anxiety (β = .34, 95% CI

[0.32, 0.36], $p < .001$), along with a four- to fivefold increase in odds of high distress (OR = 4.33, 95% CI [3.64, 5.15], $p < .001$), self-harm (OR = 4.64, 95% CI [4.00, 5.38], $p < .001$), and suicide attempt (OR = 5.02, 95% CI [3.71, 6.79], $p < .001$).

Sexual victimisation was also among the strongest predictors of psychopathology. In the unadjusted unmatched models, it was strongly associated with depression and anxiety (β = .68, 95% CI [0.64, 0.71], $p < .001$), high distress (OR = 7.28, 95% CI [6.42, 8.27], $p < .001$), self-harm (OR = 8.32, 95% CI [7.40, 9.35], $p < .001$), and suicide attempt (OR = 7.95, 95% CI [6.73, 9.38], $p < .001$). After matching and adjustment, estimates were attenuated by approximately 60–73% but remained significant for depression and anxiety (β = .27, 95% CI [0.24, 0.30], $p < .001$), along with a twofold increase in odds of high distress (OR = 2.34, 95% CI [2.05, 2.68], $p < .001$), self-harm (OR = 2.29, 95% CI [2.02, 2.59], $p < .001$), and suicide attempt (OR = 2.14, 95% CI [1.80, 2.54], $p < .001$).

Peer victimisation was robustly associated with all psychopathology outcomes. Unadjusted unmatched models showed strong associations with depression and anxiety (β = .36, 95% CI [0.34, 0.38], $p < .001$), high psychological distress (OR = 4.39, 95% CI [3.94, 4.89], $p < .001$), self-harm (OR = 4.30, 95% CI [3.92, 4.72], $p < .001$), and suicide attempt (OR = 7.71, 95% CI [6.46, 9.20], $p < .001$). These associations remained significant though attenuated by approximately 60–70% in the adjusted matched models: depression and anxiety (β = .10, 95% CI [0.08, 0.12], $p < .001$), high distress (OR = 1.84, 95% CI [1.59, 2.14], $p < .001$), self-harm (OR = 1.75, 95% CI [1.53, 1.99], $p < .001$), and suicide attempt (OR = 2.61, 95% CI [2.07, 3.29], $p < .001$).

Across the ten ACEs, the unadjusted unmatched models indicated substantial associations with adolescent psychopathology, with odds ratios frequently exceeding two- to tenfold increases for high distress, self-harm, and suicide attempt, along with corresponding increases in depression and anxiety symptoms. After matching and adjustment for measured confounders, all effect sizes were attenuated. Emotional and sexual victimisation, emotional neglect, peer victimisation, and

physical victimisation continued to display robust associations across all outcomes after matching and adjustment. However, parental substance use, divorce, bereavement, and domestic violence were no longer significant, suggesting that their associations were largely explained by pre-existing confounding.

3.5 Discussion

This study used propensity score matching to strengthen causal inference on the associations between ACEs and adolescent psychopathology within a large, nationally representative cohort of over 18,000 British children from the Millennium Cohort Study (MCS). Consistent with my hypothesis, adolescents who were exposed to ACEs between the ages of 5 and 17 exhibited significantly higher depression and anxiety symptoms, and higher odds of psychological distress, self-harm, and suicide attempt at age 17 compared to their matched counterparts without a history of childhood adversity. These findings remained robust after accounting for the co-occurrence of other ACEs and a comprehensive range of individual, familial and sociodemographic confounders, with consistent patterns observed across the complete and imputed samples. My findings align with emerging causal inference literature, reinforcing evidence that childhood adversity likely exerts a causal impact on the development of mental health problems, although part of these associations is due to confounding by pre-existing vulnerabilities (Baldwin, Wang, et al., 2023; Schoeler et al., 2018; Singham et al., 2017).

By applying the specificity approach to isolate the distinct impacts of individual ACEs, my findings provide compelling evidence that certain ACEs pose a greater risk for psychopathology than others. Specifically, I found that emotional victimisation, sexual victimisation, and emotional neglect emerged as the strongest predictors of psychopathology outcomes across all models, followed by peer victimisation, parent mental health problems, and physical victimisation. These ACEs maintained robust effect sizes after accounting for measured confounding in the propensity score matched models, suggesting they have a likely causal impact on adolescent mental health. In

contrast, divorce, bereavement, domestic violence, and parent substance use did not retain significant associations with the same psychopathology outcomes after matching and adjustment, suggesting that their initial associations were attributable to pre-existing confounding. Furthermore, the attenuation of associations for all ACEs in the adjusted matched models compared to the unadjusted unmatched models aligns with previous quasi-experimental evidence, suggesting that the observed associations between ACEs and psychopathology are likely to be partially confounded by pre-existing and co-occurring vulnerabilities (Baldwin, Wang, et al., 2023).

Emotional victimisation displayed the largest effect sizes across all psychopathology outcomes. In the adjusted matched models, adolescents exposed to emotional victimisation displayed significantly elevated risks for depression and anxiety symptoms, a fourfold increase in odds of psychological distress as well as self-harm, and a fivefold increase in odds of suicide attempt. My findings support previous quasi-experimental evidence (Baldwin, Wang, et al., 2023), as well as cross-sectional, non-quasi-experimental research that similarly identified emotional abuse as the strongest predictor of depression and anxiety symptoms, surpassing other forms of abuse and neglect (Cecil et al., 2017; Gama et al., 2021; Merrick et al., 2017). Emotional maltreatment (e.g., victimisation or abuse) may exert a particularly damaging impact on adolescent mental health due to its targeted, pervasive nature. Unlike other ACEs that involve more episodic or situational adversity, emotional maltreatment often involves chronic exposure to rejection, humiliation, or invalidation, which can fundamentally alter the victim's internal working model and attachment style, contributing to maladaptive cognitive appraisals and emotional dysregulation (Gama et al., 2021; Riggs, 2019). Consequently, these cognitive and emotional disruptions may heighten an individual's vulnerability to developing internalising and externalising psychopathology (Cecil et al., 2017; Kim & Cicchetti, 2010; Muniz et al., 2019).

Sexual victimisation was revealed as the next strongest predictor of psychopathology after adjusting for co-occurring ACEs and measured confounding via propensity score matching, with

increased risks for depression and anxiety symptoms and approximately doubled odds of psychological distress, self-harm, and suicide attempt. My findings are consistent with non-quasi-experimental prospective studies showing that sexually abused children displayed persistently higher internalising problems than their maltreated but non-sexually abused peers (Lewis et al., 2016), and propensity score matching studies reporting significantly elevated risks of internalising problems among sexually abused children compared to their non-sexually abused matched counterparts (Bentivegna & Patalay, 2022; Muniz et al., 2019; Thornberry et al., 2010). My study extends previous work by Bentivegna & Patalay (2022), who also employed propensity score matching within the MCS to examine the impact of sexual violence on adolescent psychopathology. Despite methodological differences (e.g., gender stratified analyses, matching variables used, and the calculation of risk ratios rather than odds ratios), their findings similarly indicated increased risks of psychological distress, self-harm, and suicide attempt in adolescents exposed to sexual violence. The consistency of findings across both studies, after applying independent statistical analyses on the same dataset, underscores the potentially causal impact of sexual victimisation on adolescent mental health. Additionally, my inclusion of more extensive matching variables spanning a broader developmental period may have further mitigated residual measured confounding, yielding more robust estimates of the ACE-psychopathology relationship.

Emotional neglect emerged as a particularly salient predictor of all psychopathology outcomes in the adjusted matched models, with adolescents who experienced emotional neglect exhibiting heightened risks for depression and anxiety symptoms, twice the odds of psychological distress, and over 1.6 times the odds of self-harm and suicide attempt. My findings support prior quasi-experimental evidence (Baldwin, Wang, et al., 2023) and non-quasi-experimental research linking childhood emotional neglect to psychopathology in adolescence (Glickman et al., 2021; Negriff, 2020). Importantly, my findings suggest that the absence of a nurturing, supportive parent-child relationship may be as detrimental to mental health as more overt forms of childhood adversity – a finding that warrants emphasis given the underrepresentation of emotional neglect

in the ACE literature (Kumari, 2020). Prior ACE studies have often aggregated emotional neglect within broad maltreatment composites (Sayyah et al., 2022; Thornberry et al., 2010; Westermair et al., 2018) or cumulative risk scores (Baldwin et al., 2021; Hughes et al., 2017), limiting insight into the distinct impact of emotional neglect. The specificity approach in my study highlights the distinct, potentially causal impact of emotional neglect on adolescent psychopathology, which calls for further exploration. Emerging research suggests that emotional neglect may increase the risk of depressive symptoms in adolescence through an underlying mechanism of impaired emotional clarity, perhaps more so than emotional abuse (Jessar et al., 2017). Future research should elucidate the mechanisms through which emotional neglect may shape pathways to depression, anxiety, self-harm, and suicidal ideation.

Consistent with prior research, parent mental health problems, physical victimisation, and peer victimisation were significant predictors of depression and anxiety symptoms, psychological distress, self-harm, and suicide attempt in the adjusted matched models. My findings align with prior quasi-experimental evidence (Baldwin, Wang, et al., 2023; Muniz et al., 2019; Schoeler et al., 2018; Singham et al., 2017; Thornberry et al., 2010) and non-quasi-experimental studies applying the specificity approach (Finkelhor et al., 2015; Merrick et al., 2017; Negriff, 2020), which have collectively demonstrated the heightened psychopathology risk associated with exposure to parental mental illness, physical abuse, and bullying victimisation.

Interestingly, I found that divorce, bereavement, domestic violence, and parent substance use were no longer significantly associated with psychopathology outcomes in the adjusted matched models. This attenuation suggests that the observed associations in unmatched analyses may have been largely confounded by other co-occurring risk factors. The lack of significant associations for divorce and bereavement may also reflect adolescents demonstrating resilience to these more 'normative' adversities, particularly if protective factors like social support, post-divorce parenting interventions, or family grief therapy are present to buffer the impact on mental

health (Cox et al., 2021; Hoppe et al., 2025). The non-significant associations for domestic violence and parent substance use warrant further examination, given mixed findings in the literature. While some quasi-experimental and observational studies have linked domestic violence and parent substance use to elevated psychopathology when the ACEs were examined individually (Farooq et al., 2024; Muniz et al., 2019), other research suggests these associations may diminish after accounting for co-occurring maltreatment. For example, Negriff (2020) found that household dysfunction (including divorce, domestic violence, and parent substance use) no longer predicted adolescent mental health outcomes after controlling for co-occurring experiences of abuse and neglect. This aligns with my findings and suggests that the mental health risks commonly attributed to household dysfunction may in part be driven by overlapping forms of adversity, particularly maltreatment. It is also possible that the comprehensive set of matching variables used in my study effectively captured many of the underlying risk factors that co-occur with domestic violence and parent substance use. Adjusting for these co-occurring risk factors through propensity score matching may have attenuated the observed associations, rendering them non-significant.

Alternatively, low construct validity may have contributed to the attenuation. Domestic violence was measured with a single parent-reported item of whether their partner had ever used force, potentially constraining its interpretation to physical violence while overlooking more nuanced manifestations of domestic violence (e.g., coercive control or emotional abuse) which can significantly undermine children's mental health (Katz, 2016). Moreover, child reports of witnessing domestic violence were not available. Similarly, parent substance use was primarily assessed through frequency of alcohol and drug use rather than explicit measures of substance abuse, although I attempted to refine this measure by incorporating parent reports of problematic drinking behaviours (e.g., inability to stop drinking). Thus, limited construct validity may have attenuated the associations for domestic violence and parent substance use, highlighting the need for more comprehensive, validated measures in future quasi-experimental research.

My findings should therefore be interpreted in the context of several limitations. First, while I endeavoured to derive ACE measures consistent with the original ACE scale, the MCS lacks explicit indicators for certain ACEs (e.g., parent substance abuse). This limitation reflects a broader methodological challenge underlying secondary data analysis, wherein researchers are ultimately constrained by available measures. Nevertheless, I constructed proxy measures where necessary, which may have been advantageous for more nuanced forms of adversity. For example, due to its subtle and subjective nature, emotional neglect is a relatively challenging construct to measure (Kumari, 2020). By integrating parent and child reports and coding emotional neglect as present only when the most negative response was reported (e.g., parent never expresses affection), my composite measure appeared to effectively capture the psychological impact of this ACE. Notably, emotional neglect emerged as one of the strongest predictors across all psychopathology outcomes, suggesting that nuanced measures may more accurately detect certain forms of adversity.

Second, this study did not account for the developmental timing of ACE exposure, which limits interpretation of the varying aetiologic periods linking adversity to psychopathology. While ACEs in this study were captured as binary indicators reflecting whether they occurred at least once between ages 5 and 17, emerging evidence suggests that the impact of childhood adversity may vary depending on the developmental period in which it occurs. For example, in a prospective study of MCS children, Farooq et al. (2024) found that ACE exposure in early childhood and adolescence, rather than middle childhood, was particularly predictive of co-occurring depression and self-harm. Similarly, Thornberry et al. (2010) used propensity score matching to demonstrate that maltreatment during adolescence had a more pervasive impact on a broader range of psychopathology outcomes (e.g., suicidal thoughts, substance use, criminal behaviours) compared to childhood-limited maltreatment. Thus, some of the patterns observed in the present study may reflect variation in the developmental salience of specific ACEs during the period captured by the measurement window, which only approximates the actual timing of exposure. The particularly strong associations observed for emotional, sexual, and physical victimisation may be attributable

to these interpersonal adversities exerting developmentally salient effects during the preadolescent and adolescent period captured in this study's measurement window. In contrast, the null associations for divorce, bereavement, domestic violence, and parent substance use may partially reflect a discrepancy between when these household-level adversities were measured and the sensitive periods during which they most strongly influence mental health. For example, parental divorce or bereavement may have more pronounced impacts in early childhood, whereas this study may have captured children who had already passed through the most sensitive period. Future quasi-experimental research should therefore incorporate more frequent, repeated measures of adversity across childhood and adolescence to identify sensitive periods for intervention, and clarify whether specific ACEs exert timing- and age-dependent effects on adolescent mental health.

Third, while the specificity approach demonstrated the differential impacts of individual ACEs, it did not account for the potential interactive effects of co-occurring ACEs. Future studies should consider how certain combinations of ACEs (e.g., sexual abuse) may exert synergistic effects and amplify the risk for psychopathology beyond the impact of individual ACEs (Briggs et al., 2021). Nevertheless, as I demonstrated in this chapter, a strength of the specificity approach is that it facilitates a more precise identification of the particular ACEs which confer higher psychopathology risk.

Fourth, while propensity score matching strengthens causal inference by balancing measured confounders, it cannot account for unmeasured confounding (Baldwin, Wang, et al., 2023). Thus, caution is warranted in interpreting these findings as causal effects. Future studies could benefit from integrating complementary approaches, such as genetically informative methods, to address the extent to which residual genetic confounding influences the associations between ACEs and psychopathology (Baldwin, Sallis, et al., 2023). Due to the MCS delays in releasing polygenic scores, I proceeded with using only phenotypic data for this study. In **Chapter**

4, I address this limitation by deriving my own polygenic scores to account for measured genetic confounding.

My findings have implications for future research and interventions. ACEs with the most robust associations (e.g., emotional victimisation, sexual victimisation, emotional neglect) are likely to represent more modifiable and impactful intervention targets, warranting greater emphasis in prevention and policy efforts. Conversely, ACEs whose associations were largely attenuated after accounting for pre-existing confounding (e.g., parent substance use, divorce, bereavement) may reflect adverse experiences that are less amenable to direct modification, or whose effects are intertwined with broader familial or contextual vulnerabilities. As ACEs frequently co-occur with multiple other risk factors, some ACEs may be more confounded than others and thus be more challenging to isolate in interventions. This is not to suggest that such ACEs are negligible, as all ACEs are clinically important and traumatic in their own right. Rather, for ACEs with attenuated associations, interventions may be more effective in alleviating psychopathology risk if they focus on addressing the associated contextual risk factors (e.g., socioeconomic deprivation).

In summary, this study provides robust evidence that specific ACEs, particularly emotional victimisation, sexual victimisation, and emotional neglect, are among the most potent predictors of adolescent psychopathology outcomes, after accounting for measured confounding within a robust quasi-experimental framework. My findings underscore the need for strategic interventions that directly target ACEs with the most robust associations with psychopathology (e.g., emotional victimisation), as well as buffering or resilience-enhancing approaches for other ACEs that are still vital to intervene on (e.g., domestic violence). Addressing unmeasured confounding – in particular, genetic confounding from heritable vulnerabilities – remains an ongoing challenge, and future research should continue to strengthen causal inference by applying genetically sensitive quasi-experimental approaches. In the next chapter, I explore this avenue by applying a novel method of genetically adjusted propensity scores (GAPS).

4 Genetically adjusted propensity scores of adversity

4.1 Abstract

Background: While associations between ACEs and psychopathology are well established, the extent to which they are shaped by genetic confounding remains unclear. This study aimed to strengthen causal inference about the associations between ACEs and mental health, by accounting for genetic and phenotypic vulnerabilities within a novel genetically adjusted propensity score (GAPS) matching framework.

Methods: Using genome-wide single nucleotide polymorphism (SNP) data and longitudinal phenotypic data from 9,182 children in the Millennium Cohort Study, I examined gene-environment correlations (rGE) between ACEs and polygenic scores (PGS) for psychopathology, cognition, and health. I then applied GAPS matching to strengthen causal inference about the effects of specific ACEs on adolescent psychopathology, independent of measured genetic and environmental confounding.

Results: Consistent with rGE, elevated PGSs for depression, anxiety, and suicide attempt were associated with greater ACE exposure, whereas higher PGSs for educational attainment and intelligence were associated with lower ACE exposure. GAPS analyses revealed that victimisation and emotional adversities (e.g., sexual victimisation, emotional neglect) were robustly associated with psychopathology over and above measured genetic and environmental confounding, with effect sizes ranging from βs = .14–.32 for depression and anxiety symptoms, and ORs = 1.44–5.71 for high distress, self-harm, and suicide attempt. In contrast, household-level ACEs (e.g., parent mental health problems, divorce, domestic violence) showed largely non-significant associations in both phenotypic and GAPS models (βs = –.07–.01 and ORs = 0.07–1.44), suggesting genetic and environmental confounding.

Conclusions: Children with elevated genetic liabilities for psychopathology were more likely to experience interpersonal victimisation and family dysfunction, supporting evidence for gene-environment correlation. Emotional and victimisation ACEs showed robust associations with adolescent psychopathology independent of measured confounding, whereas the observed associations between household-level ACEs and psychopathology were largely explained by genetic and environmental confounding. My findings underscore the importance of a multi-pronged approach: strengthening primary prevention to reduce direct child-targeted ACEs, while tailoring secondary support for genetically vulnerable children within their broader socioecological contexts.

4.2 Introduction

In the previous chapter, I applied propensity score matching to strengthen causal inference about the impact of ten distinct adverse childhood experiences (ACEs) on adolescent psychopathology outcomes in the Millennium Cohort Study (MCS). My findings demonstrated that the associations between ACEs and psychopathology were substantially attenuated after accounting for a wide range of measured environmental confounders. However, the potential for residual genetic confounding remains a critical issue, as the observed associations between ACEs and psychopathology are also likely to be confounded by heritable vulnerabilities for mental health problems. This can be understood through the phenomenon of gene-environment correlation (rGE), where an individual's genotype is correlated with their likelihood of exposure to certain environments, thereby making these environments heritable (Jaffee & Price, 2007).

Gene-environment correlations can be passive, evocative, or active. For example, with passive rGE (i.e., the association between a child's inherited genotype and the environment they are raised in), a parent with depression may transmit the genetic vulnerability for depression to their child and provide an adverse caregiving environment (Rice et al., 2013). Regarding evocative rGE (i.e., when a child's genetically influenced traits evoke certain responses from others), twin and adoption studies have shown that children with genetic predispositions for externalising problems may be more likely to elicit negative parenting responses (Marceau et al., 2013; O'Connor et al., 1998). In the case of active rGE (i.e., when an individual actively chooses an environment that aligns with their genotype), a genetically impulsive child may seek out delinquent peers, increasing their own involvement in delinquent behaviour (TenEyck & Barnes, 2015).

Evidence from both prospective and retrospective studies indicates that the heritability of ACEs may manifest through rGE. For example, prospective studies have demonstrated that children with higher genetic predispositions for psychiatric disorders (e.g., depression, anxiety, ADHD, and schizophrenia) faced greater risks of exposure to ACEs such as abuse, neglect,

domestic violence, parental psychopathology, parental substance abuse, and bullying victimisation (Baldwin, Sallis, et al., 2023; Sallis et al., 2021; Schoeler et al., 2019; Zwicker et al., 2020). Similarly, adults who retrospectively reported childhood maltreatment displayed higher genetic liabilities for depression, autism, ADHD, schizophrenia, and bipolar disorder (Ratanatharathorn et al., 2021; Warrier & Baron-Cohen, 2021). Importantly, such gene-environment correlations do not imply that ACE-exposed children are in any way responsible for their experiences, as safeguarding children remains a parental, familial, and societal obligation.

This growing evidence for genetic confounding highlights a key methodological challenge in ACE research: most existing studies rely on non-genetically informed observational methods, which are prone to overestimating the causal effects of ACEs on mental health (Baldwin, Sallis, et al., 2023; Baldwin, Wang, et al., 2023). There is therefore a pressing need for genetically sensitive designs capable of disentangling the environmentally mediated effects of ACEs from genetic confounding. Clarifying this distinction is not merely a methodological issue; it also has direct implications for intervention and policy. If the associations between ACEs and psychopathology primarily reflect environmental pathways, preventive strategies targeting adverse exposures are likely to reduce risk. Conversely, if these associations partially reflect genetic confounding, even successful primary prevention of ACEs may only partially reduce children's risk for psychopathology, as inherited vulnerabilities would still remain (Baldwin, Sallis, et al., 2023). In the latter scenario, interventions should focus on tailoring support for at-risk families with inherited vulnerabilities, rather than attributing the risk for psychopathology solely to the adverse environment. Thus, genetically sensitive approaches can strengthen causal inference on the impact of ACEs, clarify how heritable vulnerabilities contribute to the aetiology of psychopathology, and inform more targeted prevention and intervention strategies for at-risk families.

Such genetically sensitive approaches range from traditional family-based designs (e.g., twin studies, children of twins, and adoption studies) to more recent molecular genetic approaches

(e.g., using polygenic scores to control for measured genetic liability). Findings from family-based designs suggest that the extent of genetic confounding in ACE-psychopathology associations varies across different types of adversity. For example, twin studies have shown that childhood maltreatment and victimisation consistently predicted elevated risk for internalising and externalising psychopathology, even after accounting for genetic and shared environmental confounding (Baldwin, Wang, et al., 2023; Capusan et al., 2016; Jaffee et al., 2004; Lecei et al., 2019; Schaefer et al., 2017; Singham et al., 2017). Children of twins studies have revealed that parental depression, anxiety, divorce, and marital discord remained associated with child psychopathology after adjustment for familial confounding (D'Onofrio et al., 2007; Eley et al., 2015; McAdams et al., 2014; Silberg et al., 2010), whereas parental psychosis and substance use appeared to be genetically transmitted (Gottesman & Bertelsen, 1989; McAdams et al., 2014; Waldron et al., 2009). Adoption studies reinforce this pattern, showing that maternal depression increased offspring risk for depression and disruptive disorders via environmental transmission (McAdams et al., 2015; Tully et al., 2008), while the link between parental substance abuse and offspring ADHD risk was largely explained by genetic factors (Kendler et al., 2016). Taken together, these designs demonstrate that while some ACE–psychopathology associations persist beyond genetic confounding and reflect environmentally mediated effects, others are more plausibly explained by inherited vulnerabilities.

However, traditional family-based designs have several limitations. First, most studies focus on a single form of adversity rather than comparing associations across multiple ACEs, limiting their ability to compare the relative strength of different adversities in predicting psychopathology. Second, family-based designs often rely on relatively small or selective samples (McAdams et al., 2014). This is because ACEs often occur at the family level, reducing the likelihood of discordant exposure within twin or sibling pairs (Jaffee et al., 2004), and adoptive samples tend to underrepresent adverse childhood environments due to screening practices (Jaffee, 2017; Van IJzendoorn et al., 2009). Finally, each design holds distinct assumptions and is

susceptible to different biases, underscoring the need to triangulate findings across complementary genetically informed approaches (Baldwin, Wang, et al., 2023; Lawlor et al., 2016; Munafò & Davey Smith, 2018).

Recent advances in genome wide association studies (GWAS) offer a promising solution to address some of these challenges, by assessing heritable vulnerabilities amongst large samples of unrelated individuals through the calculation of polygenic scores. Polygenic scores aggregate the effects of many genetic variants (known as single nucleotide polymorphisms, SNPs) associated with a phenotypic trait into an individual-level score of genetic liability (Pingault et al., 2018). By using polygenic scores as a measure of genetic liability for psychopathology, researchers can test for gene-environment correlations and investigate the extent to which associations between ACEs and psychopathology may be genetically confounded in large, population-based samples (Baldwin, Sallis, et al., 2023; Ratanatharathorn et al., 2021; Sallis et al., 2021; Schoeler et al., 2019; Warrier & Baron-Cohen, 2021). Using DNA from over 11,000 children across UK and US cohorts, Baldwin, Sallis, and colleagues (2023) demonstrated that maltreatment (a composite measure of neglect and physical, sexual and emotional abuse) and parental mental illness remained robust predictors of childhood internalising and externalising psychopathology, even after accounting for genetic predisposition through polygenic scores. In contrast, parental substance abuse, criminality, and separation were largely associated with psychopathology via genetic confounding. These findings suggest that while some ACEs (e.g., maltreatment) likely exert direct environmental effects on mental health, other ACEs (e.g., parental substance abuse) may be linked to mental health primarily via genetically transmitted predispositions.

While polygenic scores are not quasi-experimental in themselves, they can be integrated into quasi-experimental frameworks to strengthen evidence for causality. In the present chapter, I embed polygenic scores within a quasi-experimental framework using a novel method proposed by Silver et al. (2022): genetically adjusted propensity score (GAPS) matching. As I demonstrated

in **Chapter 3**, traditional propensity score matching can effectively adjust for measured environmental confounders but typically does not account for genetic confounding. GAPS matching offers an innovative way to simultaneously adjust for measured genetic and environmental confounding by including polygenic scores (reflecting an individual's heritable vulnerabilities for mental health outcomes) together with the phenotypic covariates used to estimate the propensity score (Silver et al., 2022).

Thus, my aims were to (1) use genome-wide SNP data from children in the Millennium Cohort Study to derive and validate polygenic scores for psychopathology; (2) examine gene-environment correlations (i.e., whether children with elevated genetic vulnerabilities were more likely to be exposed to particular ACEs); and (3) apply GAPS matching to strengthen causal inference about the effects of ACEs on adolescent mental health outcomes, independent of measured genetic and environmental confounding. By applying GAPS in this context, the present study builds on the phenotypic results from the previous chapter to derive genetically adjusted estimates – helping to clarify which ACEs are likely to exert environmentally mediated effects on adolescent psychopathology, and which ACEs may primarily reflect pre-existing genetic liabilities.

4.3 Methods

Participants

This study used data from the UK Millennium Cohort Study (MCS), corresponding to when participants were aged 9 months, 3, 5, 7, 11, 14, and 17 years old. After imputing missing phenotypic data and including only participants with complete genetic data, the final sample consisted of 9,182 children (62.4% females; 99.5% White). As a result of these restrictions, the analytic sample was predominantly White and therefore not fully representative of the broader cohort.

Genotyping

Genotyping of the MCS cohort members and their biological parents was performed on the Infinium Global Screening Array-24 v1.0 (Fitzsimons et al., 2022). The initial genetic dataset provided by the CLS DAC consisted of 20,247 genotyped samples (https://cls-genetics.github.io/docs/MCS.html). Following quality control (QC) of the genetic data, I derived PGSs for depression, anxiety, and suicide attempt. I then filtered the sample to select individuals with complete genetic data across these PGSs and the first ten genetic principal components (PCs), resulting in a subsample of 13,108 individuals.

Imputation of missing data

This subsample was used for the imputation of missing phenotypic data, which I conducted using the same random forest algorithm described in **Methods 3.3**. Importantly, I included the PGSs and PCs as additional auxiliary variables to further enhance the accuracy of the imputed values for the phenotypic data. Following imputation, I merged the dataset with the PGSs provided by the CLS (for education, intelligence, and BMI) then restricted the sample to one cohort member per family, yielding a final analytical sample of 9,182 individuals.

Measures

ACE exposures. As detailed in **Table *3.1***, I examined ten binary ACE variables measured between age 5 and 17 as the primary exposures of interest: (1) parent mental health problems, (2) parent substance use, (3) parent divorce, (4) bereavement, (5) domestic violence, (6) emotional neglect, (7) physical victimisation, (8) emotional victimisation, (9) sexual victimisation, and (10) peer victimisation.

Psychopathology outcomes. Four mental health outcomes were measured at age 17:

1. Depression and anxiety symptoms: A continuous, standardised score derived from the Kessler (K6) Scale (Kessler et al., 2002).

2. High psychological distress: A binary variable indicating clinically significant distress (coded as present if K6 ≥ 13).
3. Self-harm: A binary variable indicating any lifetime self-harm behaviours (e.g., 'cut or stabbed yourself', 'taken an overdose of tablets'), self-reported on the MCS Young Person Self-Completion Questionnaire.
4. Suicide attempt: A binary variable indicating any lifetime suicide attempt ('Have you ever hurt yourself on purpose in an attempt to end your life?'), self-reported on the MCS Young Person Self-Completion Questionnaire.

Covariates for propensity score matching. To calculate the propensity scores, I included a comprehensive range of phenotypic and genetic covariates (i.e., potential confounders for ACE exposures and psychopathology outcomes). These were grouped into two categories for the propensity score matching analysis:

1. ***Phenotypic covariates:*** To account for measured environmental confounding, I included 36 pre-exposure risk factors measured across prenatal, infancy, and early childhood periods up to age 5 (detailed in **Appendix 6.2.1**). For each ACE model, the corresponding measure of that adversity at age 3 was excluded from the covariates to avoid overadjustment (as explained in **Table *3.2***).
2. ***Genetic covariates:*** To account for measured genetic confounding, I included PGSs for depression, anxiety, suicide attempt, educational attainment, intelligence, and BMI. The process of deriving PGSs is described below and detailed in **Appendices 6.3.1–6.3.4.**

Preregistration

Details of the preregistration, phenotypic measures, propensity score matching analysis, and missing data imputation are described in the previous chapter **Methods 3.3.** The Centre for Longitudinal Studies (CLS) Data Access Committee (DAC) had originally planned to release polygenic scores for multiple health and social traits in the last quarter of 2024, but this was

postponed until mid-2025 due to internal delays. In the interim, I learned to derive PGSs for depression, anxiety, and suicide attempt following the recommended guidelines for best practice. In June 2025, the CLS released PGSs for educational attainment, intelligence, and childhood body mass index (BMI), which I included as additional covariates to estimate the genetically adjusted propensity scores.

Statistical Analysis

Analyses were conducted using R (version 4.5.1) and the code will be made publicly available on GitHub upon publication. I derived polygenic scores using PLINK 1.9 (Purcell et al., 2007) and PLINK 2.0 (Chang et al., 2015), an open-source whole-genome association analysis toolset. Computationally intensive steps (e.g., the principal component analysis) were performed on the Oxford Advanced Research Computing (ARC) cluster (https://www.arc.ox.ac.uk/).

This study used two sources of genetic data: the target MCS cohort data for PGS calculation and external GWAS summary statistics as the base data for SNP effect sizes. I calculated PGSs for depression, anxiety, and suicide attempt using summary statistics from the most recent GWAS meta-analyses available at the time for major depressive disorder (Adams et al., 2025), anxiety disorder (Purves et al., 2020), and suicide attempt (Docherty et al., 2023). Additionally, externally derived PGS for educational attainment (Okbay et al., 2022), intelligence (Savage et al., 2018), and childhood BMI (Vogelezang et al., 2020) were provided by the CLS. I chose to include these polygenic scores because they capture heritable vulnerabilities for a wide range of mental health outcomes, and have been shown to be potential confounders of the association between ACEs and psychopathology in children and adolescents (Baldwin, Sallis, et al., 2023; Schoeler et al., 2019; Zwicker et al., 2020).

Quality control (QC) of genetic data. I applied a standardised QC pipeline to each set of GWAS summary statistics and the target MCS dataset, following established best practice guidelines (Choi et al., 2020; Marees et al., 2018; Mills et al., 2020). Briefly, individuals were

excluded based on high missingness (>2%), excess heterozygosity, or sex discordance. SNPs were filtered to exclude variants with high missingness (>3%), significant deviation from the Hardy-Weinberg equilibrium (p < 1e-6), or low minor allele frequency (<1%). A comprehensive description of the full QC pipeline is reported in **Appendix 6.3.1** and **Table *6.24***.

Principal component analysis (PCA). To control for potential confounding due to genetic ancestry, I performed a principal component analysis (PCA) on the target MCS dataset. First, the QC'd target data was pruned to generate a subset of largely independent SNPs (r^2 < 0.25 within a 200 kb window). I then conducted PCA on this pruned set of variants and retained the first 10 principal components (PCs) to be used as covariates. Visual inspection confirmed that the primary axes of genetic variation (PC1 and PC2) corresponded well with self-reported ethnicity, validating their use as covariates to account for population stratification in the subsequent regression models (**Figure 6.28**). These PCA results, along with an explanation of LD, pruning, and population stratification are detailed in **Appendix 6.3.2 and Appendix 6.3.3.**

Deriving polygenic scores. The general formula for calculating a polygenic score is to sum the number of phenotype-associated SNPs as an individual risk score, with each SNP weighted by its effect size derived from an independent discovery GWAS (Choi et al., 2020; Marees et al., 2018; Mills et al., 2020). I used the clumping and thresholding method to calculate PGSs for depression, anxiety, and suicide attempt, and determined the optimal p-value threshold for SNP inclusion via a robust five-fold cross-validation procedure. As PGS performance tends to vary across different ancestral populations (Duncan et al., 2019; Mills et al., 2020), I stratified participants into European and non-European subsets based on genetic ancestry, then randomly divided each subset into five cross-validation folds. The optimal threshold was identified as the modal best-performing threshold across the five training folds. Following cross-validation within each ancestry group, I identified the optimal threshold across both ancestry groups to derive the final standardised PGS for the whole cohort. All PGS were standardised to have a mean of 0 and

standard deviation of 1, and all PGS were normally distributed (**Figure 6.35**, **Figure 6.36**, **Figure 6.37**, **Figure 6.38**, **Figure 6.39**, **Figure 6.40**). Details of the clumping and thresholding method and five-fold cross-validation pipeline are provided in **Appendix 6.3.4.**

To correct for multiple comparisons, all *p*-values were adjusted using the False Discovery Rate (FDR) procedure (Benjamini & Hochberg, 1995). The FDR was implemented for all analyses in this chapter: the gene-environment correlations, PGS-psychopathology regressions, and all outcome models (PGS-only, phenotype-only, and GAPS).

Gene-environment correlation (rGE) analysis. To test for gene-environment correlations (rGE), I fit a series of logistic regression models to examine whether each PGS predicted exposure to each of the 10 ACEs. Each model tested a single PGS as the predictor of a binary ACE outcome, adjusting for covariates. The general formula of the single-PGS model was:

$$logit(P(ACE = 1)) = \beta_0 + \beta_1 PGS + \beta_2 Sex + \beta_3 Ethnicity + \beta_4 PC_1 + \cdots + \beta_{13} PC_{10}$$

Where:

- **ACE** is a binary variable indicating exposure to a specific ACE (0 = no, 1 = yes).
- **PGS** refers to the polygenic score of interest (e.g., depression, anxiety, suicide attempt, education, intelligence, or BMI), standardised to mean 0 and SD 1.
- $\mathbf{PC_1–PC_{10}}$ are the first 10 genetic principal components to adjust for population stratification.
- $\boldsymbol{\beta_0}$ is the intercept.
- $\boldsymbol{\beta_1–\beta_3}$ are regression coefficients for PGS, sex, and ethnicity; $\boldsymbol{\beta_4–\beta_{13}}$ are coefficients for the 10 genetic principal components.

To examine the unique contribution of each PGS, I also fit multivariate logistic regression models including all PGSs simultaneously. Each model predicted ACE exposure from the combined set of PGSs and covariates. The general formula of the multi-PGS model was:

$$logit\big(P(ACE = 1)\big) = \beta_0 + \beta_1 PGS\_Depression + \beta_2 PGS\_Anxiety + \beta_3 PGS\_Suicide + \beta_4 PGS\_Education + \beta_5 PGS\_Intelligence + \beta_6 PGS\_BMI + \beta_7 Sex + \beta_8 Ethnicity + \beta_9 PC_1 + \cdots + \beta_{18} PC_{10}$$

PGS-psychopathology models. To examine whether PGS predicted adolescent psychopathology, I fit linear regression models for the continuous outcome (depression and anxiety symptoms) and logistic regression models for the binary outcomes (psychological distress, self-harm, and suicide attempt). The general formula for the single-PGS outcome model was:

$$Continuous\ Psychopathology\ Outcome = \beta_0 + \beta_1 PGS + \beta_2 Sex + \beta_3 Ethnicity + \beta_4 PC_1 + \cdots + \beta_{13} PC_{10}$$

$$logit(P(Binary\ Psychopathology\ Outcome = 1)) = \beta_0 + \beta_1 PGS + \beta_2 Sex + \beta_3 Ethnicity + \beta_4 PC_1 + \cdots + \beta_{13} PC_{10}$$

To assess the independent contribution of each PGS, I also fit multivariate models including all PGSs simultaneously. The general formula for the multi-PGS outcome model was:

$$Continuous\ Psychopathology\ Outcome = \beta_0 + \beta_1 PGS\_Depression + \beta_2 PGS\_Anxiety + \beta_3 PGS\_Suicide + \beta_4 PGS\_Education + \beta_5 PGS\_Intelligence + \beta_6 PGS\_BMI + \beta_7 Sex + \beta_8 Ethnicity + \beta_9 PC_1 + \cdots + \beta_{18} PC_{10}$$

$$logit(P(Binary\ Psychopathology\ Outcome = 1)) = \beta_0 + \beta_1 PGS\_Depression + \beta_2 PGS\_Anxiety + \beta_3 PGS\_Suicide + \beta_4 PGS\_Education + \beta_5 PGS\_Intelligence + \beta_6 PGS\_BMI + \beta_7 Sex + \beta_8 Ethnicity + \beta_9 PC_1 + \cdots + \beta_{18} PC_{10}$$

Genetically adjusted propensity score (GAPS) matching. For each of the 10 ACEs, matched datasets were created using the 'MatchIt' package in R (Ho et al., 2011). To maximise

sample size and covariate balance, I replicated the full matching procedure described in **Methods 3.3**, incorporating the polygenic scores alongside the phenotypic matching variables (**Appendix 6.2.1**). By conditioning on a genetically adjusted propensity score (GAPS), individuals were balanced not only on observed phenotypic covariates[1] but also on measured genetic liability to depression, anxiety, suicide attempt, education, intelligence, and BMI, enabling comparisons between participants with similar combined genetic and phenotypic risk of exposure to ACEs.

In the previous chapter, I used four levels of increasing adjustment to demonstrate how propensity score matching influenced the associations between ACEs and psychopathology (**Table *3.3***). In the present study, I used three levels of propensity scores to facilitate a direct comparison of estimates derived from a traditional propensity score model (i.e., using phenotypic covariates only) versus a genetically adjusted propensity score model (**Table *4.1***).

Table 4.1 Levels of propensity scores for regression models.

	Propensity Score Level	Purpose
1	PGS only.	The propensity score was estimated using only the polygenic scores to adjust for measured genetic confounding.
2	Phenotype only.	The propensity score was estimated using only the phenotypic covariates to adjust for measured environmental confounding.
3	GAPS model. (PGS + phenotypic covariates).	The propensity score was estimated using both the polygenic scores and phenotypic covariates to adjust for measured genetic and environmental confounding.

Outcome modelling on matched datasets. To strengthen causal inference about the effects of each of the 10 ACEs on the four psychopathology outcomes, I fit weighted regression models on the matched datasets generated using the three propensity score levels (PGS-only,

[1] Although the same phenotypic covariates were used, note that the phenotypic estimates in this chapter differ from those in the previous chapter due to differences in analytic samples. The prior chapter used the full imputed sample (N = 18,539), whereas the current propensity score analyses (PGS-only, phenotype-only, and GAPS) were restricted to the genotyped subsample (N = 9,182) with complete data on all six polygenic scores (depression, anxiety, suicide attempt, education, intelligence, and BMI).

phenotype-only, and the fully specified GAPS model). All models were adjusted for sex, ethnicity, and the other nine ACEs to isolate the specific effect of the ACE exposure of interest. I originally intended to also adjust for the 10 genetic PCs. However, this specification failed to converge for certain ACE-outcome combinations due to multicollinearity introduced by the matching process. Systematic diagnostic tests (in which I excluded each covariate in turn) revealed that this model instability was driven by the inclusion of the 10 PCs within specific matched subsets. To ensure model stability, I excluded the 10 PCs from the final model specification. This more parsimonious approach remains robust, as the potential confounding effects of genetic ancestry were already accounted for during matching in the PGS-only and GAPS models. Thus, the general formula for the matched dataset outcome model was:

$$Continuous\ Psychopathology\ Outcome = \beta_0 + \beta_1 ACE\_of\_interest + \beta_2 ACE_2 + \cdots + \beta_{10} ACE_{10} + \beta_{11} Sex + \beta_{12} Ethnicity$$

$$logit(P(Binary\ Psychopathology\ Outcome = 1)) = \beta_0 + \beta_1 ACE\_of\_interest + \beta_2 ACE_2 + \cdots + \beta_{10} ACE_{10} + \beta_{11} Sex + \beta_{12} Ethnicity$$

4.4 Results

Descriptive statistics

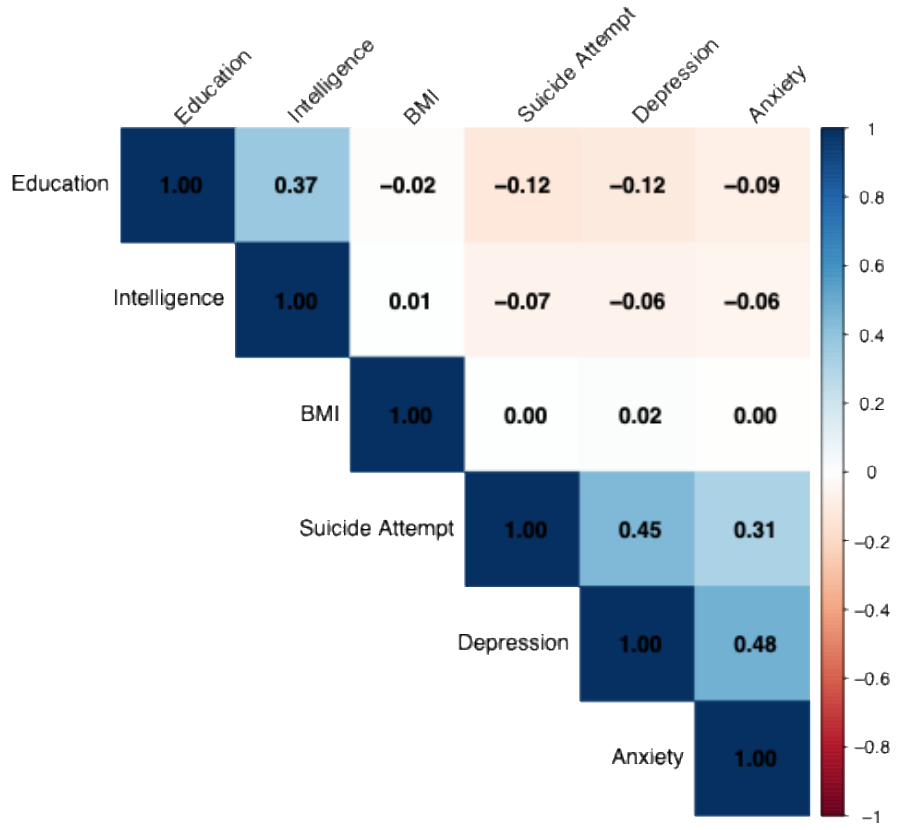
To retain statistical power and minimise bias from missingness, all analyses were conducted on the imputed phenotypic dataset merged with complete genetic data (N = 9,182). Descriptive statistics for the complete genotyped sample are reported below in **Table *4.2***.

Table 4.2 Descriptive statistics for the MCS genotyped sample (N = 9,182).

Millennium Cohort Study (MCS)		
ACEs (5 to 17 years)	**n exposed**	**% exposed**
Parent mental health problems	457	4.98
Parent substance use	1,457	15.87
Parent divorce	758	8.26
Bereavement	73	0.80
Domestic violence	278	3.03
Emotional neglect	963	10.49
Physical victimisation	1,048	11.41
Emotional victimisation	2,644	28.80
Sexual victimisation	270	2.94
Peer victimisation	1,375	14.97
Psychopathology (17 years)	**M(SD)/n**	**Range/%**
Depression and anxiety symptoms	3.88 (3.07)	0 – 24
High psychological distress	278	3.03
Self-harm	449	4.89
Suicide attempt	156	1.70

To assess the relationships between the polygenic scores (and potential shared genetic architecture), I examined the correlations among the six PGSs (**Figure 4.1**). The PGSs for depression, anxiety, and suicide attempt were moderately to strongly intercorrelated (r = .31 to .48). Education PGS and intelligence PGS were also positively correlated (r = .37). The cognitive PGSs displayed modest, negative correlations with the psychopathology PGSs (r = -.06 to -.12). The BMI PGS was largely independent of all other PGSs. Overall, these correlations justify the use of a multi-PGS model to disentangle the independent predictive effects of each PGS.

Figure 4.1 Correlation matrix of the six polygenic scores (PGS).



Single-PGS Gene-Environment Correlation (rGE)

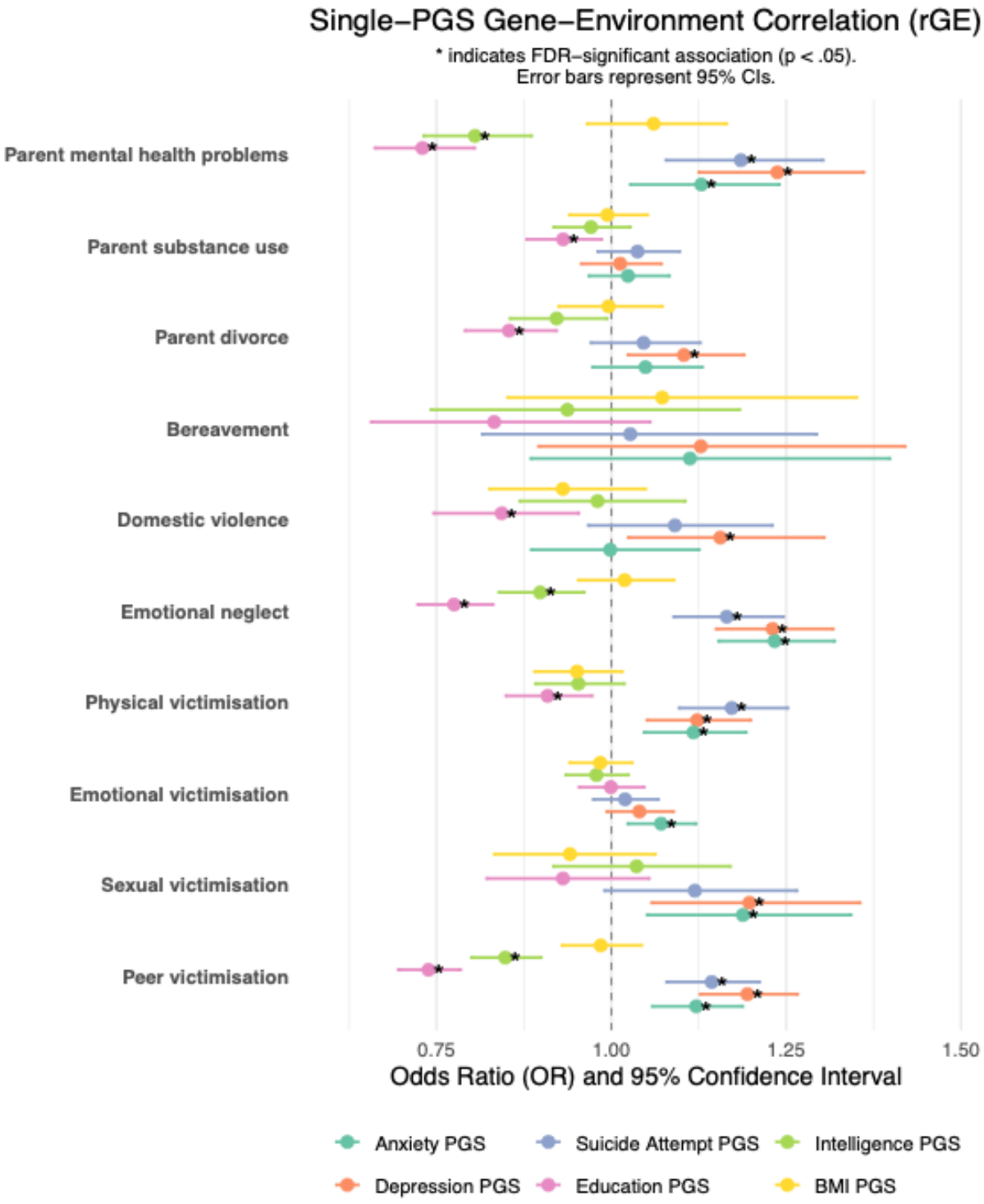
Gene-environment correlation (rGE) results for the single-PGS models are presented in **Figure 4.2**, with detailed results reported in the appendix (**Table *6.25***). There were robust associations between the psychopathology PGSs (i.e., depression, anxiety, suicide attempt PGSs) and increased odds of experiencing several ACEs. All three psychopathology PGSs were associated with increased odds of being exposed to parent mental health problems (*OR*s = 1.13-1.24, all *p*-values < .03), emotional neglect (*OR*s = 1.17-1.23, all *p*-values < .001), physical victimisation (*OR*s = 1.12-1.17, all *p*-values ≤ .003), and peer victimisation (*OR*s = 1.12-1.19, all *p*-values < .001). Depression PGS (*OR* = 1.20, 95% CI [1.06, 1.36], *p* = .013) and anxiety PGS (*OR* = 1.19, 95% CI [1.05, 1.34], *p* = .016) were also associated with exposure to sexual victimisation. Depression PGS was associated with higher odds of parent divorce (*OR* = 1.10, 95% CI [1.02, 1.19], *p* = .025) and domestic violence (*OR* = 1.16, 95% CI [1.02, 1.30], *p* = .042). Anxiety PGS

was also associated with slightly higher odds of emotional victimisation (*OR* = 1.07, 95% CI [1.02, 1.12], $p < .01$). However, the psychopathology PGSs were not associated with parent substance use or bereavement.

Notably, higher PGSs for education and intelligence were consistently associated with reduced odds of exposure to several ACEs, suggesting potential protective rGE. There were particularly strong protective associations between education PGS and parent mental health problems (*OR* = 0.73, 95% CI [0.66, 0.80], $p < .001$), emotional neglect (*OR* = 0.78, 95% CI [0.72, 0.83], $p < .001$), and peer victimisation (*OR* = 0.74, 95% CI [0.70, 0.78], $p < .001$). Education PGS was also significantly associated with lower risk of exposure to parent substance use, parent divorce, domestic violence, and physical victimisation (*OR*s = 0.84-0.93, all *p*-values < .05). Intelligence PGS showed similar but generally weaker protective associations, with significantly reduced odds for parent mental health problems (*OR* = 0.81, 95% CI [0.73, 0.89], $p < .001$), emotional neglect (*OR* = 0.90, 95% CI [0.84, 0.96], $p = .006$), and peer victimisation (*OR* = 0.85, 95% CI [0.80, 0.90], $p < .001$). Neither education nor intelligence PGSs were associated with bereavement, emotional victimisation, or sexual victimisation. BMI PGS was not associated with any of the ACEs.

Overall, the single-PGS models provided evidence of rGE for multiple forms of childhood adversity. Children with higher genetic vulnerabilities for depression, anxiety, and suicide attempt were more likely to experience ACEs involving family dysfunction and interpersonal victimisation. In contrast to these risk-related findings, higher genetic propensity for educational attainment and intelligence was consistently associated with lower risk of ACE exposure, suggesting potential protective effects. None of the PGSs were associated with bereavement, indicating that this form of adversity might be less susceptible to heritable influences. Finally, there was no evidence of rGE between genetic liability to higher BMI and exposure to ACEs.

Figure 4.2 Forest plot of single-PGS gene-environment correlations.



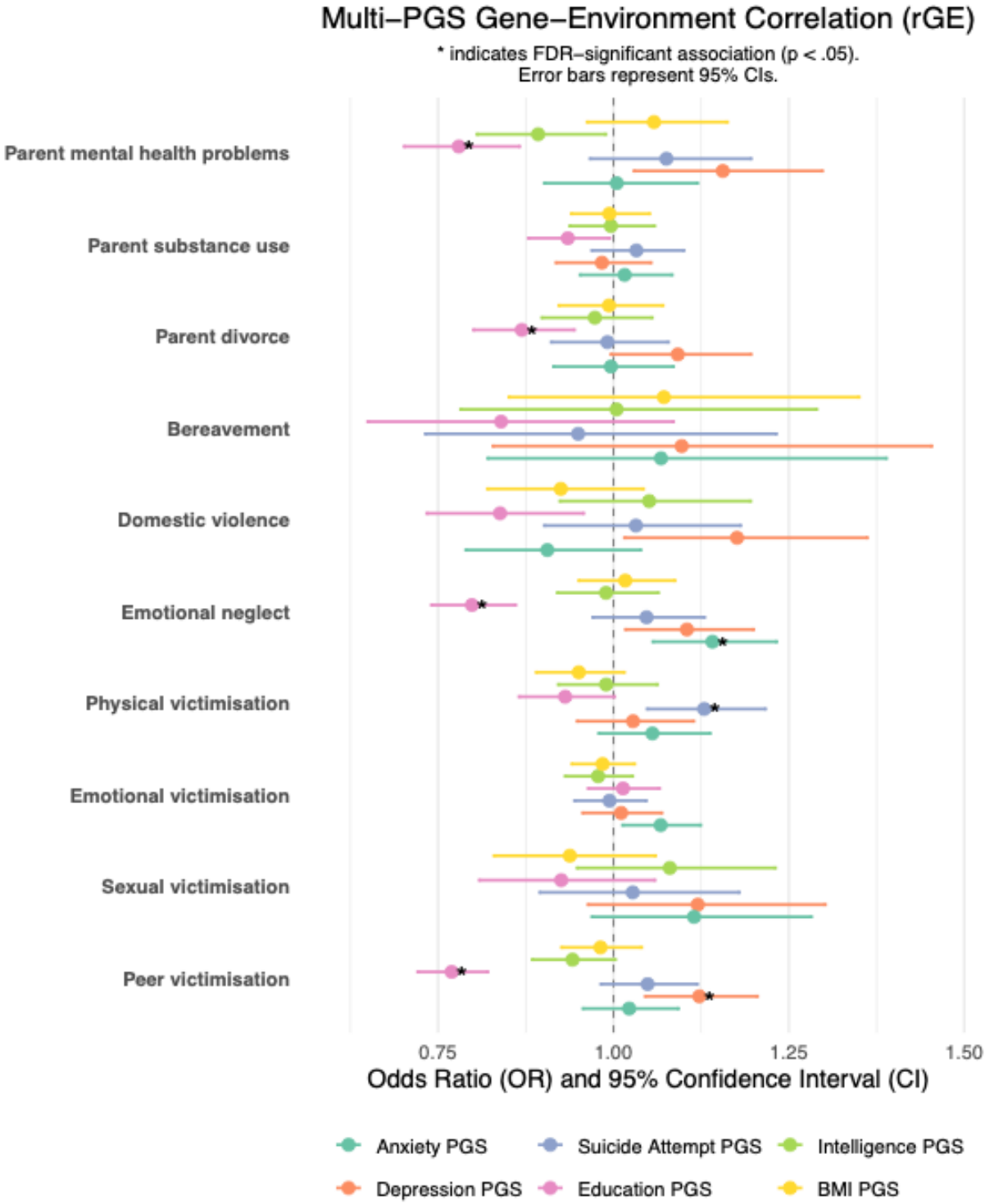
Multi-PGS Gene-Environment Correlation (rGE)

Gene-environment correlation (rGE) results for the multi-PGS models are presented in **Figure 4.3**, with detailed results reported in the appendix (**Table *6.26***). After including all PGSs simultaneously and correcting for multiple comparisons, many of the rGE findings from the single-PGS models were attenuated. For example, although higher depression PGS was initially associated with increased odds of exposure to parent mental health problems, this association did not survive the FDR correction (*OR* = 1.16, 95% CI [1.03, 1.30], p = .087).

Several PGSs remained independently associated with specific ACEs even after adjusting for other genetic liabilities. Higher anxiety PGS (*OR* = 1.14, 95% CI [1.06, 1.23], p = .011) and education PGS (*OR* = 0.80, 95% CI [0.74, 0.86], p < .001) remained significant predictors of emotional neglect, indicating independent rGE for increased and decreased risk, respectively. Similarly, higher depression PGS (*OR* = 1.12, 95% CI [1.05, 1.21], p = .013) and education PGS (*OR* = 0.77, 95% CI [0.72, 0.82], p < .001) maintained their risk and protective rGE associations with peer victimisation. Higher suicide attempt PGS remained independently associated with increased odds of exposure to physical victimisation (*OR* = 1.13, 95% CI [1.05, 1.22], p = .013).

Education PGS consistently showed protective associations in the multi-PGS models, reducing the likelihood of exposure to parent mental health problems, parent divorce, emotional neglect, and peer victimisation (*OR*s = 0.77-0.87, all p-values ≤ .011). However, no significant rGE associations were observed for parent substance use, bereavement, domestic violence, emotional victimisation, or sexual victimisation after accounting for other PGSs and multiple testing. After controlling for the other PGSs, intelligence PGS no longer predicted exposure to any ACEs in the multi-PGS models. As with the single-PGS models, BMI continued to display no significant associations with any ACEs in the multi-PGS models.

Figure 4.3 Forest plot of multi-PGS gene-environment correlations.



Associations between Polygenic Scores and Psychopathology Outcomes

Results for the single-PGS models are presented in **Figure 4.4**, with detailed results reported in the appendix (**Table *6.27***). Results for the multi-PGS models are presented in **Figure 4.5**, with detailed results reported in the appendix (**Table *6.28***).

Overall, the single-PGS models indicated that higher genetic liability for depression, anxiety, and suicide attempt was associated with greater risk for psychopathology outcomes (βs = 0.02-0.03, ORs = 1.15–1.31, all *p*-values < .05), although these associations were largely attenuated after accounting for the influence of multiple PGSs (βs = 0.00-0.02, ORs = 1.00–1.23, all *p*-values > .05), in line with our understanding of the shared genetic architecture of psychopathology. In contrast, the protective influence of higher education PGS remained robust across all models, being associated with lower risk for all psychopathology outcomes (β = –0.04, ORs = 0.74–0.84, all *p*-values < .05). In the single-PGS and multi-PGS models, there were no significant associations between intelligence PGS and BMI PGS with psychopathology. Together with the rGE findings, these results strengthen the case for treating polygenic scores as measured genetic confounders, given that most PGSs (except BMI PGS) were consistently associated with both exposures (ACEs) and outcomes (psychopathology). These findings directly support the inclusion of PGSs in the calculation of propensity scores for the subsequent GAPS analysis.

Figure 4.4 Forest plot of single-PGS psychopathology associations.

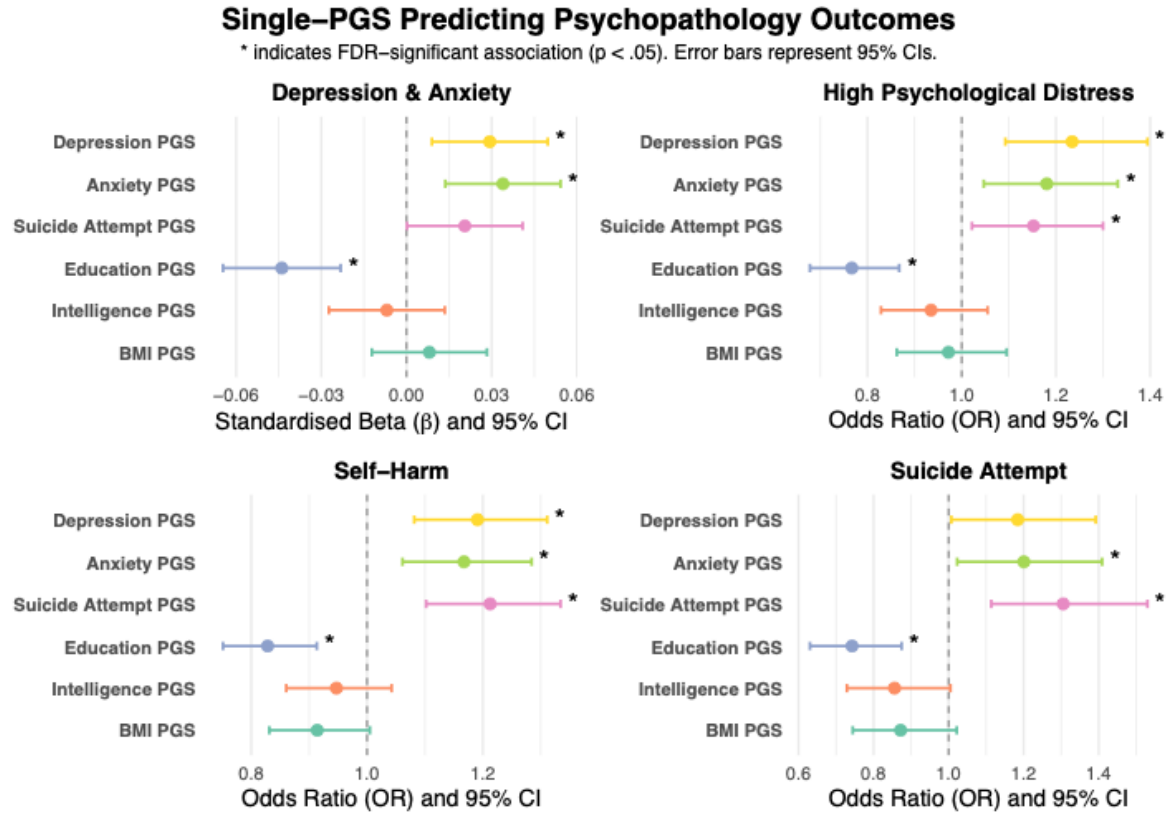
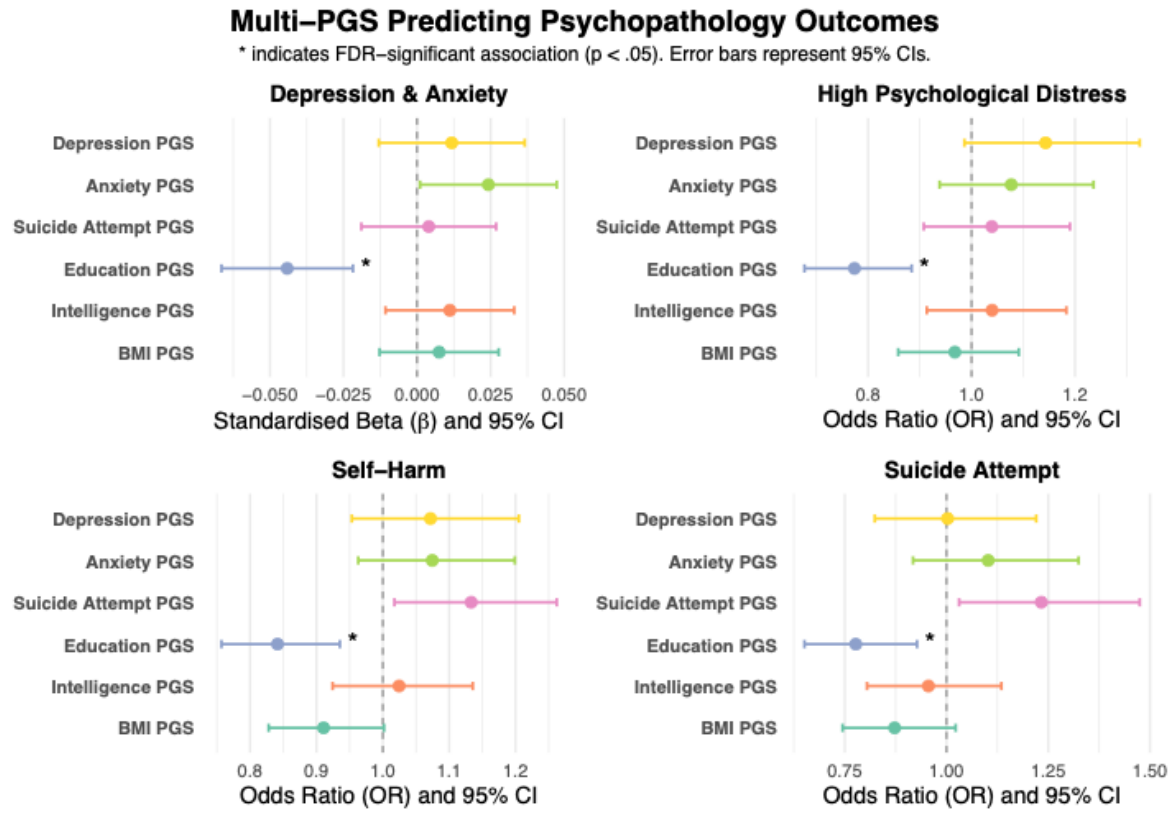


Figure 4.5 Forest plot of multi-PGS psychopathology associations.



Genetically Adjusted Propensity Score (GAPS) Matching

The following plots present the three levels of propensity scores (PGS-only, phenotype-only, GAPS) for each outcome: depression and anxiety symptoms (**Figure 4.6**), high psychological distress (**Figure 4.7**), self-harm (**Figure 4.8**), and suicide attempt (**Figure 4.9**). Detailed results are available in the appendix (**Table *6.29*, Table *6.30*, Table *6.31*, Table *6.32***).

Across the ten ACEs, a distinct pattern emerged. Household-level adversities (parental mental health problems, substance use, divorce, bereavement, and domestic violence) showed little evidence of independent associations with adolescent psychopathology once measured genetic and environmental confounding were accounted for, with most associations largely attenuated in the GAPS models. In contrast, direct, child-targeted adversities — particularly emotional neglect, and physical, emotional, sexual, and peer victimisation — remained strongly associated with elevated risk of depression and anxiety symptoms, high psychological distress, self-harm, and suicide attempt. These findings suggest that the most consistent and independent predictors of adolescent psychopathology were experiences of victimisation and neglect, whereas associations with household-level ACEs may be explained by shared genetic or environmental liabilities. Detailed results for each adversity are presented below.

Parent mental health problems were inconsistently associated with psychopathology. In the PGS-only and phenotype-only models, exposure was linked to lower depression and anxiety symptoms and lower odds of distress and self-harm, though these associations were inconsistent across approaches. In the GAPS models, associations were non-significant between parental mental health problems with depression and anxiety (β = –0.07, 95% CI [–0.15, 0.00], p = .091), high distress (OR = 0.15, 95% CI [0.01, 1.97], p = .106), and suicide attempt (OR = 0.51, 95% CI [0.11, 2.43], p = .479), although lower odds of self-harm remained significant (OR = 0.15, 95% CI [0.03, 0.77], p = .006). These findings suggest that the observed associations between parental

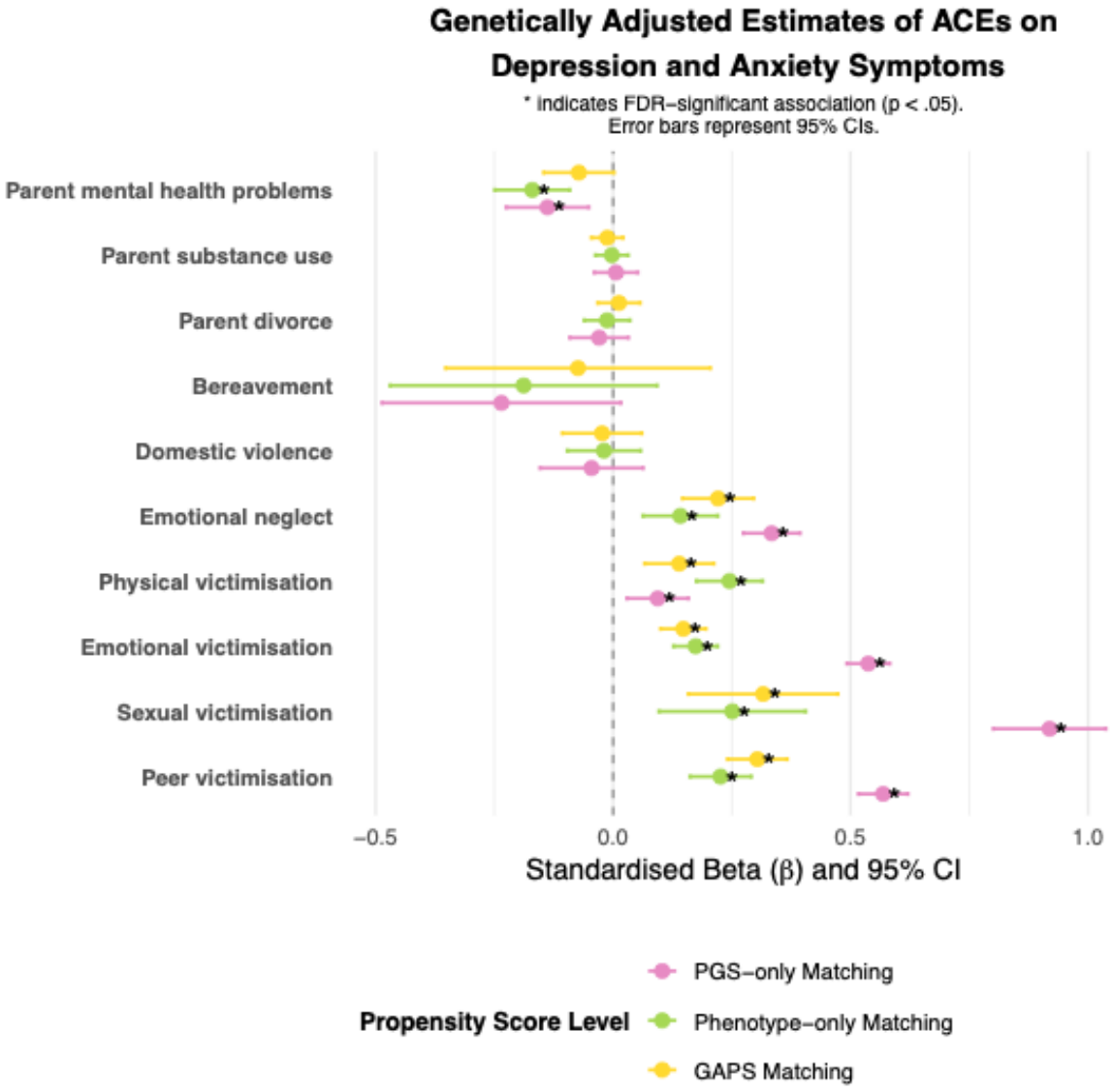
mental health problems and adolescent psychopathology were largely accounted for by measured genetic and environmental confounding.

Parent substance use was not consistently associated with psychopathology outcomes. PGS-only and phenotype-only models suggested lower odds of distress, with little evidence for associations with other outcomes. In the GAPS models, associations remained largely null for depression and anxiety (β = –0.01, 95% CI [–0.05, 0.02], p = .557), while lower odds of distress persisted (OR = 0.07, 95% CI [0.01, 0.85], p = .003), and small reductions in risk for self-harm (OR = 0.38, 95% CI [0.11, 1.27], p = .133) and suicide attempt (OR = 0.20, 95% CI [0.02, 2.18], p = .204) were not statistically significant. Overall, this suggests that associations between parental substance use and psychopathology were likely attributable to measured genetic and environmental confounding.

Parent divorce was not consistently associated with psychopathology outcomes. PGS-only models indicated lower odds of distress and self-harm, but no significant associations were observed in the phenotype-only models. In the GAPS models, associations were non-significant: depression and anxiety (β = 0.01, 95% CI [–0.03, 0.06], p = .660), high distress (OR = 0.22, 95% CI [0.02, 2.95], p = .242), self-harm (OR = 0.37, 95% CI [0.08, 1.78], p = .242), and suicide attempt (OR = 0.24, 95% CI [0.02, 3.01], p = .272). This suggests that apparent associations between parent divorce and psychopathology were largely accounted for by measured confounding.

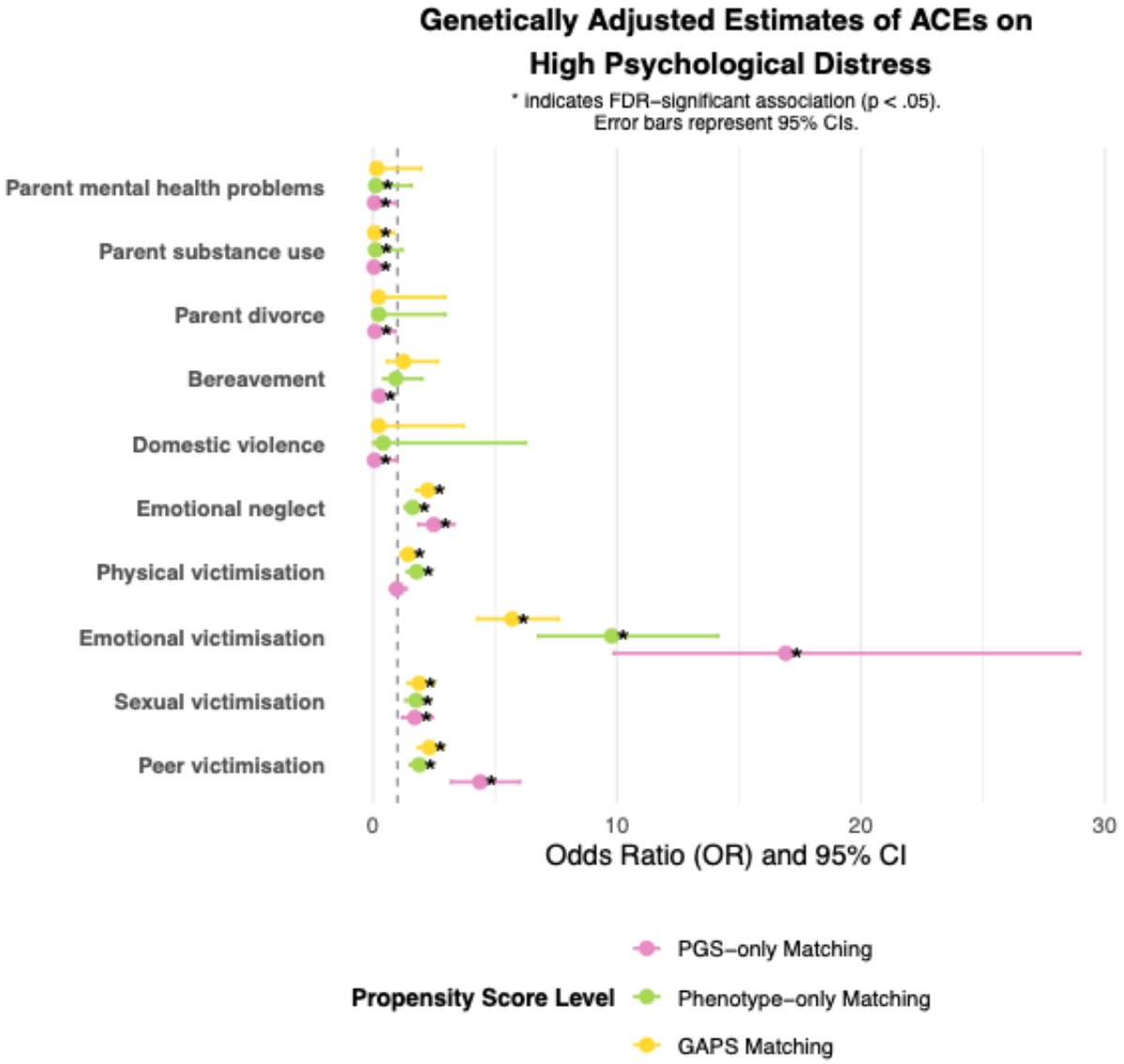
Bereavement was not consistently associated with psychopathology outcomes. In the PGS-only model, bereavement was associated with lower odds of distress, but this was not replicated for other outcomes or in phenotype-only models. In the GAPS models, all associations were non-significant: depression and anxiety (β = –0.07, 95% CI [–0.35, 0.20], p = .665), high distress (OR = 1.24, 95% CI [0.58, 2.65], p = .660), self-harm (OR = 1.44, 95% CI [0.78, 2.68], p = .342), and suicide attempt (OR = 0.62, 95% CI [0.25, 1.55], p = .369). This indicates no independent associations between bereavement and adolescent psychopathology.

Figure 4.6 GAPS estimates of ACEs on depression and anxiety symptoms.



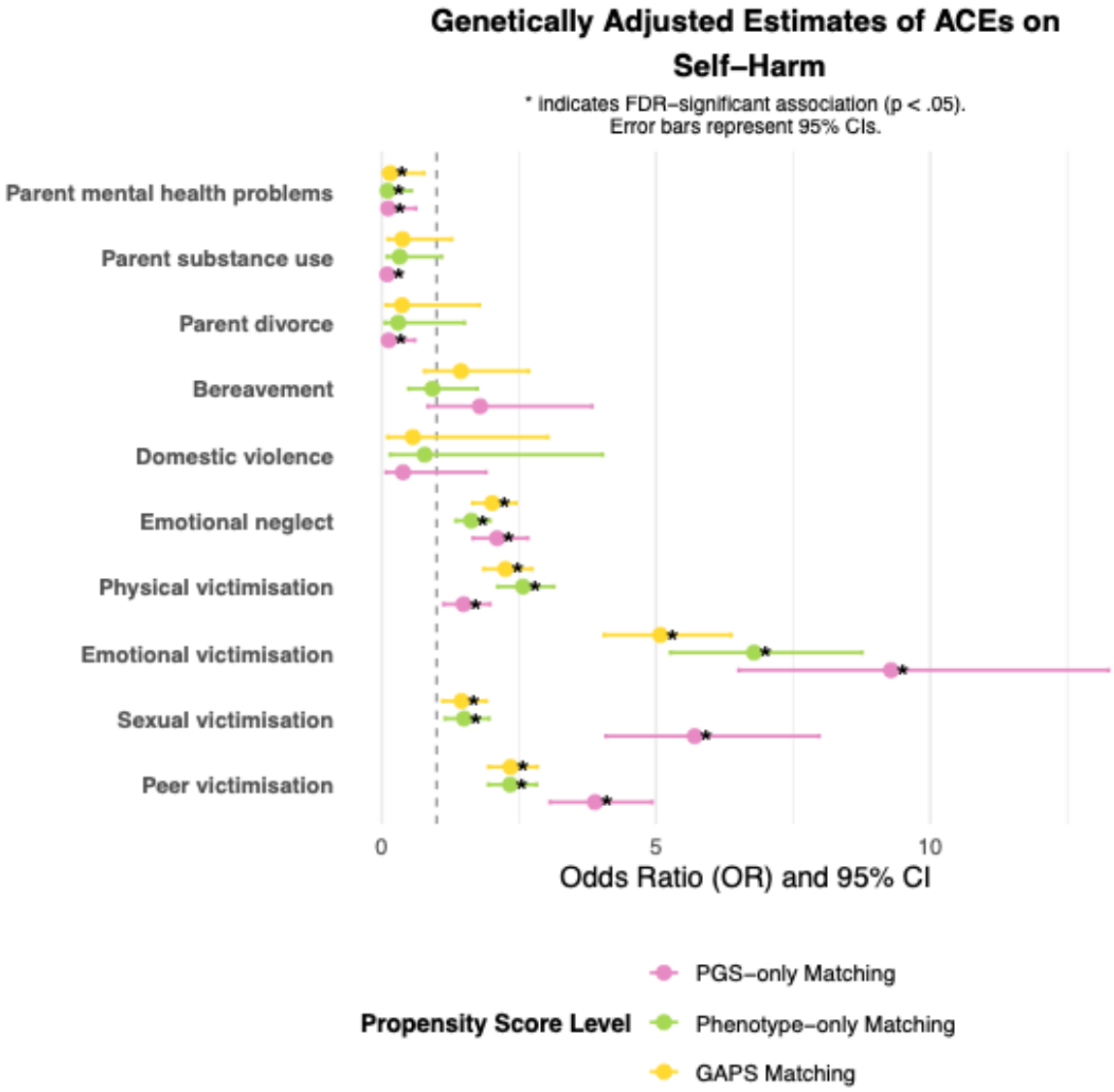
Domestic violence was not consistently associated with psychopathology outcomes. In the PGS-only model, lower odds of distress were observed, but no significant associations were found for other outcomes or in phenotype-only models. In the GAPS models, associations were non-significant across all outcomes: depression and anxiety (β = –0.02, 95% CI [–0.11, 0.06], p = .660), high distress (OR = 0.23, 95% CI [0.01, 3.71], p = .287), self-harm (OR = 0.57, 95% CI [0.11, 3.03], p = .567), and suicide attempt (OR = 0.48, 95% CI [0.03, 7.21], p = .660). This suggests that associations between domestic violence and psychopathology were likely attributable to measured genetic and environmental confounding.

Figure 4.7 GAPS estimates of ACEs on high psychological distress.



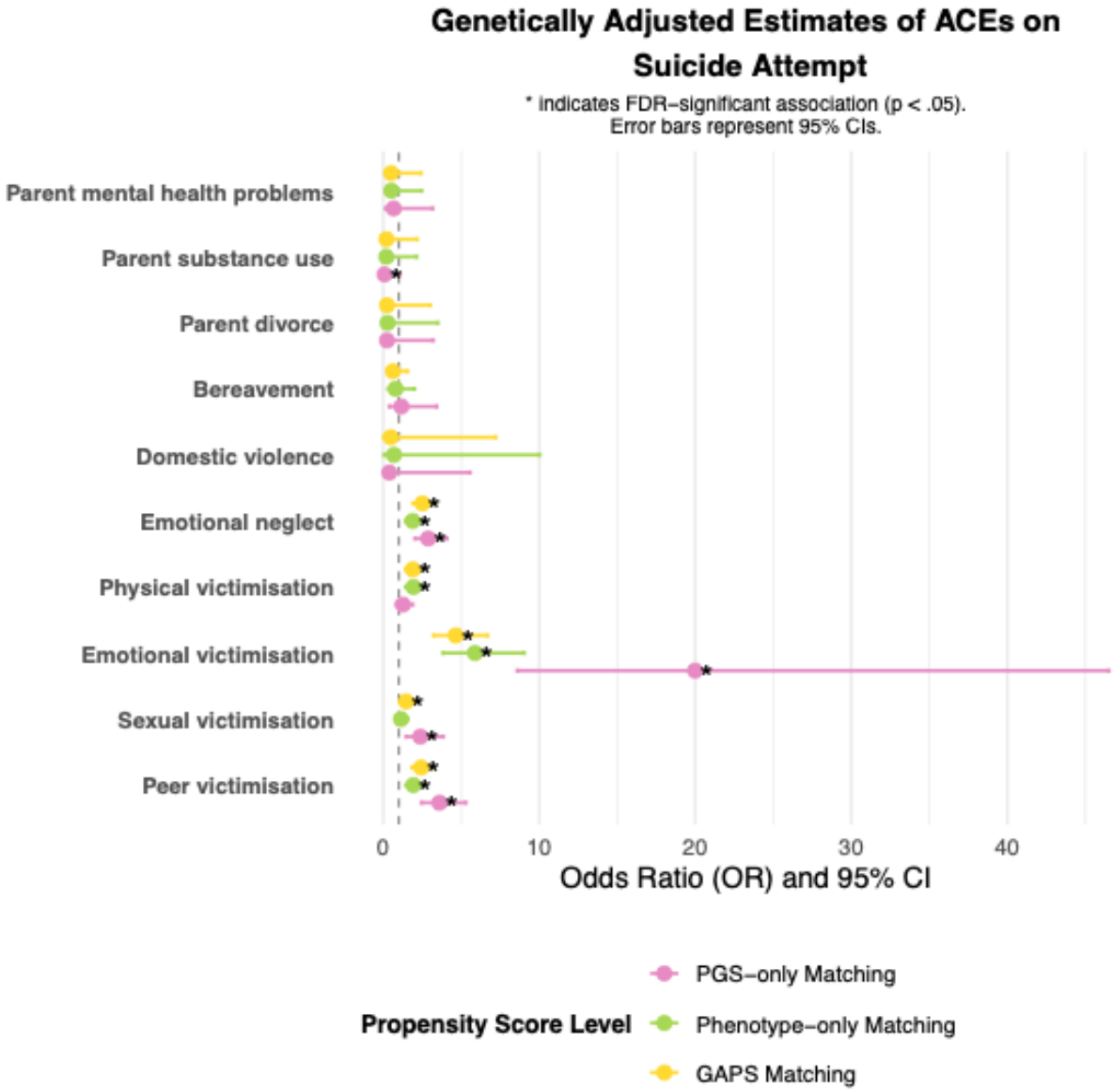
Emotional neglect was strongly associated with increased risk of psychopathology. PGS-only models indicated robust associations, while phenotype-only models suggested slightly smaller but still consistent associations. In the GAPS models, associations remained significant across outcomes: depression and anxiety (β = 0.18, 95% CI [0.12, 0.25], $p < .001$), high distress (OR = 2.24, 95% CI [1.73, 2.91], $p < .001$), self-harm (OR = 2.64, 95% CI [2.11, 3.29], $p < .001$), and suicide attempt (OR = 2.49, 95% CI [1.78, 3.48], $p < .001$). These findings indicate that emotional neglect showed robust and independent associations with adolescent psychopathology beyond measured genetic and environmental confounding.

Figure 4.8 GAPS estimates of ACEs on self-harm.



Physical victimisation was consistently associated with elevated risk of psychopathology. PGS-only models suggested small associations, while phenotype-only models showed stronger associations. In the GAPS models, associations remained significant: depression and anxiety (β = 0.14, 95% CI [0.07, 0.21], $p < .001$), high distress (OR = 1.44, 95% CI [1.14, 1.82], $p = .006$), self-harm (OR = 2.25, 95% CI [1.86, 2.74], $p < .001$), and suicide attempt (OR = 1.89, 95% CI [1.42, 2.52], $p < .001$). These findings indicate consistent associations between physical victimisation and psychopathology beyond measured genetic and environmental confounding.

Figure 4.9 GAPS estimates of ACEs on suicide attempt.



Emotional victimisation was consistently and strongly associated with psychopathology outcomes. PGS-only models suggested very large associations, while phenotype-only models indicated smaller but still significant associations. In the GAPS models, associations remained robust: depression and anxiety (β = 0.15, 95% CI [0.10, 0.20], $p < .001$), high distress (OR = 5.71, 95% CI [4.28, 7.60], $p < .001$), self-harm (OR = 5.08, 95% CI [4.05, 6.37], $p < .001$), and suicide attempt (OR = 4.64, 95% CI [3.22, 6.69], $p < .001$). These findings provide strong evidence for robust associations between emotional victimisation and adolescent psychopathology, over and above measured genetic and environmental confounding.

Sexual victimisation was consistently associated with higher risk of psychopathology. PGS-only models suggested large associations, while phenotype-only models produced more modest but still significant associations. In the GAPS models, associations remained significant: depression and anxiety (β = 0.32, 95% CI [0.16, 0.47], $p < .001$), high distress (OR = 1.89, 95% CI [1.43, 2.50], $p < .001$), self-harm (OR = 1.46, 95% CI [1.11, 1.91], $p = .012$), and suicide attempt (OR = 1.47, 95% CI [1.05, 2.04], $p = .046$). These results suggest that sexual victimisation is robustly associated with elevated psychopathology, independent of measured genetic and environmental confounding.

Peer victimisation was strongly associated with elevated risk of psychopathology. PGS-only models suggested stronger associations, while phenotype-only models showed more modest but still significant associations. In the GAPS models, associations remained significant across outcomes: depression and anxiety (β = 0.30, 95% CI [0.24, 0.37], $p < .001$), high distress (OR = 2.31, 95% CI [1.85, 2.87], $p < .001$), self-harm (OR = 2.35, 95% CI [1.94, 2.83], $p < .001$), and suicide attempt (OR = 2.43, 95% CI [1.83, 3.21], $p < .001$). This indicates that peer victimisation is consistently linked to increased psychopathology risk, beyond measured genetic and environmental confounding.

Finally, a small number of counterintuitive associations (e.g., lower odds of distress following bereavement or domestic violence, and inflated estimates for victimisation in PGS-only models) were observed, but these were likely spurious, reflecting issues such as poor covariate balance, collider bias, or low exposure prevalence (see **Appendix 6.3.8**, **Table *6.33*** for sensitivity analysis and detailed discussion). Importantly, such anomalies were consistently attenuated or resolved in the GAPS models, which yielded stable and plausible associations overall.

4.5 Discussion

To my knowledge, this study is the first to apply genetically adjusted propensity score (GAPS) matching to strengthen causal inference about the effects of ACEs on adolescent psychopathology. My first aim was to derive and validate polygenic scores (PGS) for depression, anxiety, and suicide attempt using genome-wide SNP data from children in the Millennium Cohort Study (MCS). I applied the standard clumping and thresholding method, enhanced by a robust five-fold cross-validation procedure to generate standardised, individual-level measures of genetic predisposition for psychopathology. I then validated these polygenic scores as plausible genetic confounders underlying the ACE-psychopathology relationship by demonstrating that higher depression, anxiety, and suicide attempt PGSs predicted increased risk of both ACE exposures and psychopathology outcomes.

My second aim was to examine gene-environment correlations (rGE), testing whether children with higher genetic vulnerabilities were more likely to be exposed to specific forms of childhood adversity. Consistent with previous genetically informed research (Baldwin, Sallis, et al., 2023; Sallis et al., 2021; Schoeler et al., 2019; Zwicker et al., 2020), I found evidence for rGE across multiple ACEs. In the single-PGS models, higher genetic risk for depression, anxiety, and suicide attempt predicted greater likelihood of exposure to parent mental health problems, likely reflecting passive rGE in the intergenerational transmission of psychopathology (Rice et al., 2013). These PGSs also predicted exposure to family dysfunction (e.g., parent divorce, domestic violence, emotional neglect) and interpersonal victimisation (e.g., physical, sexual, emotional, and peer victimisation), indicating that children with elevated genetic liability for psychopathology may be more likely to encounter familial and social adversities. In contrast, the BMI PGS did not predict exposure to any ACE, contrary to prior research linking higher BMI PGS with increased risk of bullying victimisation (Schoeler et al., 2019). This discrepancy may reflect sample-specific differences or differences in GWAS source data, as the BMI PGS in this study was derived from a discovery GWAS of childhood BMI (Vogelezang et al., 2020) whereas Schoeler et al. (2019) used

an adult BMI GWAS (Yengo et al., 2018). Interestingly, bereavement showed no significant associations with any PGS, suggesting that this form of adversity may be more exogeneous in nature as bereavement typically arises from external or uncontrollable events (e.g., accidents or illness), rather than psychosocial processes linked to heritable vulnerabilities. However, a more selective pattern of gene-environment correlation emerged after accounting for shared variance across PGSs in the multi-PGS models. Specifically, only depression PGS remained associated with peer victimisation, while anxiety PGS predicted emotional neglect, and suicide attempt PGS predicted physical victimisation. The attenuation of associations in the multi-PGS models highlights the importance of adjusting for polygenic overlap when examining rGE, given their shared genetic architecture (Levey et al., 2019; Mei et al., 2022), which is also widely conceptualised as the general psychopathology 'p-factor' (Allegrini et al., 2020; Caspi et al., 2014).

Another key finding from the rGE analysis was the protective associations between the cognitive PGSs (i.e., educational attainment and intelligence) and ACE exposure. In the single-PGS models, higher genetic propensity for educational attainment and intelligence was consistently associated with lower odds of exposure to a wide range of adversities (e.g., parent mental health problems, substance use, divorce, domestic violence, emotional neglect, physical and peer victimisation). In the multi-PGS models, the protective rGE of education PGS remained robust, while the associations for intelligence PGS attenuated to non-significance – likely due to its shared genetic variance with education PGS (**Figure 4.1**). My findings support previous evidence linking higher education and intelligence PGSs with reduced exposure to bullying victimisation (Schoeler et al., 2019), as well as phenotypic evidence demonstrating that higher childhood IQ predicted lower risk of adversity exposure (Breslau et al., 2006; Zwicker et al., 2020). One plausible explanation for the protective rGE of education PGS is 'genetic nurture', a phenomenon in which parental genes – including those not directly inherited by the child – can influence offspring outcomes by shaping the environment that parents create for their children (Kong et al., 2018). A parent's genetic variants that are associated with their own higher educational

attainment may also shape their tendency to provide more supportive, cognitively stimulating, and health-oriented caregiving environments across development into adulthood (Wertz et al., 2023), thereby reducing their child's exposure to adversity.

My third aim was to apply GAPS matching to strengthen causal inference about the effects of ACEs on adolescent psychopathology. Across all three matching strategies (PGS-only, phenotype-only, and GAPS matching), I found that the ACEs most robustly associated with psychopathology were those that involved direct harm or interpersonal threat to the child (i.e., emotional neglect and emotional, physical, sexual, and peer victimisation). These findings align with genetically informed and quasi-experimental evidence for the likely causal contribution of childhood maltreatment and bullying victimisation to mental health problems (Baldwin, Sallis, et al., 2023; Baldwin, Wang, et al., 2023; Schoeler et al., 2018; Warrier et al., 2021). By examining individual subtypes of neglect and victimisation, my findings extend this literature by strengthening causal inference about the effects of each form of victimisation (e.g., emotional, physical, or sexual), rather than treating maltreatment as a composite construct. The particularly harmful effects of emotional victimisation and neglect are noteworthy, as these adversities showed the largest and most consistent effect sizes across all psychopathology outcomes. For example, in the most stringent GAPS-matched models, emotional victimisation yielded an approximately fivefold increase in odds for high psychological distress, self-harm, and suicide attempt. These findings reinforce the notion discussed in my previous **Chapter 3** that emotional forms of maltreatment may be especially potent as they target an individual's sense of worth, safety, and belonging, leaving deeper scars on emotional development and leading to increased psychopathology risk (Cecil et al., 2017; Gama et al., 2021; Kim & Cicchetti, 2010; Riggs, 2019).

In contrast, I found that ACEs reflecting broader household dysfunction – specifically parent mental health problems, substance use, divorce, bereavement, and domestic violence – largely displayed non-significant associations in the final GAPS models. This aligns with findings

from quasi-experimental family-based studies which demonstrated that associations between household-level ACEs (e.g., parent substance use, divorce) and psychopathology were genetically confounded (D'Onofrio et al., 2007; Kendler et al., 2016; Waldron et al., 2009). This pattern is also consistent with the previous chapter's propensity score matching (PSM) analysis, which revealed non-significant associations for household-level ACEs after adjusting for environmental confounding. Together, these findings suggest that household-level or more 'indirect' adversities may be associated with psychopathology primarily through hereditary vulnerabilities or other co-occurring risk factors, given that their effects were largely attenuated after accounting for measured genetic and environmental confounding. It is possible that shared method variance with the adolescent self-reported psychopathology outcomes may have accounted for these findings, as most household-level ACEs were parent-reported, whereas most victimisation ACEs were self-reported. However, I mitigated this by combining multi-informant reports where available (e.g., to derive emotional neglect and peer victimisation). Moreover, previous genetically informed research which used parent-reported child psychopathology outcomes similarly found that household-level adversities were predominantly associated with psychopathology via genetic confounding (Baldwin, Sallis, et al., 2023).

Interestingly, although parent mental health problems were robust predictors of adolescent psychopathology in the previous chapter's phenotypic PSM models (**Figure 3.2**, **Figure 3.3**, **Figure 3.4**, **Figure 3.5**), these associations were largely non-significant in the present chapter's phenotypic and GAPS models (**Figure 4.6**, **Figure 4.7**, **Figure 4.8**, **Figure 4.9**). A possible contributor to this discrepancy is sample differences: the present analyses were restricted to the smaller, predominantly White genotyped subsample with lower rates of parent and child psychopathology overall (*Table **4.2***) than the full imputed cohort (*Table **3.4***). Alternatively, these findings may suggest that once children's genetic predispositions for psychopathology, educational attainment, intelligence, and BMI were accounted for via polygenic scores, the apparent environmental contribution of parent mental health problems to adolescent psychopathology was

substantially diminished. These findings are surprising as they contrast with family-based studies (generally expected to account for greater genetic confounding than polygenic scores), which have shown environmentally mediated effects of parental depression and anxiety on offspring psychopathology outcomes, even after adjustment for genetic confounding in twin, children of twins, and adoption designs (Ahmadzadeh et al., 2021; Eley et al., 2015; Jami et al., 2021; McAdams et al., 2015; Silberg et al., 2010; Tully et al., 2008). However, as many of these family-based studies used parent reports for both their own and their child's symptoms, shared method variance may have inflated the previously observed associations between parent and child mental health (Ahmadzadeh et al., 2021). Overall, these results suggest that, at least in the predominantly White genotyped MCS subsample, parent-child psychopathology associations were largely explained by shared genetic liability, with little residual environmental influence on adolescent psychopathology once polygenic risks, pre-exposure vulnerabilities, and co-occurring adversities were accounted for.

This study has several limitations that should be acknowledged. First, because polygenic scores capture only a small proportion of the total heritability of complex traits, they cannot fully account for genetic confounding (Mills et al., 2020). This may have led to residual unmeasured genetic confounding, potentially inflating the estimated effects of childhood adversity on psychopathology. This limitation reflects the well-documented missing heritability problem, i.e., the gap between high heritability estimates from twin and family studies and the substantially smaller proportion of variance explained by genetic variants identified in GWAS (Maher, 2008). To address this challenge, recent innovative studies have applied genetic sensitivity analysis (Gsens), a novel method that combines PGSs with heritability estimates to model the extent of genetic confounding under scenarios in which PGSs capture additional genetic variance (Baldwin, Sallis, et al., 2023; Pingault et al., 2021). Consistent with my findings on household-level ACEs, the application of Gsens revealed that genetic confounding accounted for large proportions of the observed associations between household-level ACEs and child psychopathology (Baldwin, Sallis,

et al., 2023). Thus, while Gsens has so far only been implemented in classic regression models, adapting it for use with GAPS matching could represent a promising direction for future research.

Second, a key limitation of the present study is the lack of representativeness in the genotyped sample. The GWAS summary statistics used to derive the PGSs were based almost exclusively on individuals of European ancestry. Although I conducted a sensitivity analysis on the non-European subsample during PGS calculation (**Appendix 6.3.4**), the final analytical sample was restricted to children with complete genetic data, resulting in a predominantly White genotyped sample. This reflects known demographic skews in genotyped subsamples of population cohorts, where participation and genetic consent are not random (Taylor et al., 2018). Consequently, estimates of both genetic and environmental influences may be biased, and findings are unlikely to generalise across more diverse populations. This issue is particularly critical for genetically informed designs, as polygenic scores derived from European ancestry GWAS demonstrate lower predictive validity in non-European ancestries (Duncan et al., 2019). While this limitation does not undermine the internal validity of the GAPS models presented here, it nevertheless highlights the need for more diverse, non-Eurocentric genotyped samples to enhance the accuracy and generalisability of polygenic scores in global populations, while also advancing equity in genomics research (Mills et al., 2020).

Third, the PGSs in this study (apart from the childhood BMI PGS derived by the CLS) were constructed from adult-based GWAS due to the lack of available GWAS focused on childhood psychopathology. For example, the depression PGS I calculated was based on the Psychiatric Genomics Consortium's largest GWAS meta-analysis of adult major depression available at the time of this study (Adams et al., 2025). Moreover, given that large-scale GWAS for suicide attempt have only recently reached sufficient power for PGS construction (Docherty et al., 2023), this study is one of the first to investigate whether genetic liability to suicide attempt is associated with exposure to specific ACEs, an area that remains relatively underexplored in the

literature. However, PGSs constructed from adult-based GWAS may not fully capture genetic influences on early-onset mental health conditions. This highlights the need for future GWAS efforts that specifically target child and adolescent psychopathology using large, diverse, longitudinal youth cohorts. As GWAS sample sizes and diversity steadily increase, future PGSs will likely capture more genetic variance and improve the precision of genetically adjusted estimates.

Finally, although the GAPS approach accounts for a comprehensive set of measured confounders, the possibility of residual confounding from unmeasured genetic or environmental factors can never be fully eliminated. This reflects an inherent limitation underlying all observational research; findings should therefore be interpreted as strengthening, rather than definitively establishing, causal inference. In future research, I plan to include a wider range of PGSs to capture more genetic confounding: specifically, polygenic scores for schizophrenia, ADHD and autism, which have been shown to influence exposure to ACEs and psychopathology (Baldwin, Sallis, et al., 2023; Ratanatharathorn et al., 2021; Warrier & Baron-Cohen, 2021).

Importantly, while constrained by available data, I demonstrated how the GAPS approach can strengthen causal inference: GAPS effect sizes were attenuated and more precise compared to the non-genetically adjusted or PGS-only propensity score models, elucidating the extent to which both genetic and environmental confounding shape the observed associations between ACEs and psychopathology. Moreover, it is reassuring that the triangulation of my findings with other distinct, family-based quasi-experimental approaches supported a consistent pattern overall: emotional neglect and victimisation adversities remained consistent predictors of psychopathology independent of measured confounding, whereas household-level ACEs appeared to be primarily linked to psychopathology via pre-existing genetic and environmental vulnerabilities.

Overall, this study has important implications for research and practice. It is essential that researchers account for genetic confounding when examining the potentially causal relationships between ACEs and mental health. Given the gene-environment correlations observed for each

ACE in this study, there is a risk that neglecting the shared genetic influences between ACE exposure and psychopathology may lead to inflated estimates of environmental effects and misdirected conclusions about modifiable risk factors. As demonstrated by my phenotypic PSM and GAPS analyses, even well-designed observational studies employing robust causal inference techniques may still overestimate causal effects if underlying genetic liabilities are not accounted for. The GAPS approach provides a powerful tool for disentangling the potentially causal effects of adversity exposure from measured gene-environment confounding, and future studies should continue integrating genetically sensitive designs within causal inference frameworks to yield more robust and accurate estimates.

Regarding policy and practice, my findings reinforce the critical importance of preventing and intervening on adverse childhood experiences. Emotional neglect, as well as emotional, physical, sexual, and peer victimisation were among the ACEs with the most robust associations across all adolescent psychopathology outcomes, suggesting that primary prevention efforts should focus on safeguarding children from these specific adversities. My findings regarding the presence of genetic and environmental confounding in household-level ACEs do not imply these adversities are negligible; rather, they indicate that interventions may be more effective when they address the broader context of family dysfunction and other co-occurring risk factors through holistic approaches, such as the socioecological systems framework (Austin et al., 2020; Bronfenbrenner, 2000). Moreover, ACEs that may be genetically confounded (e.g., parent mental health problems) could benefit from targeted secondary prevention efforts that support both parents and children (e.g., parent-child interventions and accessible family mental health care). Overall, my findings point to the value of a multi-pronged approach – reinforcing primary prevention efforts to reduce direct child-targeted ACEs, along with tailoring secondary interventions for genetically vulnerable children within their broader socioecological contexts.

5 Discussion

This thesis aimed to strengthen causal inference in understanding the relationship between childhood adversity and adolescent psychopathology. Despite the wealth of research demonstrating associations between adverse childhood experiences (ACEs) and psychopathology, (1) there is no universal paradigm to operationalise ACEs, (2) the extent to which these associations are confounded by pre-existing vulnerabilities remains uncertain, and (3) addressing genetic confounding represents an ongoing challenge. To address these research gaps, (1) **Chapter 2** demonstrated how ACEs can be meaningfully operationalised as data-driven dimensions, (2) **Chapter 3** used quasi-experimental methods to strengthen causal inference about the effects of individual ACEs on psychopathology outcomes, and (3) **Chapter 4** accounted for measured genetic confounding using a novel genetically informed design. In the following sections, I summarise the main findings of each empirical chapter, then discuss the implications, strengths, and limitations of this thesis, and finally outline future research directions.

5.1 Summary of empirical chapters

In **Chapter 2**, I used an exploratory data-driven approach to examine whether there were meaningful dimensions of childhood adversity across two longitudinal cohorts, the UK Millennium Cohort Study (MCS) and the US Adolescent Brain Cognitive Development Study (ABCD). Existing research has often relied on confirmatory approaches that impose *a priori* categorisations of ACEs, introducing bias and potentially obscuring patterns from the data. By replicating a preregistered exploratory factor analysis without pre-defined dimension categories, I found that ACEs converged across the two distinct populations as common underlying dimensions of parental threat, deprivation, and victimisation. The consistency of these dimensions, despite the sociodemographic and measurement differences between the UK and US populations, suggests that these dimensions are meaningful and not sample-specific. In both populations, parental drug and alcohol use clustered with other parental threat-related ACEs, low household income and lack of neighbourhood safety loaded onto the deprivation dimension, and multiple

forms of interpersonal victimisation clustered together. However, two instrument-specific dimensions were unique to each cohort: parental discipline in the MCS and traumatic events in the ABCD, highlighting how data-driven dimensions of adversity may nonetheless be partially driven by shared method variance. Notably, I found that victimisation emerged as the strongest predictor of internalising and externalising psychopathology over the other dimensions, underscoring the particularly harmful influence of interpersonal victimisation on adolescent mental health compared to other adversities. My findings expand dimensional theories of adversity by suggesting that in addition to threat and deprivation, victimisation is a distinct dimension of adversity that demonstrates the strongest associations with adolescent psychopathology. Having established in Chapter 2 that some dimensions were more strongly associated with psychopathology than others, Chapter 3 shifted the focus to specificity by examining which individual adversities might be driving these associations.

In **Chapter 3**, I applied propensity score matching (PSM) to strengthen causal inference about the relationships between ten individual ACEs and adolescent psychopathology. Leveraging the rich phenotypic data from the MCS, I used PSM to balance participants on pre-exposure confounders spanning the prenatal, infancy, and early childhood periods, approximating conditional exchangeability between ACE-exposed and unexposed groups. The associations for all ten ACEs across all psychopathology outcomes were attenuated by approximately 30–80% in the fully adjusted PSM models, suggesting that many of the observed associations in my unadjusted, unmatched models – and in prior non-quasi-experimental research – were likely to be confounded by pre-existing individual, familial, and sociodemographic vulnerabilities. Applying the specificity approach revealed that certain ACEs (particularly emotional victimisation, sexual victimisation, and emotional neglect) were the strongest predictors of psychopathology across all outcomes. Emotional victimisation emerged as the most potent predictor of depression and anxiety symptoms, with a fourfold increase in high distress and self-harm, and a fivefold increase in suicide attempt. Emotional neglect and sexual victimisation also displayed substantially elevated

psychopathology risks, highlighting the particularly severe mental health impact of targeted, interpersonal adversity. In contrast, family-level ACEs such as divorce, bereavement, domestic violence, and parent substance use no longer predicted adolescent psychopathology after adjusting for confounders, suggesting these relationships may reflect confounding by pre-existing vulnerabilities. In sum, Chapter 3 provides robust quasi-experimental evidence that certain ACEs have particularly potent and potentially causal links with adolescent psychopathology, while other adversities appear more confounded by broader contextual risk factors. This underscores the need for future research and interventions to be guided by ACEs conferring the most robust associations with psychopathology, while also addressing the underlying vulnerabilities associated with more confounded adversities. These findings provided the foundation for Chapter 4, in which I integrated polygenic scores into PSM to account for measured genetic confounding.

In **Chapter 4**, I extended the phenotypic quasi-experimental framework of Chapter 3 to address residual genetic confounding using the novel method of genetically adjusted propensity score (GAPS) matching, which integrates polygenic scores alongside phenotypic covariates in the propensity score. After deriving and validating polygenic scores for psychopathology (i.e., depression, anxiety, and suicide attempt) in the MCS cohort, I found that children with elevated genetic liabilities for psychopathology were more likely to experience interpersonal victimisation and family dysfunction, supporting evidence for gene-environment correlation. After accounting for measured genetic and environmental liabilities, I found that the ACEs with the most robust associations with psychopathology were those that involved direct, interpersonal harm: specifically, emotional neglect and emotional, physical, sexual, and peer victimisation, consistent with Chapter 3. In contrast, ACEs reflecting household dysfunction (e.g., parent substance use, divorce, domestic violence) displayed largely non-significant associations in the phenotypic and GAPS models, reinforcing the notion that their associations with psychopathology were likely to be genetically and environmentally confounded. Notably, the associations between parent mental health problems and adolescent psychopathology were largely diminished in the GAPS models,

juxtaposing the significant associations displayed in Chapter 3's phenotypic PSM models. While this pattern may reflect sample differences between the full imputed cohort in Chapter 3 and smaller genotyped subsample in Chapter 4, this finding suggests that the observed associations between parent and child psychopathology are likely to be genetically confounded, as further emphasised by the gene-environment correlations observed in this study. Altogether, Chapter 4 increases our understanding of how different ACEs are linked to adolescent mental health: while some adversities demonstrate robust and likely causal relationships with psychopathology (e.g., victimisation and emotional maltreatment), others appear more influenced by genetic and environmental confounding (e.g., household dysfunction adversities), and some may largely reflect hereditary vulnerabilities (e.g., parent mental health problems). These distinctions provide implications for intervention and prevention strategies which I discuss in the following section.

5.2 Theoretical and practical implications

The findings from this thesis advance our understanding of how childhood adversity shapes adolescent psychopathology, with several important implications for research and practice. First, this thesis has implications for improving the way that we operationalise ACEs. By demonstrating that distinct dimensions of ACEs were differentially associated with internalising and externalising psychopathology, **Chapter 2** provides empirical support for moving beyond the cumulative risk model of operationalising adversity towards a data-driven, multi-dimensional approach. Evidently, ACEs do not contribute to psychopathology in equivalent ways, and collapsing them into a single cumulative score risks obscuring their distinct effects. When deriving dimensions of adversity, my findings suggest that researchers should apply data-driven methods instead of approaching the data with pre-defined categories that may obscure the underlying naturally occurring patterns. Although conceptual models such as DMAP are undoubtedly valuable in elucidating how childhood adversity influences developmental psychopathology, the over-reliance on *a priori* constructs may constrain the possible explanations that the data can reveal (Smith & Pollak, 2021). My application of exploratory factor analysis is one effective example of

how data-driven methods can reveal meaningful dimensions of adversity across populations, and other data-driven approaches (e.g., latent class analysis or network analysis) can likewise provide informative insights (Lacey & Minnis, 2020; Lian et al., 2022; Sheridan et al., 2020). Nevertheless, data-driven approaches are not infallible as they remain susceptible to measurement biases, such as shared method variance. ACEs measured by the same instrument, and reported by the same person, are likely to converge together, as seen with the parental discipline dimension in the MCS, and the traumatic events dimension in the ABCD (Chow et al., 2025). This methodological issue is difficult to elude in secondary datasets, where researchers are ultimately constrained by the available measures. However, shared method variance can be mitigated by combining reports across time points, multiple informants (e.g., parent, teacher, child), and data sources (e.g., interviews, questionnaires, official records). Such strategies can help to disentangle meaningful patterns from measurement artefacts and reduce bias from relying on a single measuring instrument. If future studies continue to derive meaningful dimensions such as threat, deprivation, and victimisation across populations in spite of shared method variance and different data-driven approaches, this will further strengthen their empirical and external validity.

While **Chapter 2** contributes to the literature by demonstrating the value of operationalising ACEs as data-driven dimensions, a more critical implication lies beyond determining the best statistical technique. Regardless of whether an exploratory or confirmatory approach is applied, ACEs consistently cluster together in meaningful dimensions to influence psychopathology in distinct ways (Brieant et al., 2023; Chow et al., 2025; Sisitsky et al., 2023), and these dimensions should be addressed in research and practice. First, research should clarify the individual ACEs within each dimension that are causally related to psychopathology, as I demonstrated using the specificity approach in **Chapters 3 and 4.** If evidence for causality is found, research should then examine the potential mechanisms for each ACE, and test whether ACEs within the same dimension share the same underlying mechanisms as the DMAP framework suggests. DMAP-informed research suggests that threat-based ACEs are linked to

psychopathology via heightened stress-response circuitry and emotional dysregulation, whereas deprivation-based ACEs are associated with diminished prefrontal cortex volume and impaired executive functioning (Lambert et al., 2017; Machlin et al., 2019; McLaughlin et al., 2019). As my findings demonstrated that victimisation emerged as the dimension with the strongest associations with psychopathology, future studies should investigate whether victimisation ACEs influence psychopathology through distinct mechanistic pathways than threat and deprivation. Outside of the dimensional framework, neuroimaging evidence suggests that peer victimisation may increase psychopathology risk via structural decreases in putamen and caudate volume (Quinlan et al., 2020), with victimised youths displaying heightened activation in neural regions implicated in social rejection, risk-taking, and reward processing (Ke et al., 2022). However, a large proportion of the neuroimaging evidence on adversity mechanisms is cross-sectional and thus cannot infer causality (Ke et al., 2022; McLaughlin et al., 2019). Moreover, the neurocognitive pathways of threat versus deprivation have been criticised for their lack of specificity, as the heightened amygdala-prefrontal circuitry typically associated with threat has also been observed after experiences of deprivation (Gee et al., 2013; Smith & Pollak, 2021; VanTieghem & Tottenham, 2017). Thus, longitudinal studies are needed to determine whether the neurocognitive pathways through which ACE dimensions influence psychopathology are orthogonal or non-independent, as well as to investigate critical periods for intervention and how these pathways can be targeted to improve developmental outcomes.

If research evidence supports distinct neurocognitive mechanisms, then therapeutic interventions could be tailored according to ACE dimensions. For example, if threat-based ACEs (e.g., abuse) are found to increase psychopathology via impaired fear processing and emotional dysregulation, treatments could help victims to process trauma, regulate emotions, and unlearn hypervigilance and hostile attributions. One such feasible approach is Trauma-Focused Cognitive Behavioural Therapy (TF-CBT) (de Arellano et al., 2014). If deprivation-based ACEs (e.g., neglect) are found to increase psychopathology via maladaptive attachment and diminished executive

functioning, interventions could address disrupted attachment styles, foster cognitively stimulating environments, and strengthen executive functioning skills. This may be achieved through home-visiting programs such as the Attachment and Biobehavioural Catch-up, which aims to enhance parental sensitivity and children's attachment security (Dozier & Bernard, 2017). Furthermore, if victimisation-based ACEs are found to increase psychopathology via cognitive distortions of rejection, individual-level CBT could be tailored towards victims with a focus on improving rejection sensitivity, self-esteem, and coping skills (Ke et al., 2022; Lydecker, 2022).

As the presence of one ACE significantly increases the risk of other additional ACEs (Dong et al., 2004), policies and interventions should also focus on targeting the most recurrent, harmful clusters of adversities that tend to co-occur together in the population. Crucially, specific pairings of ACEs can amplify risk in maladaptive, synergistic ways; for instance, sexual abuse has been termed 'the most synergistically reactive ACE' as the pairing of sexual abuse with other ACEs is associated with disproportionately worse psychopathology outcomes (Briggs et al., 2021; Putnam et al., 2020). Once again, these patterns challenge the cumulative risk model, which posits that each additional ACE has an equal impact on health outcomes. My findings from **Chapter 3 and Chapter 4** align with the literature on synergistic adversities, as sexual victimisation emerged as one of the most potent predictors of psychopathology. However, I also found that emotional victimisation demonstrated the strongest associations with psychopathology independent of measured genetic and environmental confounding, closely followed by emotional neglect. This suggests that, at least when examined in isolation in the MCS cohort, the individual impact of emotional maltreatment may surpass that of sexual victimisation. As ACEs rarely occur in isolation, future research could compare the synergistic combinations of 1) emotional maltreatment and sexual abuse, 2) emotional maltreatment and other adversities, and 3) sexual abuse and other adversities in prospective longitudinal datasets. Moreover, as existing synergistic literature has largely employed non-quasi-experimental designs (Briggs et al., 2021), future research should investigate the most prevalent and harmful synergistic ACEs using causal inference methods. A

better understanding of synergistic adversities – particularly after accounting for genetic and contextual vulnerabilities – will inform practitioners in clinical settings on how best to treat victims of synergistic ACEs, who are likely to exhibit disproportionately worse mental health symptoms that require tailored treatment and additional support.

In **Chapters 3 and 4**, I applied the specificity approach to operationalise ACEs. This revealed emotional maltreatment (i.e., emotional victimisation and neglect) and interpersonal victimisation as the strongest predictors of adolescent psychopathology across all outcomes, with robust associations maintained even in the most stringent, genetically adjusted quasi-experimental models. In contrast, household dysfunction adversities (e.g., parental substance use, divorce, domestic violence) were no longer significantly associated with psychopathology after adjusting for measured genetic and environmental confounding. Future research should continue applying genetically informed quasi-experimental methods to investigate this distinction further, such that findings can be triangulated across different designs to strengthen causal inference. For example, regarding direct child-targeted adversities, potential causal links with psychopathology have been similarly reported for child abuse, neglect, and victimisation in meta-analyses of genome-wide association studies, family-based studies, and other quasi-experimental designs (Baldwin, Wang, et al., 2023; Schoeler et al., 2018; Warrier et al., 2021). Regarding indirect household-level adversities, genetically confounded associations with psychopathology have likewise been found for parental substance abuse, divorce, and criminality in genetically sensitive and family-based studies (Baldwin, Sallis, et al., 2023; D'Onofrio et al., 2007; Kendler et al., 2016; Waldron et al., 2009).

Notably, in **Chapter 4**, I found that the associations between parent mental health problems and adolescent psychopathology were largely diminished after accounting for genetic and environmental confounding in the GAPS analysis. These findings contrast evidence from family-based studies which have generally shown environmentally transmitted pathways between parental depression and anxiety to offspring psychopathology, independent of genetic

confounding (Ahmadzadeh et al., 2021; Eley et al., 2015; Jami et al., 2021; McAdams et al., 2015; Silberg et al., 2010; Tully et al., 2008). However, shared method variance may have inflated previous estimates of intergenerational associations, as many of these family-based studies used parent reports on both their own and their offspring's mental health symptoms (Ahmadzadeh et al., 2021). Given that the relationship between parent and offspring mental health is bidirectional (Jami et al., 2021; Pérez-Edgar et al., 2021), it is also possible that adjusting for child polygenic scores for psychopathology may have attenuated the associations in my GAPS analysis. Nevertheless, my findings suggest that, at least in the predominantly White genotyped MCS subsample, parent-child psychopathology associations were largely confounded by pre-existing genetic vulnerabilities. Since my study represents a first novel application of GAPS to study childhood adversity, future studies should replicate the GAPS approach on larger, more ancestrally diverse populations to ascertain whether the relationship between parent and child psychopathology is genetically or environmentally transmitted, or perhaps a combination of both.

Taken together, the findings from my thesis and current quasi-experimental evidence suggest a likely causal relationship between direct child-targeted ACEs and mental health problems, whereas indirect household-level ACEs may be more confounded by pre-existing genetic and contextual vulnerabilities. This distinction between direct child-targeted adversities and indirect household-level adversities has theoretical and practical implications. Given their likely causal contributions to psychopathology, future research should clarify the mechanisms through which emotional maltreatment and victimisation ACEs shape pathways to depression, anxiety, self-harm, and suicidality. It is especially critical for research to identify the mechanisms which underlie the progression from suicide ideation to attempt in order to predict and prevent fatal suicide attempts (Kirshenbaum et al., 2024). Additionally, the distinct impacts of emotional abuse and neglect should be explored further, given that emotional abuse and neglect are typically aggregated together as a maltreatment composite in ACE literature (Sayyah et al., 2022; Thornberry et al., 2010; Westermair et al., 2018). Emerging evidence suggests that emotional neglect may impair

emotional clarity (i.e., the ability to identify one's own emotions) more so than emotional abuse, which may in turn increase the risk of depression in adolescence (Jessar et al., 2017). Such mechanisms could be targeted in therapeutic treatments for emotional neglect.

Given the large proportion of confounding observed in household-level ACEs, research should focus on disentangling the most prevalent and modifiable contextual risk factors (e.g., socioeconomic deprivation) that co-occur with household dysfunction adversities (e.g., parent substance use) to better inform policy and intervention design. In this thesis, I conceptualise deprivation as a dimension of adversity within the DMAP framework, while also recognising it as a structural condition that shapes exposure to adversity. Even within DMAP, deprivation reflects an overarching structural absence of cognitive and socioeconomic inputs in a child's environment (McLaughlin & Sheridan, 2016), rather than a discrete adversity. Socioeconomic deprivation is a global systemic issue that repeatedly places vulnerable populations at higher risk of ACE exposure (Madigan et al., 2023; Walsh et al., 2019). Deprivation operates upstream of ACEs by exacerbating stress pathways, limiting access to protective resources (e.g., healthcare, education, transport, greenspace), and heightening exposure to environmental and social hazards (e.g., alcohol availability, crime, pollution, fast food consumption) (Schroeder et al., 2022). In these ways, deprivation produces and amplifies the conditions in which household dysfunction ACEs become more likely, more severe, and less avoidable (Walsh et al., 2019). Recognising deprivation as a structural determinant of ACEs highlights the need for upstream policy and intervention responses that directly address socioeconomic inequalities. Interventions which focus solely on individual-level therapeutic support, while beneficial and important, may not substantially reduce the prevalence of ACEs if families continue to live in chronic poverty, housing instability, and under-resourced communities. Increasing access to community resources (e.g., housing, transportation, childcare services) has the potential to mitigate the association between household poverty and cumulative ACE exposure; for example, simply providing universal access to transportation could eliminate approximately 21% of the income-based inequality for children experiencing three or

more ACEs (Blair et al., 2019). Therefore, evidence for contextual confounding underscores the necessity to shift towards upstream prevention and address the heritable, social, and structural vulnerabilities that engender childhood adversity in the first place.

In **Chapter 4,** I also found evidence supporting gene-environment correlation (rGE), where children with elevated genetic liabilities for psychopathology (specifically, depression, anxiety, and suicide attempt) were more likely to experience interpersonal victimisation and family dysfunction. For interpersonal victimisation, this may reflect evocative rGE; for example, children who are genetically prone to depression may appear withdrawn or become upset easily, increasing their susceptibility as targets for victimisation. On the other hand, rGE may be passive for family dysfunction ACEs, where children receive both the genetic predisposition and the adverse rearing environment predisposing them to psychopathology from their parents (Rice et al., 2013). Emerging methods such as family trio designs (i.e., examining within-family polygenic scores) can be implemented to distinguish between passive and evocative rGE (Baldwin, Sallis, et al., 2023). For example, if the child's PGS for a mental health outcome predicts ACE exposure after controlling for their parents' PGS, this is indicative of evocative rGE (Sallis et al., 2021). In contrast, if the parents' PGS predicts the ACE after controlling for the child's PGS, this would likely indicate passive rGE (Warrier et al., 2021).

Evidence for gene-environment correlation does not imply that certain ACEs are genetically determined or inevitable, nor does evidence for genetic confounding diminish the necessity of intervening on indirect household-level adversities. Rather, these findings highlight the need for policies and interventions that recognise and respond to both heritable vulnerabilities and environmental risk. This could include improving access to high-quality mental healthcare for families with a history of psychiatric difficulties and implementing policies that aim to break the intergenerational cycle of adversities. For example, two-generation programmes offer coordinated services for parents (e.g., parenting skills, cash transfers) and children (e.g., childcare, early

education) to promote the psychological and economic wellbeing of vulnerable families (Sommer et al., 2024). Researchers have also advocated for pre-parenting psychotherapy in individuals with a history of ACEs to minimise the intergenerational transmission of childhood adversity (Linden & LeMoult, 2022). The manifestation of heritable vulnerabilities in families may also be mitigated by early intervention programmes. For example, quasi-experimental evidence has shown that the Incredible Years Program, originally designed for children at risk for conduct problems, significantly reduced harsh parenting in parents who self-reported a history of child maltreatment (Hurlburt et al., 2013), and increased the probability of case closure by 43% in child protection services for child neglect (Leclair Mallette et al., 2021). A randomised trial of the Nurse-Family Partnership, targeted at low-income unmarried mothers, found that those who received nurse home visits during pregnancy and infancy had fewer verified reports of child abuse and neglect compared to the comparison group (Olds et al., 1997). Importantly, I underscore that the ethical framing of heritable vulnerabilities is sensitive and must be handled delicately. It is crucial that the ACE is never placed upon the child as his or her responsibility, nor should the evidence be used to implicate parents; instead, the emphasis should be on the adverse *conditions* – genetic, social, and structural – that ultimately give rise to ACEs (Kelly-Irving & Delpierre, 2019).

In sum, the findings from my thesis support the call for a multi-pronged prevention and treatment approach to prevent, mitigate, and treat childhood adversity, with the idea that the prongs are complementary and should be run in parallel (Linden & LeMoult, 2022). A multi-pronged approach entails: (1) universal primary prevention to reduce exposure to ACEs such as whole-school anti-bullying interventions (Bowes et al., 2024) and population-level policies that strengthen parenting, childcare, and economic support for families (Ottley et al., 2022), (2) secondary prevention and intervention for at-risk groups like home visiting programmes (Dozier & Bernard, 2017; Olds et al., 1997), and (3) tertiary treatments that are accessible and evidence-based, for example, trauma-focused CBT (de Arellano et al., 2014). Considering my findings within this multi-pronged framework, policies and interventions which target emotional maltreatment

and victimisation are most likely to reduce child psychopathology in the population, given that the associations between direct child-targeted ACEs and psychopathology primarily reflect causal pathways. In contrast, tailored secondary strategies should address the pre-existing vulnerabilities in children exposed to more contextually confounded household-level ACEs in order to improve child welfare, family functioning, and developmental outcomes.

5.3 Strengths and limitations

The specific strengths and limitations of each empirical study have already been discussed in their respective chapters (**Discussion 2.5, 3.5, and 4.5**). In this section, I review the general strengths and limitations of this thesis. With regard to strengths, first, this thesis benefits from the use of prospectively reported longitudinal measures in two large, nationally representative cohorts: the UK MCS and US ABCD Study. By observing the same group of participants repeatedly over time, longitudinal studies strengthen causal temporality, i.e., the fundamental concept that a cause (e.g., ACE) must precede its effect (e.g., psychopathology) in chronological time (Hernán & Robins, 2024). The MCS and ABCD provided rich, in-depth information on individual, familial, and sociodemographic factors, which I leveraged to construct a multifaceted examination of childhood adversity and adolescent psychopathology. To enhance the reliability of my measures, I used prospective reports which minimised recall bias, combined multi-informant reports where available, and imputed missing data to mitigate bias from participant attrition.

Second, a major strength of this thesis is the application of data-driven, quasi-experimental, and genetically informed methods. The methodological rigour of these advanced statistical techniques strengthens the validity of my findings and contributes to advancing the field of ACE research. In particular, this thesis offers a novel contribution to the literature by applying GAPS matching to strengthen causal inference about the effects of individual ACEs on adolescent psychopathology – a method which, to my knowledge, has not been used to study childhood adversity until the present thesis. Future studies can continue applying GAPS matching to

unrelated individuals in large-scale population cohorts such as the MCS, increasing the statistical power and generalisability of results beyond traditional family-based designs (e.g., twin and children of twins studies) while strengthening causal inference.

Third, this thesis carries out open science practices including preregistration, coding all analyses in the open-source R programming language, and publishing analysis code on a public GitHub repository. Such practices help to enhance research transparency, combat questionable research practices such as p-hacking, and promote overall reproducibility of scientific research (Nelson et al., 2018; Nosek et al., 2018). Reproducibility is a particularly critical issue when utilising publicly available secondary datasets, and there is a need for better data harmonisation across cohort studies (Adhikari et al., 2021). Even within the same dataset, subjective practices in defining ACE measures can result in inconsistent dimensions of adversity across studies (Awada et al., 2023; Sisitsky et al., 2023). Thus, my publicly available code to derive ACE measures in the MCS and ABCD will be conducive to improving reproducibility across both cohorts.

While this thesis advances our understanding of how childhood adversity shapes adolescent psychopathology, the findings should be interpreted within the context of its limitations. A primary limitation is this thesis did not test for timing effects, as not all ACEs were assessed consistently across all time points (e.g., in the MCS, most victimisation ACEs were assessed from age 14 onwards, whereas other ACEs were assessed from age 9 months or 3 years onwards). However, the timing of ACE exposure may influence the degree of psychopathology risk. For instance, a recent MCS study which examined ACEs with consistent timing data (i.e., parent mental health problems, domestic violence, divorce, parental substance use, smacking, and bullying) found that ACE exposures in early childhood (9 months to 5 years) and adolescence (11 years) were more strongly associated with depression and self-harm than exposures in middle childhood, i.e., age 7 (Farooq et al., 2024). However, as the study by Farooq et al. (2024) did not account for genetic confounding or control for other co-occurring ACEs, causality cannot be inferred. Future

research should use quasi-experimental methods to explore how the timing of ACE exposure impacts mental health outcomes, as this can better inform researchers and clinicians on potential sensitive periods which should be targeted in treatments and interventions. Statistical techniques such as G-methods offer a promising avenue to understand time-varying effects within a causal inference framework (Naimi et al., 2017).

Another limitation of this thesis is that its findings, while reflective of the contemporary UK and US contexts, are not representative of the global population. ACE research has historically studied Western, educated, industrialised, rich, and democratic (WEIRD) samples (Henrich et al., 2010), with more than 90% of the literature dominated by studies conducted in North America or Europe (Madigan et al., 2023). Critically, while ACEs are recognised as a global issue, there is a significant knowledge gap on the prevalence and health impact of ACEs in non-Western, low- and middle-income countries (Sawyer et al., 2024). As discussed in **Chapter 4**, there is a similar dearth of non-European representation in genetic studies (Duncan et al., 2019). To truly understand ACEs as a universal public health issue, it is necessary for ACE research to move towards non-Western-centric contexts and include more diverse ethnic and socioeconomic populations. With tools such as the Atlas of Longitudinal Datasets (Arseneault, 2025), researchers can discover a wide variety of datasets from around the world to achieve this goal.

Additionally, the MCS and ABCD are low-risk cohorts, where most participants (fortunately) reported relatively low rates of abuse and neglect. The underrepresentation of children with more severe adverse experiences in this thesis limits the extrapolation of findings to high-risk individuals from minoritised and underprivileged backgrounds, who are most likely to experience poly-adversity (Le et al., 2016; Madigan et al., 2023). However, high-risk families are often difficult to retain in longitudinal studies due to challenges such as unstable living conditions, limited transportation, and fear of legal repercussions (Graziotti et al., 2012), although in certain instances cohorts that oversampled high-risk families have achieved high retention, such as the E-

Risk Longitudinal Twin Study (Fisher et al., 2015). Research has also highlighted the genetic risk for dropout in longitudinal studies, demonstrating that higher polygenic scores for depression, schizophrenia, and ADHD were associated with lower participation rates (Taylor et al., 2018). To ensure that ACE research is representative and accurately informs interventions for the individuals who need them most, strategies such as increased incentives, persistent communication, and establishing rapport with vulnerable families have been shown to be effective in improving participant retention (Graziotti et al., 2012).

Finally, while this thesis strengthened causal inference by accounting for measured genetic and environmental confounding within a quasi-experimental framework, residual unmeasured confounding may have nonetheless influenced the observed ACE-psychopathology associations. Unmeasured confounding is an inherent limitation underlying all observational research and addressing it remains an ongoing challenge. The development of methods to mitigate unmeasured confounding is a research field in itself, with methods ranging from classic randomisation to more innovative strategies such as propensity score methods, regression discontinuity designs, and instrumental variable analysis (Streeter et al., 2017). Thus, it is important that researchers continue to (1) implement such techniques to ensure that credible inferences of causality are being drawn from observational research, and (2) triangulate across quasi-experimental designs as findings that converge across methods provide stronger support than findings from any individual method (Baldwin, Wang, et al., 2023; Lawlor et al., 2016; Munafò & Davey Smith, 2018).

5.4 Future research directions

With the main findings and implications of this thesis in mind, I recommend several promising directions for future research to continue advancing our understanding of the relationship between childhood adversity and psychopathology.

1. **Identifying victimisation mechanisms using causal inference methods.** As this thesis found victimisation ACEs to be most strongly associated with adolescent psychopathology,

future research should use causal inference methods to investigate the mechanisms through which victimisation ACEs increase psychopathology risk. For example, causal mediation analysis is ideal for testing hypothesised mediating pathways. It decomposes the total effect of the exposure (e.g., victimisation) into direct and indirect effects within the counterfactual framework (Byeon & Lee, 2023), clarifying how much of the risk is transmitted through a specific mediator (e.g., social withdrawal), thereby providing clear targets for intervention.

2. **Examining synergistic ACEs using causal inference methods.** This thesis revealed emotional maltreatment and sexual victimisation as the strongest predictors of psychopathology, independent of genetic and contextual confounding. However, existing studies on synergistic ACEs have largely used non-quasi-experimental designs (Briggs et al., 2021), limiting their ability to infer causality. Future research should compare the synergistic combinations of emotional maltreatment and sexual victimisation using causal inference methods. For example, propensity score matching could be applied to match individuals on measured confounders, then compare psychopathology outcomes between synergistic (emotional and sexual abuse) and non-synergistic (emotional or sexual abuse only) groups.
3. **Investigating time-varying ACEs using causal inference methods.** To determine if there are sensitive periods (e.g., infancy, early childhood, adolescence) where ACE exposure has a more potent impact on psychopathology, future research could apply G-methods, a class of causal inference techniques specifically designed to account for time-varying exposures and confounders (Naimi et al., 2017). G-methods can be used to investigate timing of ACE exposure (e.g., whether parental substance abuse in early childhood is more predictive of adolescent conduct problems than parental substance abuse in adolescence) while also accounting for time-varying confounders whose influence on the outcome changes over time and is also affected by past exposures (e.g., socioeconomic status).
4. **Replicating the GAPS approach on more diverse populations.** This thesis represents one of the first applications of GAPS to study childhood adversity in a large, longitudinal

cohort; however, it was conducted on a predominantly White genotyped sample. There is a need for future research to apply GAPS on more ethnically diverse, non-Eurocentric populations to produce findings that are globally generalisable.

5. **Shifting from a risk-based to strengths-based approach.** While this thesis focused on studying childhood adversity with an overarching risk-based approach, future research should shift towards a strengths-based approach that investigates protective factors contributing to resilience in the context of adversity. There is growing interest in the concept of positive childhood experiences (PCEs) as counterparts to ACEs, but evidence has so far been correlational (Han et al., 2023). Thus, future studies could investigate the relationships between PCEs and favourable outcomes, amidst or after childhood adversity, using a causal inference framework such as the twin-difference design (Stock et al., 2025).

5.5 Concluding remarks

In conclusion, this thesis advances the literature by demonstrating how ACEs can be meaningfully operationalised as data-driven dimensions and rigorously studied within quasi-experimental, genetically informed frameworks. It showcases the ways in which ACEs cluster together as distinct dimensions with differential links to internalising and externalising psychopathology, and reveals the substantial impact of emotional maltreatment and interpersonal victimisation on adolescent depression and anxiety, psychological distress, self-harm, and suicide attempt. This thesis also demonstrates the presence of genetic and environmental confounding inflating the observed associations between ACE exposures and psychopathology outcomes, highlighting the need for future studies to address such confounding with robust causal inference methods. The findings from this thesis have theoretical and practical implications, such as tailoring interventions according to potential mechanisms underlying ACE dimensions, as well as clarifying the pathways through which emotional maltreatment and interpersonal victimisation give rise to psychopathology. While my findings highlight the importance of identifying ACEs with more robust evidence of causal effects, this does not imply that such ACEs should be prioritised in

isolation or at the expense of other adversities in policy and intervention efforts. ACEs frequently co-occur and interact within broader familial, socioeconomic, and structural contexts; thus, the effectiveness of intervening on any single exposure is likely to depend on wider contextual conditions. Accordingly, policy responses may benefit from targeting modifiable ACEs with stronger causal associations where intervention is feasible, while also developing buffering or resilience-enhancing approaches for ACEs whose associations with psychopathology may be more confounded by contextual risk factors or less amenable to direct intervention. Children with elevated genetic and contextual vulnerabilities may warrant early identification and support, not as a deterministic risk categorisation, but to ensure that protective resources are allocated to those who may be more susceptible to encountering adversity and developing psychopathology, even in the absence of overt harm. Ultimately, my findings support the call for a multi-pronged approach: strengthening universal, primary prevention to reduce exposure to ACEs, while also tailoring secondary interventions and tertiary treatments for vulnerable children within their socioecological contexts. By strengthening causal inference in understanding the relationship between childhood adversity and adolescent psychopathology, this thesis substantiates the necessity of treating childhood adversity as a public health priority to improve child welfare, safeguard children's development, and reduce the overall burden of psychopathology in the population.

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6 Appendices

6.1 Supporting Information for Chapter 2.

Figure 6.1 Flowchart of participants in the Millennium Cohort Study.

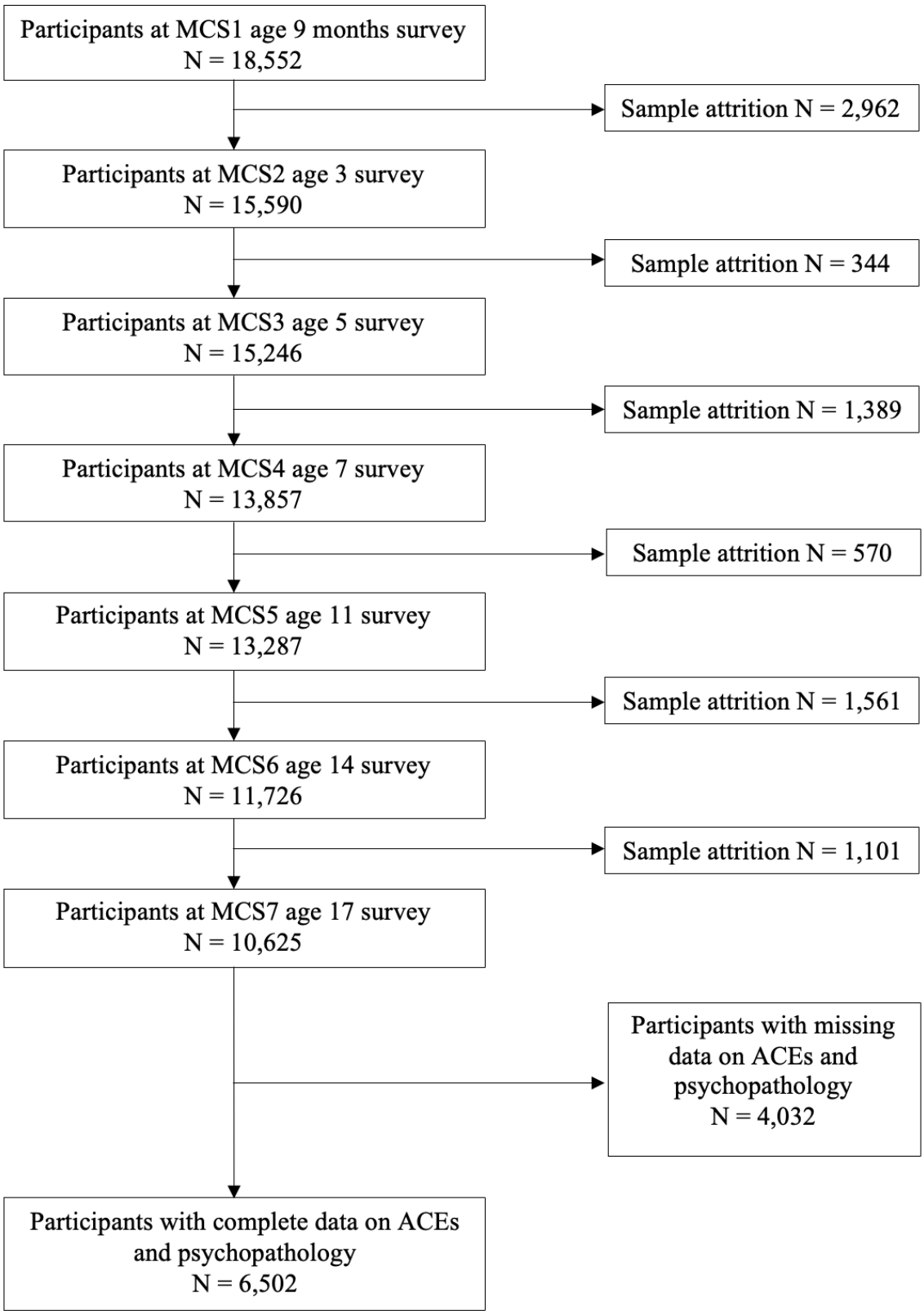


Table 6.1 Missing data per variable before imputation in the MCS.

Variable	*Complete n*	*Missing n*	*Missing %*
Poor parental mental health	18,312	227	1.22
Frequent parental alcohol use	18,521	18	0.10
Parental drug use	15,574	2,965	15.99
Single parent	18,521	18	0.10
Unhappy parental relationship	16,383	2,156	11.63
Domestic violence	16,233	2,306	12.44
Harsh parental discipline	15,163	3,376	18.21
Parental smacking	15,118	3,421	18.45
Negative home environment	13,863	4,676	25.22
Peer victimisation	16,420	2,119	11.43
Verbal victimisation	10,787	7,752	41.81
Physical victimisation	10,786	7,753	41.82
Theft victimisation	10,782	7,757	41.84
Sexual victimisation	10,781	7,758	41.85
Low household income	18,513	26	0.14
Neighbourhood deprivation	17,844	695	3.75
Unsafe home area	16,351	2,188	11.80
Low cognitive stimulation	16,377	2,162	11.66
Internalising symptoms	9,398	9,141	49.31
Externalising symptoms	9,399	9,140	49.30

Figure 6.2 Flowchart of participants in the ABCD Study.

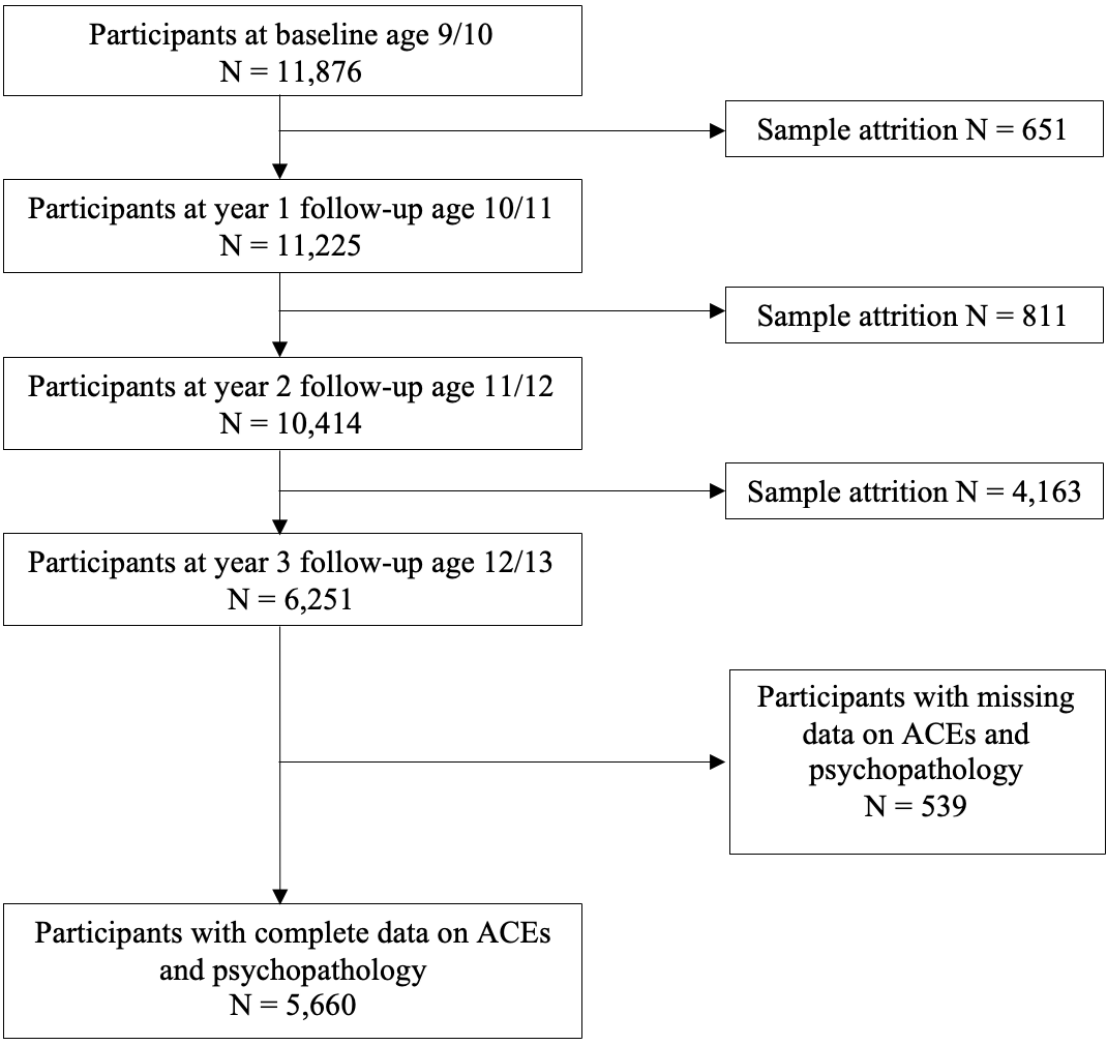


Table 6.2 Missing data per variable before imputation in the ABCD.

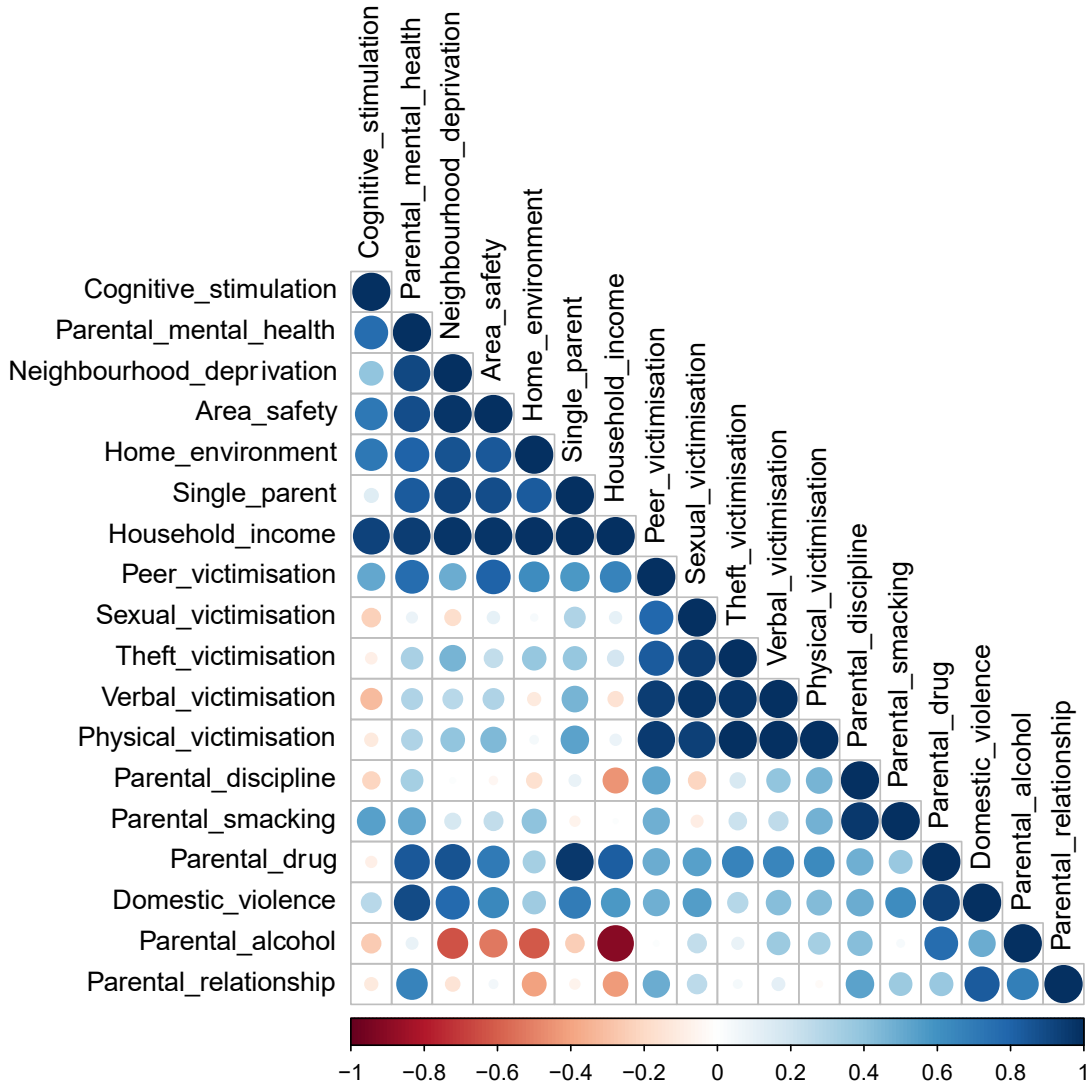
Variable	*Complete n*	*Missing n*	*Missing %*
Physical abuse	11,836	40	0.34
Emotional abuse	11,836	40	0.34
Sexual abuse	11,836	40	0.34
Domestic violence	11,836	40	0.34
Accident requiring medical attention	11,836	40	0.34
Natural disaster	11,836	40	0.34
Community violence	11,836	40	0.34
Bereavement	11,836	40	0.34
Emotional neglect	11,876	0	0
Parental psychopathology	11,784	92	0.77
Parental alcohol abuse	11,876	0	0
Parental drug abuse	11,607	269	2.27
Parental criminality	11,446	430	3.62
Parental separation	11,409	467	3.93
Peer victimisation	10,392	1,484	12.50
Cyber victimisation	10,361	1,515	12.76
Unsafe neighbourhood	11,441	435	3.66
Low household income	10,607	1,269	10.69
Internalising symptoms	6,169	5,707	48.05
Externalising symptoms	6,169	5,707	48.05

6.1.1 Exploratory factor analysis (EFA) on the MCS complete sample.

First, we examined the factorability of the ACE measures. Bartlett's test of sphericity was significant, $\chi^2(153) = 69{,}222.13$, $p<.001$, indicating the presence of patterned relationships among the ACE measures. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was acceptable (KMO = 0.79), indicating the presence of latent factors.

We estimated the tetrachoric correlations among the 18 ACEs and plotted the tetrachoric correlation matrix with hierarchical clustering to group together similar measures. As there are visible clusters of between-measure correlations (e.g., between low household income and neighbourhood deprivation, and frequent parental alcohol use and parental drug use), it is evident there are at least two latent factors underlying the ACE measures (**Figure 6.3**).

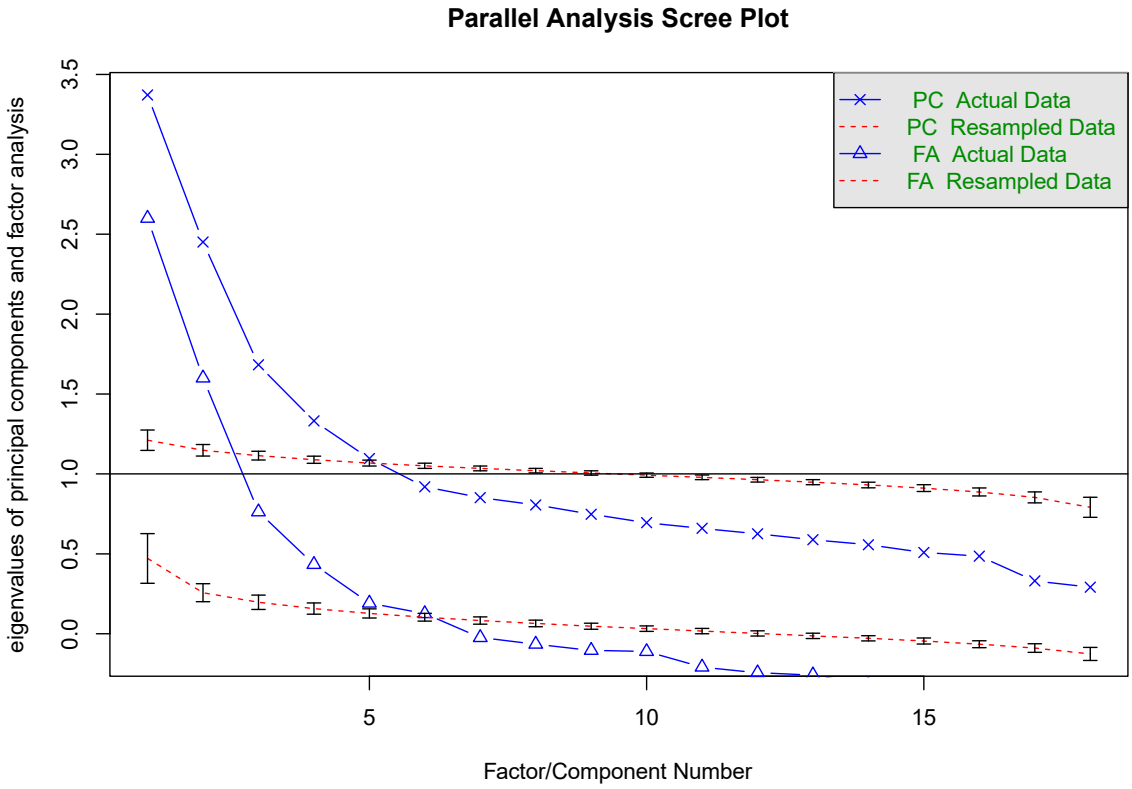
Figure 6.3 Correlation matrix of ACEs in the MCS complete sample.



Note. Darker circles represent stronger correlations (blue for positive, red for negative).

Parallel analysis was used to determine how many factors should be retained in the exploratory factor analysis. We conducted parallel analysis with 1,000 Monte-Carlo simulations for both principal components (PC) and principal axis factoring (FA). As PC is a data reduction method that does not distinguish between shared and unique variance to reveal the underlying factor structure, we consulted the FA solution which recommended the optimal number of factors to retain was five (**Figure 6.4**).

Figure 6.4 Parallel analysis scree plot for the MCS complete sample.



Note. For both PC and FA, there were five factors generated above the 99th percentile (represented as error bars connected by red dashed lines).

Nevertheless, as FA parallel analysis is liable to selecting too many factors, Lim and Jahng (2019) recommended that parallel analysis should be regarded as a guide to factor extraction, not a fixed estimate. Thus, we looked to additional criteria. According to Cattell's scree test (Cattell, 1966), the scree plot indicates three to four factors before the point of inflexion.

Altogether, parallel analysis and Cattell's scree test recommended the extraction of three to five factors. The cumulative risk model assumes that ACEs would load onto a single latent factor, while DMAP proposes that ACEs load onto two factors of threat and deprivation. Thus, we conducted EFA to fit one, two, three, four, and five-factor models.

Model fit indices for one through five-factor models are presented in **Table *6.3***. As predicted by the parallel analysis, the five-factor model had the best fit according to the indices, followed by the four-factor, three-factor, two-factor, and one-factor models.

Table 6.3 EFA fit indices for the MCS complete sample.

Factors	χ^2	RMSEA [90% CI]	RMSR	TLI	BIC	χ^2 *p*-value
1	43735.73	0.132 [0.131, 0.133]	0.12	0.31	42409.00	<.001
2	19078.33	0.093 [0.092, 0.094]	0.07	0.65	17918.67	<.001
3	11399.50	0.077 [0.076, 0.078]	0.05	0.76	10397.08	<.001
4	7404.13	0.067 [0.066, 0.069]	0.03	0.82	6549.12	<.001
5	5431.04	0.063 [0.062, 0.064]	0.03	0.84	4713.62	<.001

Note. RMSEA = root mean square error of approximation; RMSR = root mean square residual (RMSR); TLI = Tucker-Lewis index (TLI); BIC = Bayesian Information Criterion.

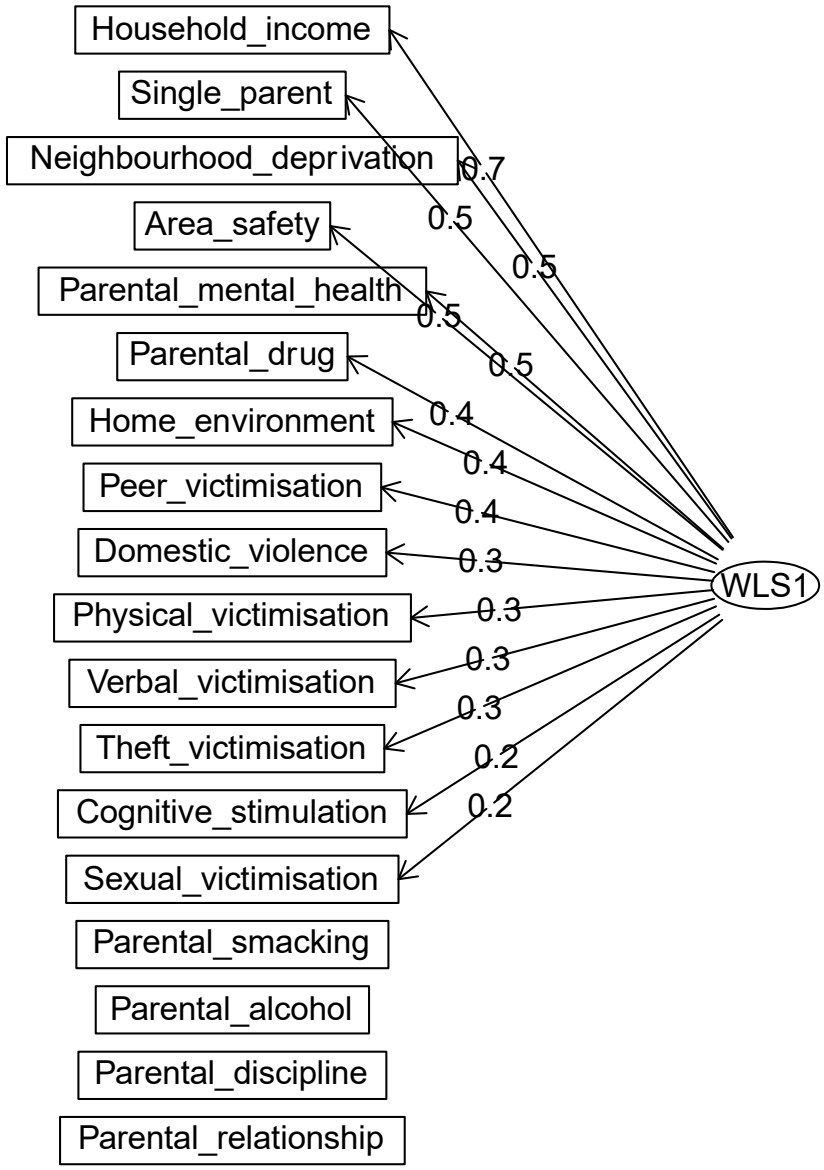
Criteria for a good fit are as follows: RMSEA < 0.06; RMSR < 0.08; TLI > 0.95.

As the likelihood of the model increases, the BIC decreases; thus, a lower BIC indicates better fit.

We evaluated the best fitting model according to absolute and relative fit indices (RMSEA < 0.06, RMSR < 0.08, and TLI > 0.95 indicated good fit; Hu & Bentler, 1999). We also considered if the best fitting model had the "cleanest" factor structure: factor loadings equal to or more than 0.30, with no or few item cross loadings (Costello & Osborne, 2005).

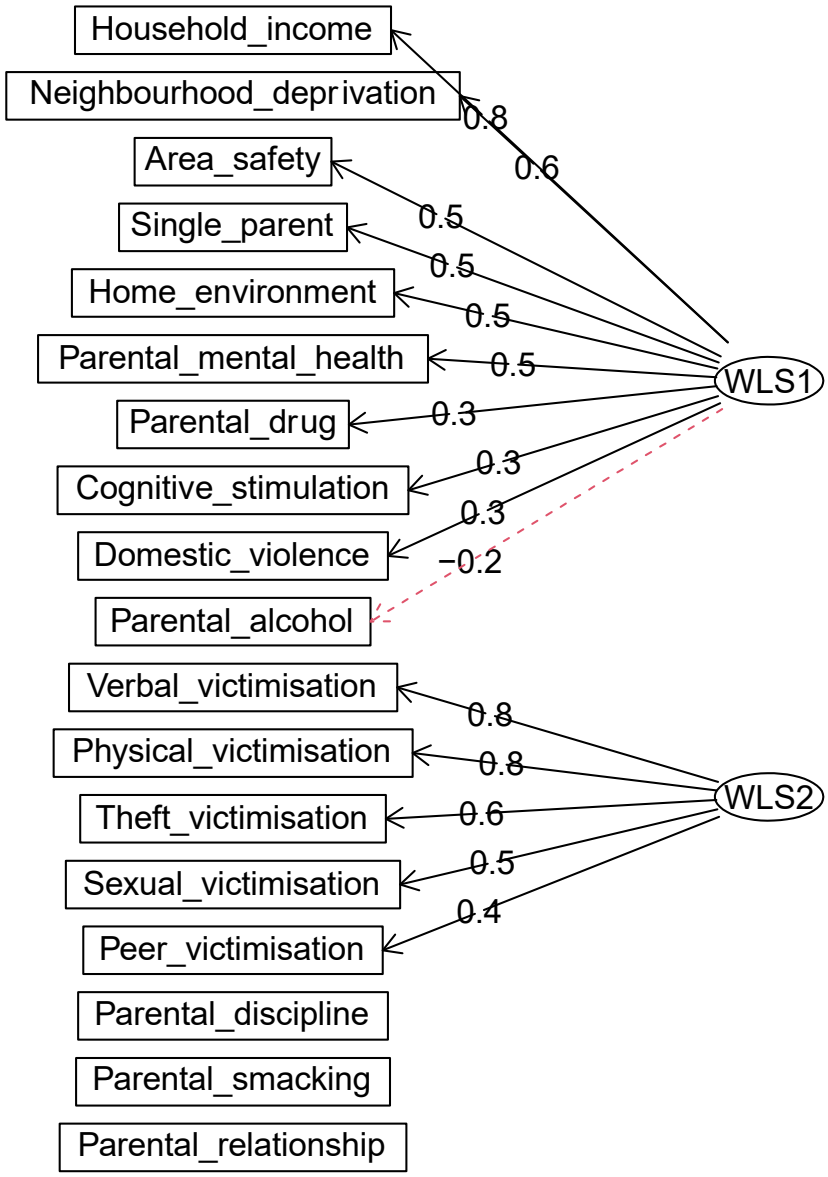
Overall consideration of the fit indices and factor structure suggested the four-factor model fit the MCS data optimally. The four factors were labelled deprivation, victimisation, parental threat, and parental discipline. After selecting the optimal model, we extracted factor scores and tested the associations between each factor and adolescent psychopathology.

Figure 6.5 One-factor model for the MCS complete sample.



The one-factor model (**Figure 6.5**) indicated poor fit indices compared to the rest of the models, and two ACE measures (low cognitive stimulation and sexual victimisation) had low loadings of 0.20. Parental smacking, frequent parental alcohol use, harsh parental discipline, and unhappy parental relationship did not load onto the one-factor model. As all ACE measures did not load onto a single factor, there was a lack of evidence for the cumulative risk model.

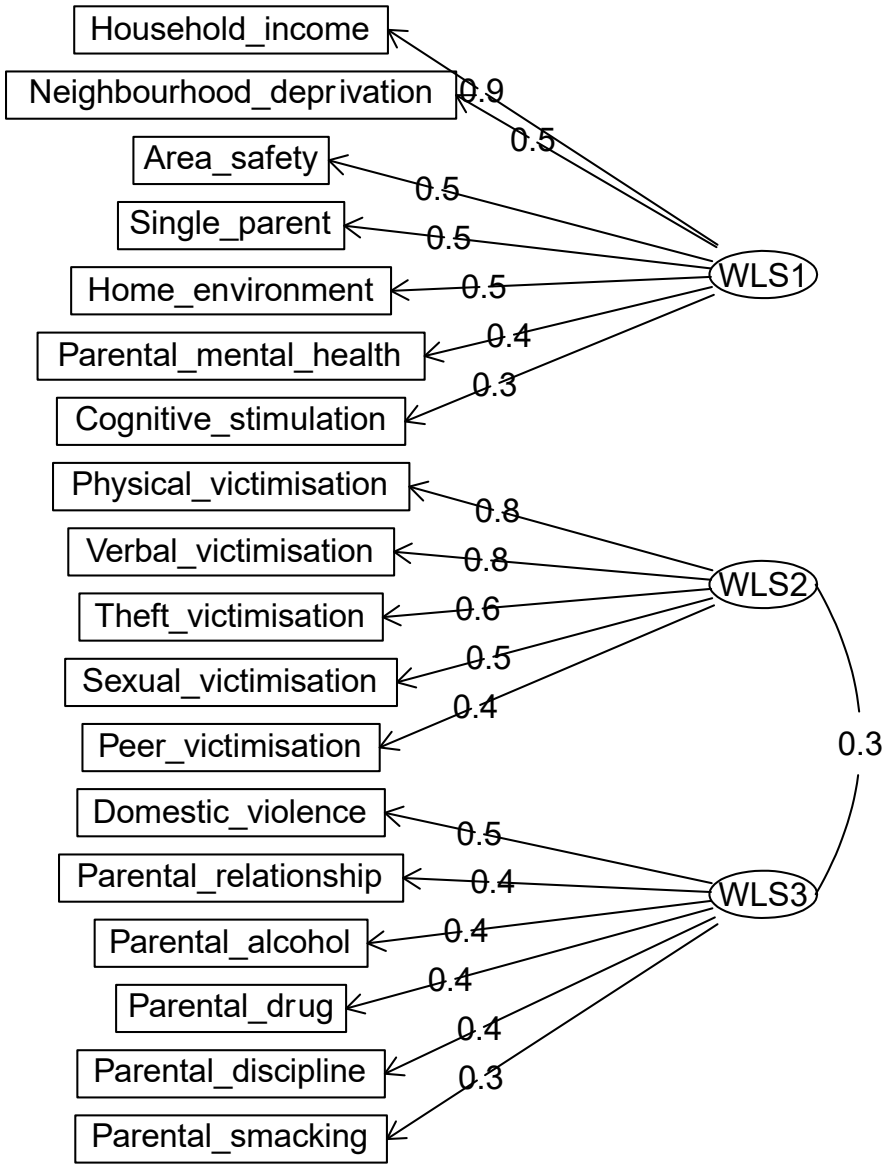
Figure 6.6 Two-factor model for the MCS complete sample.



The two-factor model (**Figure 6.6**) had better fit indices than the one-factor model. Harsh parental discipline, parental smacking, and unhappy parental relationship did not load onto the two-factor model. Although there appeared to be two factors of threat/deprivation-related events and victimisation, there was no distinction between threat and deprivation ACEs to support DMAP.

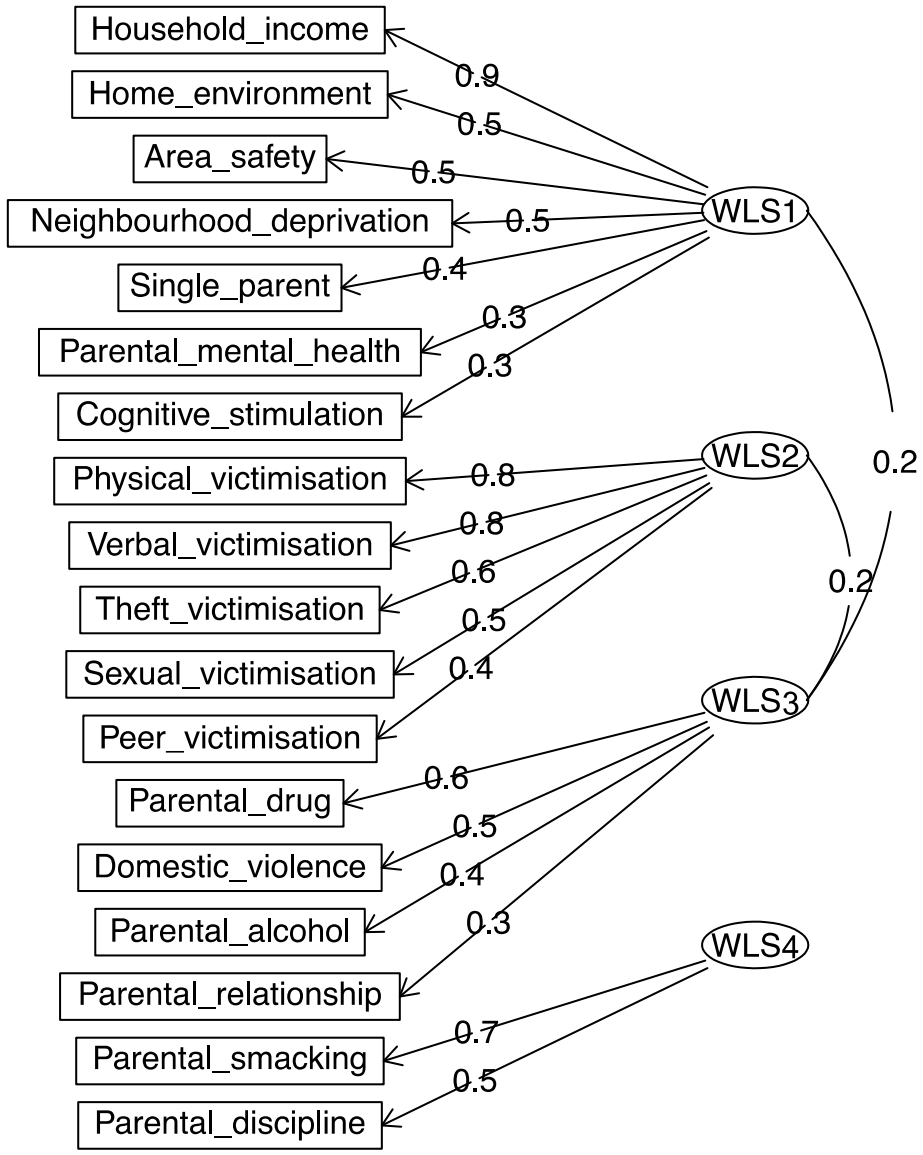
Note. Notably, frequent parental alcohol use correlated negatively with the first factor, which comprised of deprivation-related ACE measures. This might reflect the pattern of wealthier families affording higher alcohol consumption.

Figure 6.7 Three-factor model for the MCS complete sample.



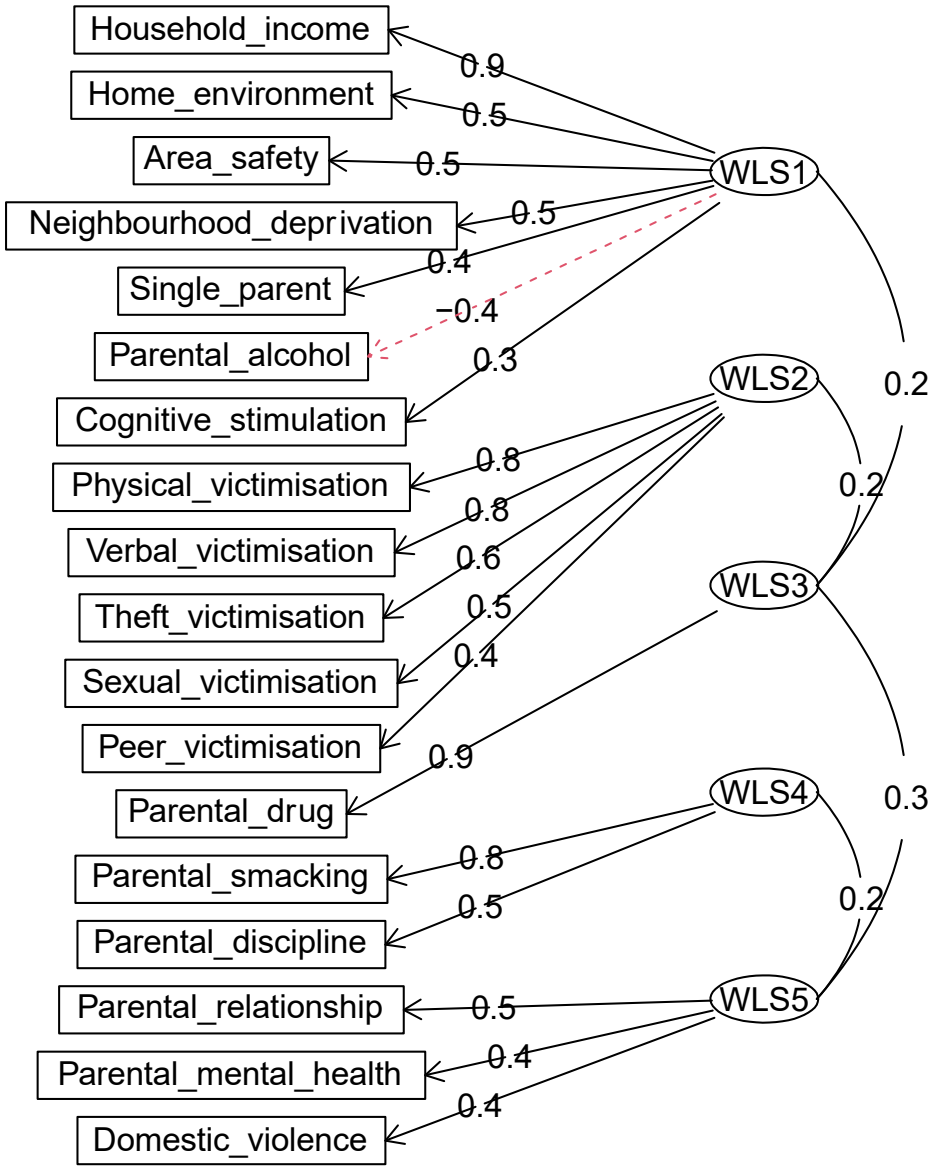
The three-factor model (**Figure 6.7**) had better fit indices than the two-factor model, with all items loading onto three factors. The second and third factor were moderately correlated ($r = 0.30$) but their respective ACE measures loaded onto distinct dimensions.

Figure 6.8 Four-factor model for the MCS complete sample.



The four-factor model (**Figure 6.8**) was the second-best fitting model in terms of fit indices, with all loadings equal to or above 0.30. The first three factors were moderately correlated with each other ($r = 0.20$), but their respective ACE measures loaded onto distinct dimensions.

Figure 6.9 Five-factor model for the MCS complete sample.



The five-factor model (**Figure 6.9**) demonstrated the best fit indices, but the third factor consisted of only one item (parental drug use), indicating model instability. All five factors were correlated with each other (r = 0.20-0.30).

Note. Notably, frequent parental alcohol use correlated negatively with the first factor, which comprised of deprivation-related ACE measures. This might reflect the pattern of wealthier families affording higher alcohol consumption.

6.1.2 Exploratory factor analysis (EFA) on the MCS imputed sample.

EFA fit indices for the MCS imputed sample are presented in **Table 6.4**, which were broadly consistent with the EFA fit indices for the MCS complete sample (**Table *6.3***).

Table 6.4 EFA fit indices for the MCS imputed sample.

Factors	χ^2	RMSEA [90% CI]	RMSR	TLI	BIC	χ^2 *p*-value
1	60737.40	0.156 [0.155, 0.157]	0.15	0.32	59410.67	<.001
2	28746.84	0.114 [0.113, 0.116]	0.08	0.63	27587.18	<.001
3	13525.57	0.084 [0.083, 0.085]	0.05	0.80	12523.15	<.001
4	12031.58	0.086 [0.085, 0.087]	0.03	0.80	11176.58	<.001
5	7767.37	0.075 [0.074, 0.077]	0.03	0.84	7049.95	<.001

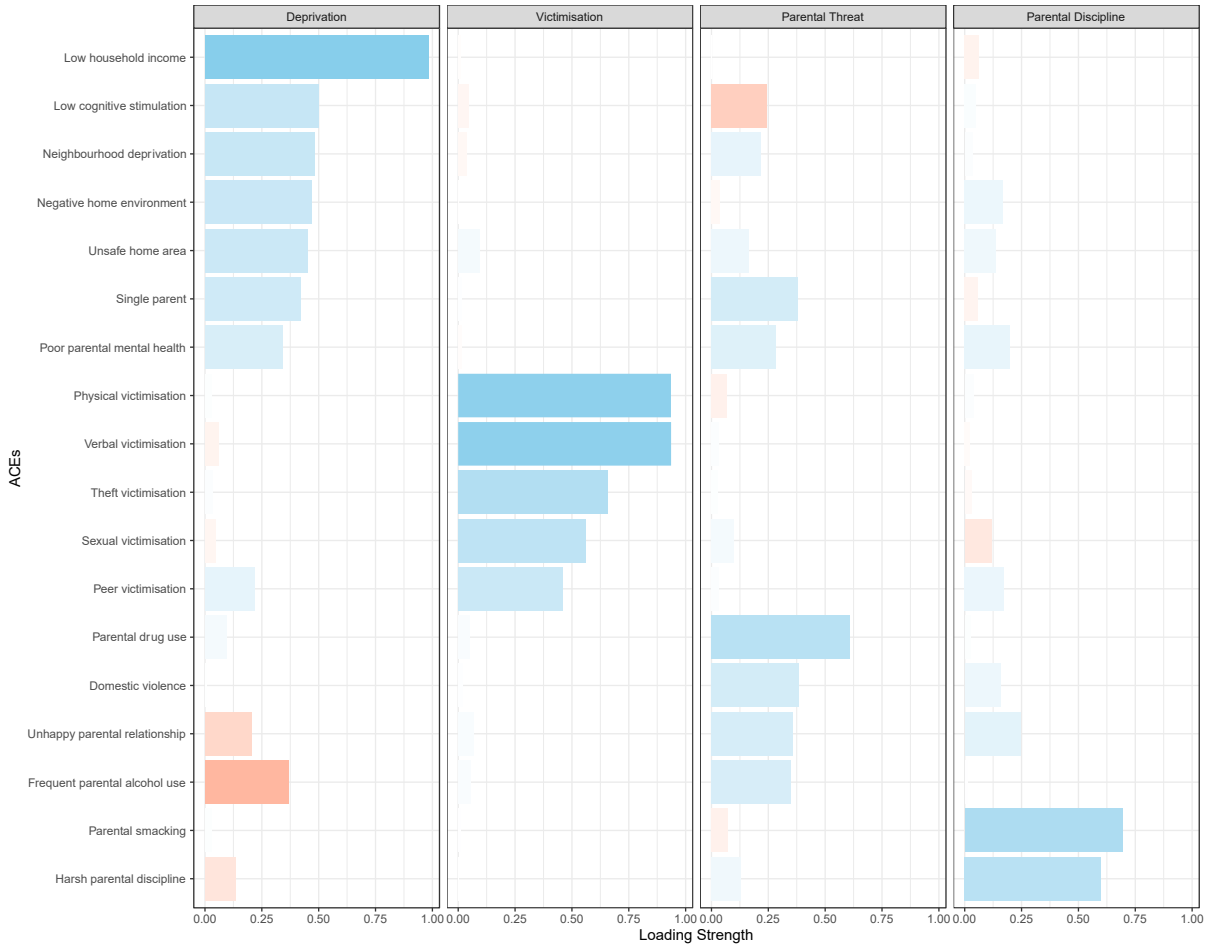
Note. RMSEA = root mean square error of approximation; RMSR = root mean square residual (RMSR); TLI = Tucker-Lewis index (TLI); BIC = Bayesian Information Criterion.

Criteria for a good fit are as follows: RMSEA < 0.06; RMSR < 0.08; TLI > 0.95.

As the likelihood of the model increases, the BIC decreases; thus, a lower BIC indicates better fit.

Plotting the factor loadings of the four-factor model for the MCS imputed sample (**Figure 6.10**) revealed identical factors of deprivation, victimisation, parental threat, and parental discipline as the complete sample (**Figure 6.8**). Thus, the imputed sample and complete sample produced consistent results despite their differences in missingness, demonstrating the validity of the four-factor model of deprivation, victimisation, parental threat, and parental discipline.

Figure 6.10 Four-factor model for the MCS imputed sample.

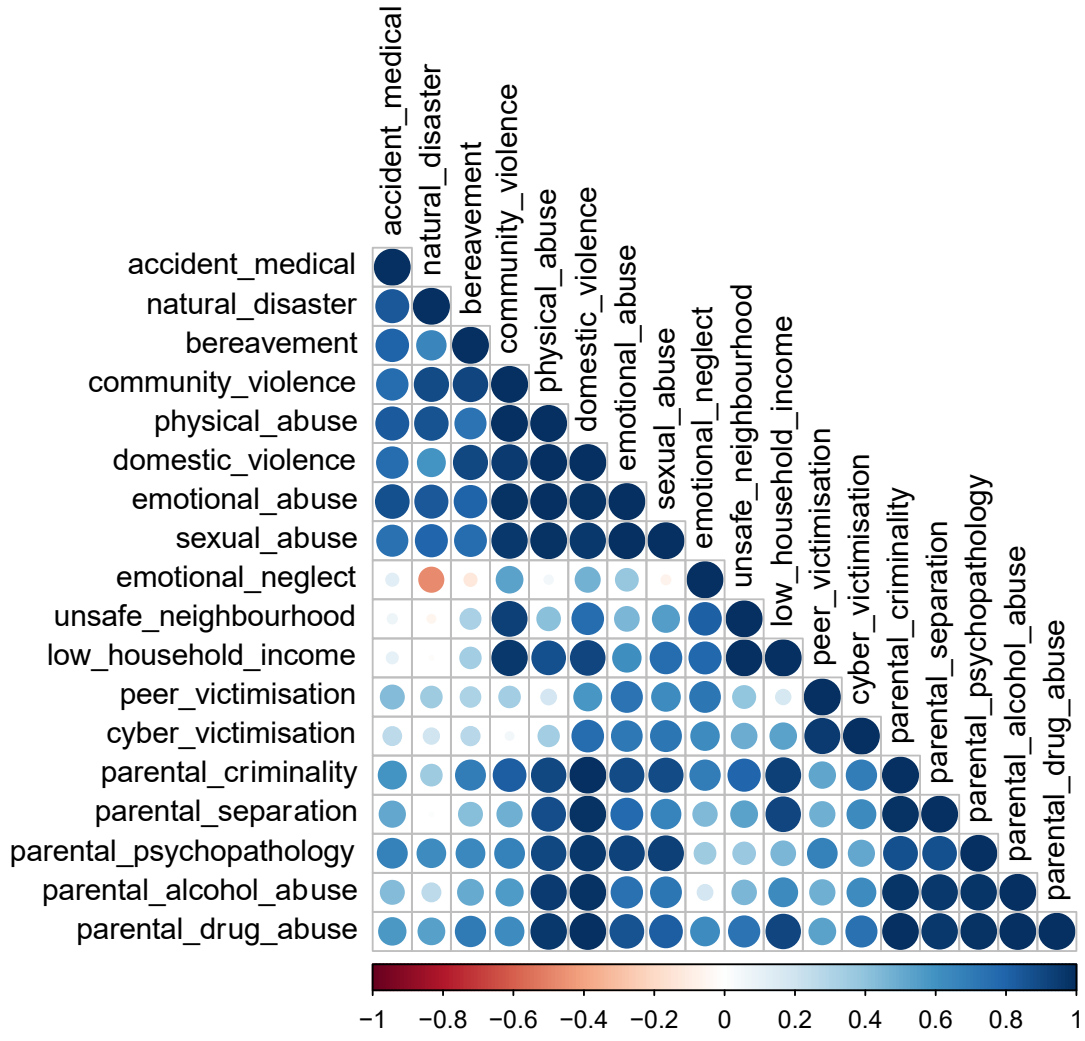


6.1.3 Exploratory factor analysis (EFA) on the ABCD complete sample.

First, we examined the factorability of the ACE measures. Bartlett's test of sphericity was significant, $\chi^2(153) = 69{,}200.17$, $p<.001$, indicating the presence of patterned relationships among the ACE measures. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was acceptable (KMO = 0.79), indicating the presence of latent factors.

We estimated the tetrachoric correlations among the 18 ACEs and plotted the tetrachoric correlation matrix with hierarchical clustering to group together similar measures. As there are visible clusters of between-measure correlations (e.g., between physical abuse and emotional abuse, and parental alcohol abuse and parental drug abuse), it is evident there are at least two latent factors underlying the ACE measures (**Figure 6.11**).

Figure 6.11 Correlation matrix of ACEs in the ABCD complete sample.

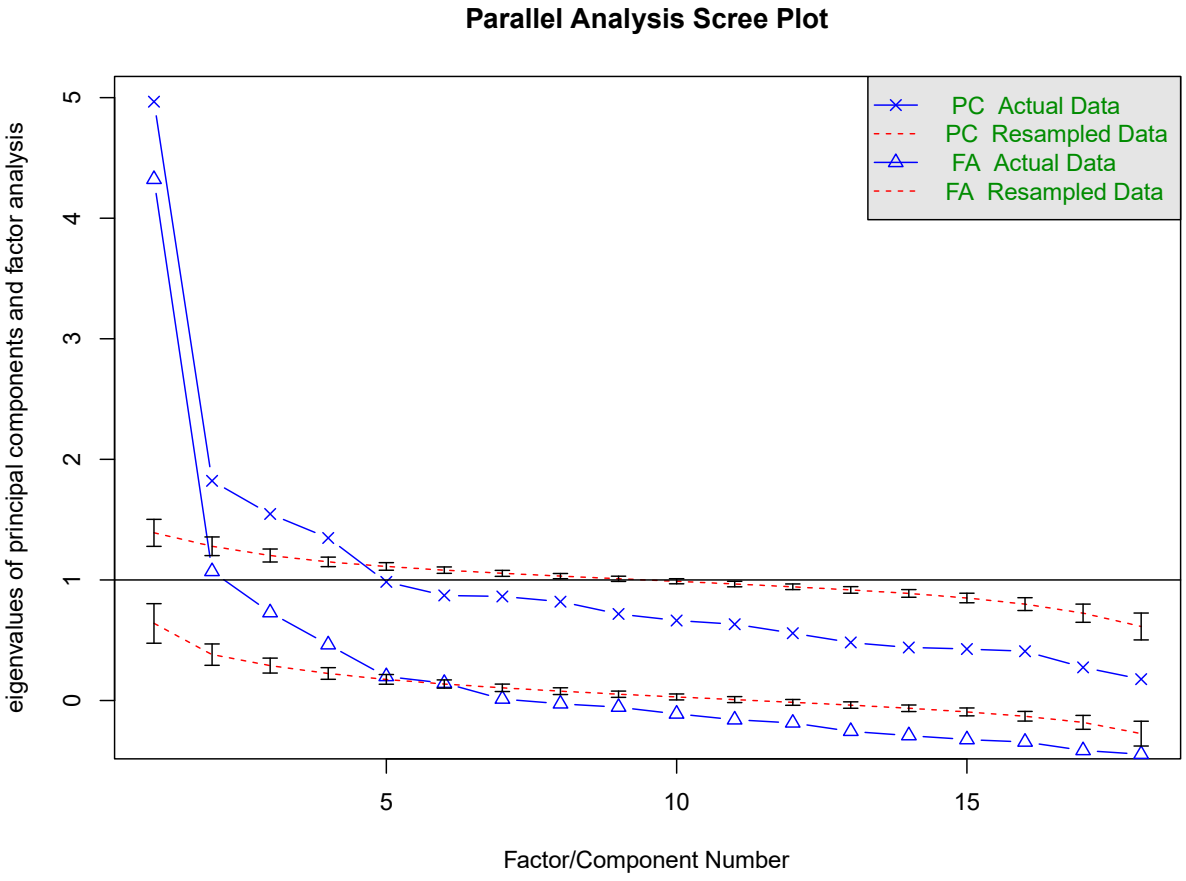


Note. Darker circles represent stronger correlations (blue for positive, red for negative).

We conducted parallel analysis on the ABCD sample with 1,000 Monte-Carlo simulations for both principal components (PC) and principal axis factoring (FA). Parallel analysis recommended the optimal number of factors to retain was four (**Figure 6.12**). According to Cattell's scree test, the scree plot indicates two to three factors before the point of inflexion.

Altogether, parallel analysis and Cattell's scree test recommended the extraction of two to four factors. The cumulative risk model assumes that ACEs would load onto a single latent factor, while DMAP proposes that ACEs load onto two factors of threat and deprivation. Thus, we conducted EFA to fit one, two, three, and four-factor models.

Figure 6.12 Parallel analysis scree plot for the ABCD complete sample.



Note. For both PC and FA, there were four factors generated above the 99th percentile (represented as error bars connected by red dashed lines).

Model fit indices for one through four-factor models are presented in **Table 6.5**. As predicted by the parallel analysis, the four-factor model had the best fit according to the indices, followed by the three-factor, two-factor, and one-factor models.

Table 6.5 EFA fit indices for the ABCD complete sample.

Factors	χ^2	RMSEA [90% CI]	RMSR	TLI	BIC	χ^2 *p*-value
1	28188.57	0.132 [0.131, 0.134]	0.10	0.54	26921.96	<.001
2	18247.88	0.114 [0.112, 0.115]	0.07	0.66	17140.77	<.001
3	15672.67	0.113 [0.112, 0.115]	0.06	0.66	14715.67	<.001
4	8565.06	0.091 [0.089, 0.092]	0.03	0.78	7748.80	<.001

Note. RMSEA = root mean square error of approximation; RMSR = root mean square residual (RMSR); TLI = Tucker-Lewis index (TLI); BIC = Bayesian Information Criterion.

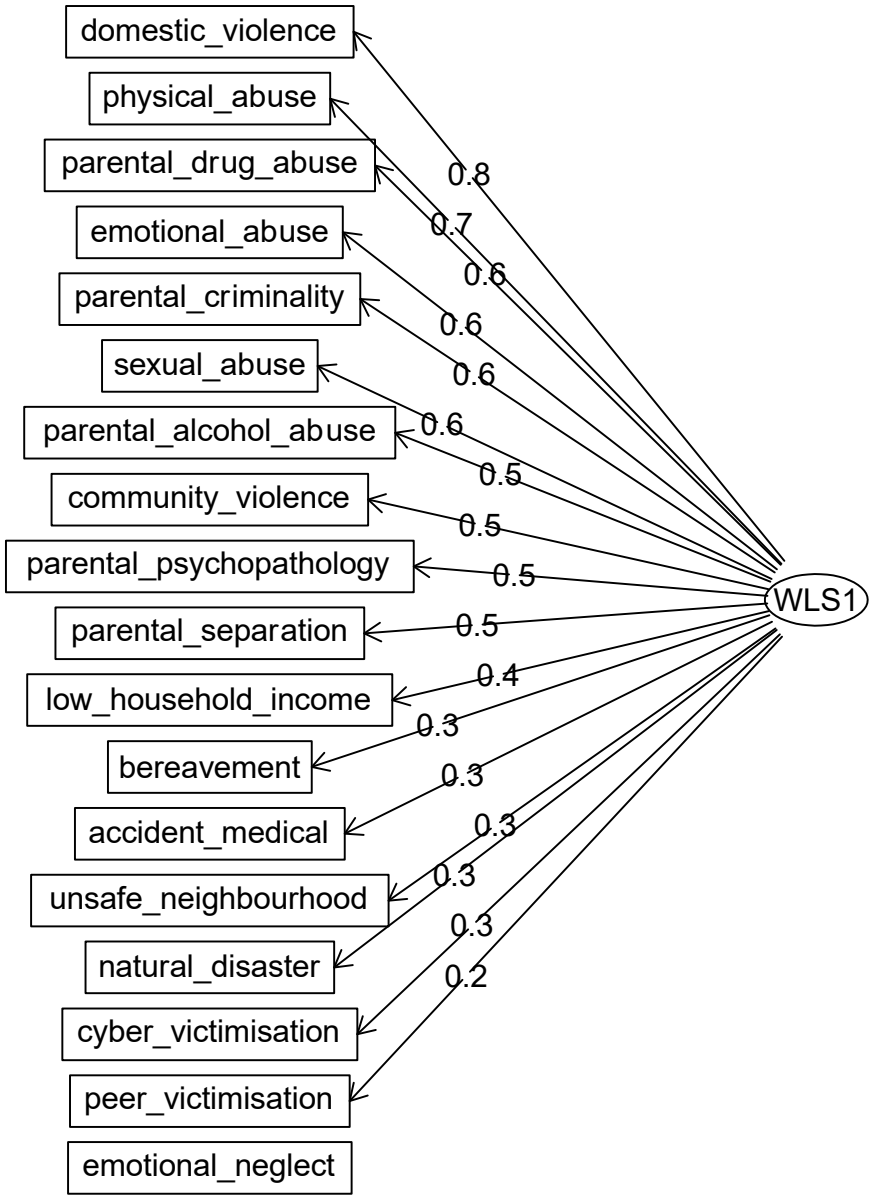
Criteria for a good fit are as follows: RMSEA < 0.06; RMSR < 0.08; TLI > 0.95.

As the likelihood of the model increases, the BIC decreases; thus, a lower BIC indicates better fit.

As with the MCS sample, we evaluated the best fitting model according to absolute and relative fit indices (RMSEA < 0.06, RMSR < 0.08, and TLI > 0.95 indicated good fit; Hu & Bentler, 1999). We also considered if the best fitting model had the "cleanest" factor structure: factor loadings equal to or more than 0.30, with no or few item cross loadings (Costello & Osborne, 2005).

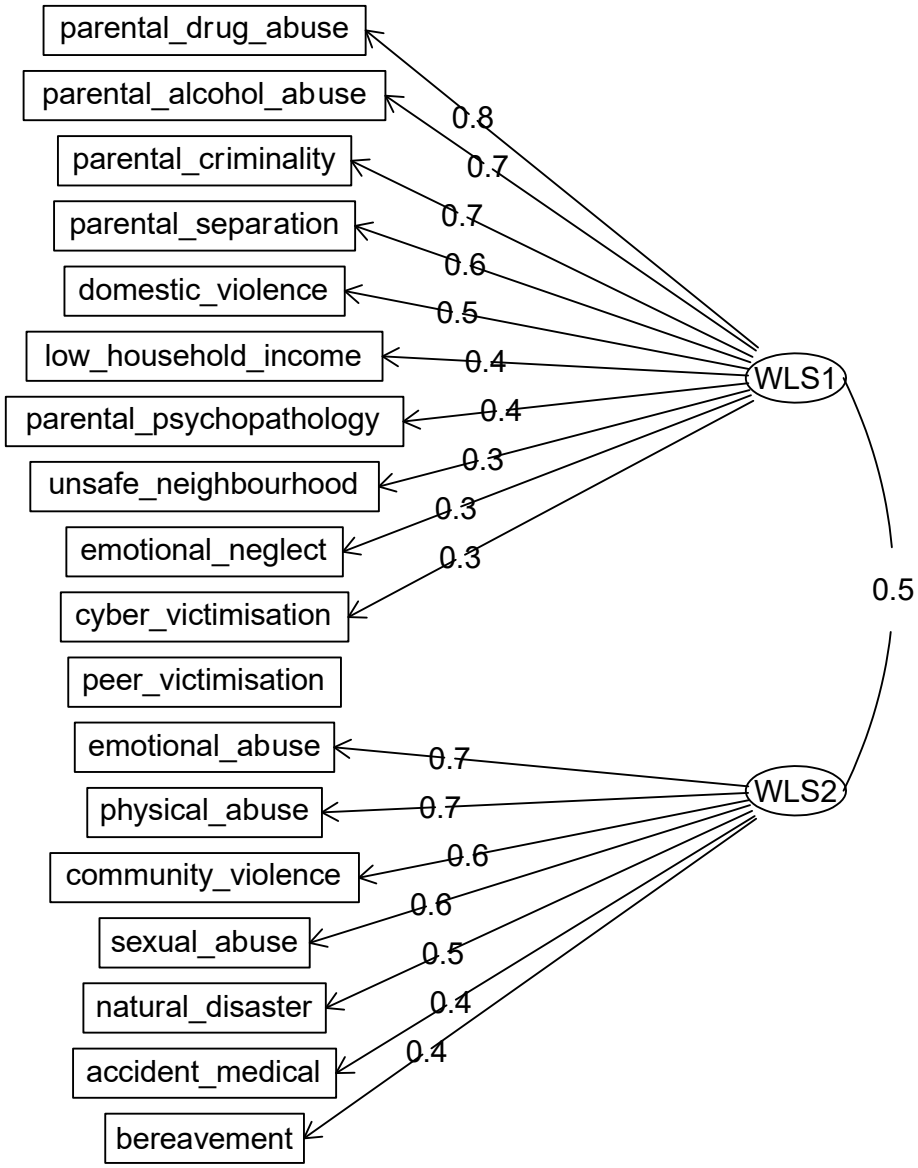
Overall consideration of the fit indices and factor structure criteria suggested the four-factor model fit the ABCD data optimally. The four factors were labelled traumatic events, parental threat, deprivation, and victimisation. After selecting the optimal model, we extracted factor scores and tested the associations between each factor and adolescent psychopathology.

Figure 6.13 One-factor model for the ABCD complete sample.



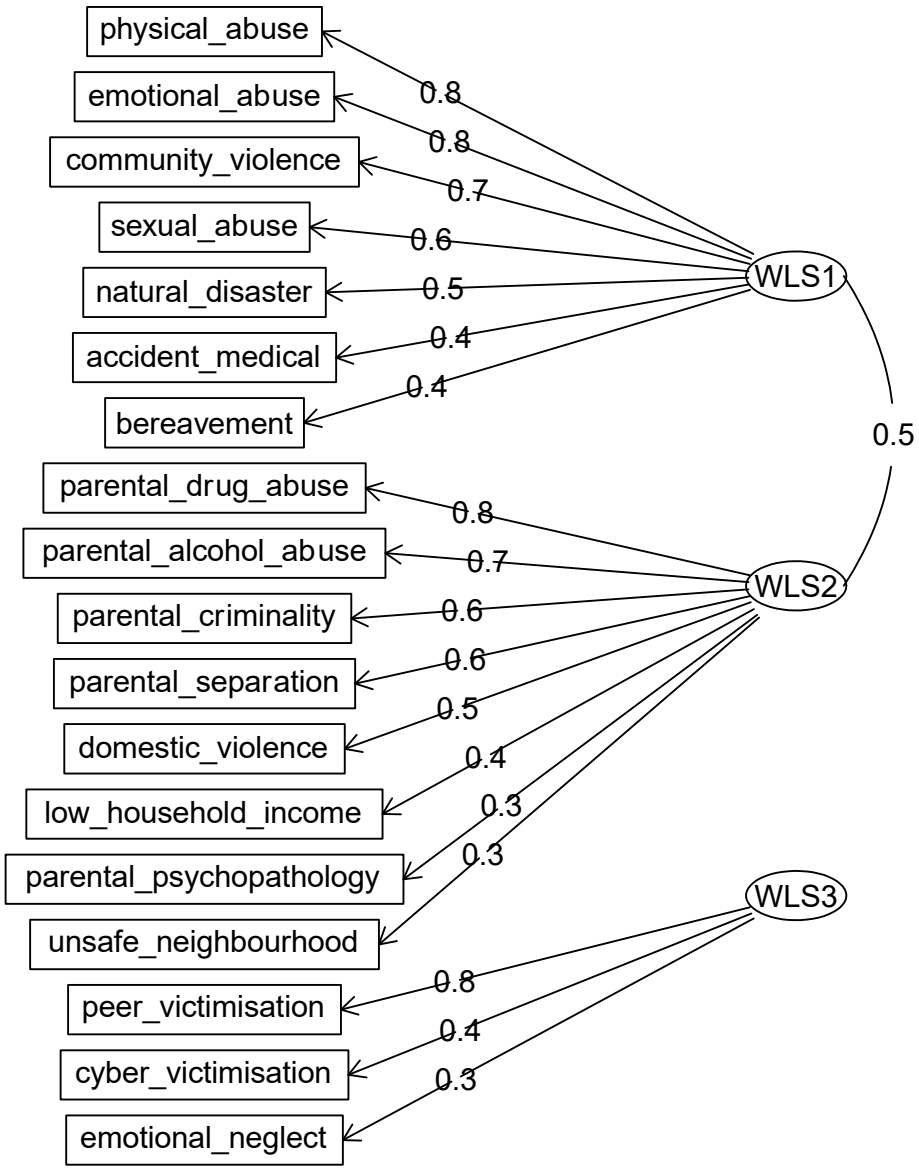
The one-factor model (**Figure 6.13**) indicated poor fit indices compared to the rest of the models, and one ACE measure (peer victimisation) had a low loading of 0.20. Emotional neglect did not load onto the one-factor model. Given that all ACE measures did not load onto a single factor, there was a lack of evidence to support the cumulative risk model.

Figure 6.14 Two-factor model for the ABCD complete sample.



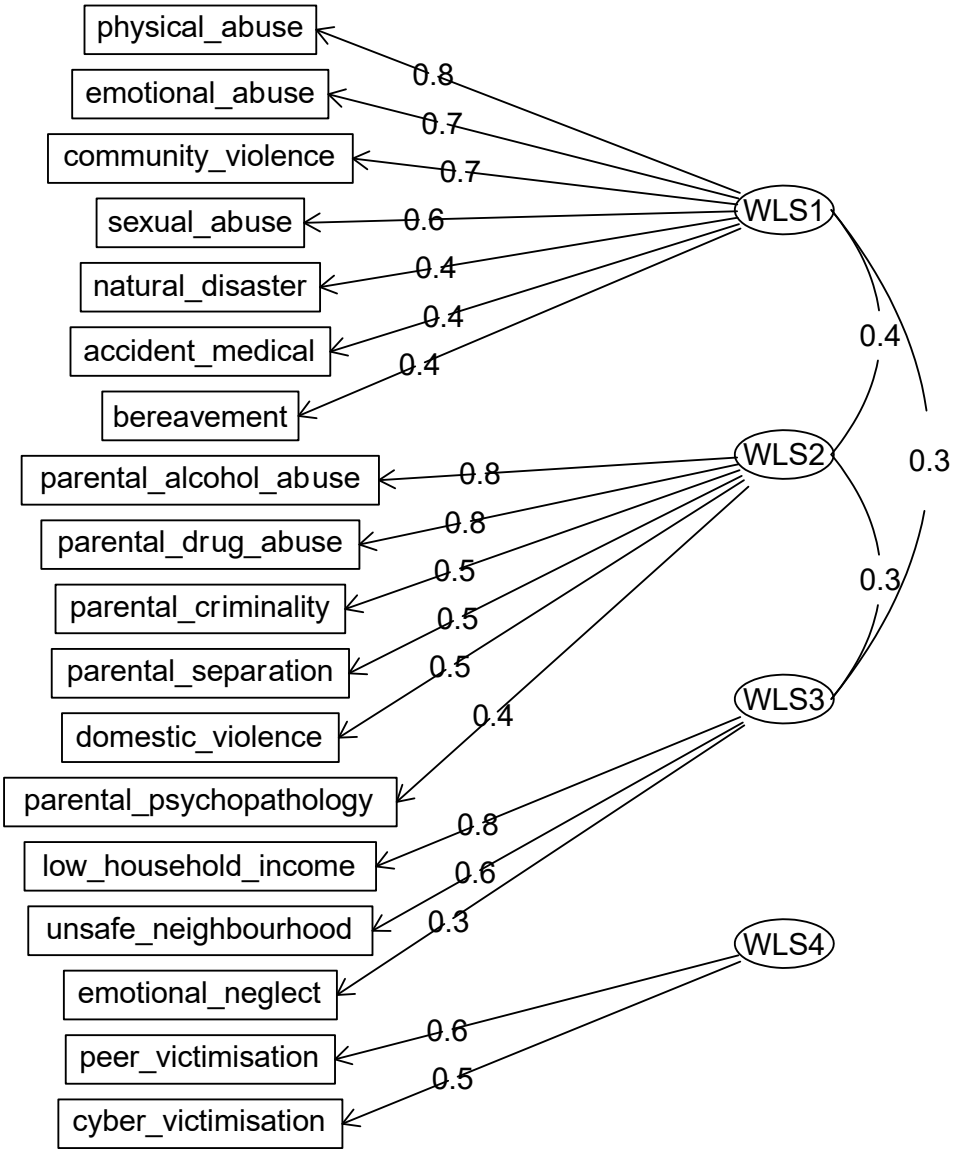
The two-factor model (**Figure 6.14**) had better fit indices than the one-factor model. Peer victimisation did not load onto the two-factor model. The first and second factors were correlated (r = 0.50) but their respective ACE measures loaded onto distinct dimensions. Although there appeared to be two factors of threat/deprivation-related events and traumatic events, there was no distinction between threat and deprivation ACEs to support DMAP.

Figure 6.15 Three-factor model for the ABCD complete sample.



The three-factor model (**Figure 6.15**) had better fit indices than the two-factor model, with all items loading onto three factors. The first and second factors were identical to the two-factor model, except that emotional neglect, peer victimisation and cyber victimisation loaded onto the third factor.

Figure 6.16 Four-factor model for the ABCD complete sample.



The four-factor model (**Figure 6.16**) demonstrated the best fit indices, with all loadings equal to or above 0.30. The first three factors were moderately correlated with each other (r = 0.30-0.40) but their respective ACE measures loaded onto distinct dimensions.

6.1.4 Exploratory factor analysis (EFA) on the ABCD imputed sample.

EFA fit indices for the ABCD imputed sample are presented in **Table *6.6***, which were broadly consistent with the EFA fit indices for the ABCD complete sample (**Table 6.5**).

Table 6.6 EFA fit indices for the ABCD imputed sample.

Factors	χ^2	RMSEA [90% CI]	RMSR	TLI	BIC	χ^2 *p*-value
1	28986.87	0.134 [0.133, 0.135]	0.10	0.53	27720.26	<.001
2	18760.36	0.115 [0.114, 0.117]	0.07	0.65	17653.25	<.001
3	16056.97	0.115 [0.113, 0.116]	0.06	0.65	15099.97	<.001
4	8566.52	0.091 [0.089, 0.092]	0.04	0.79	7750.27	<.001

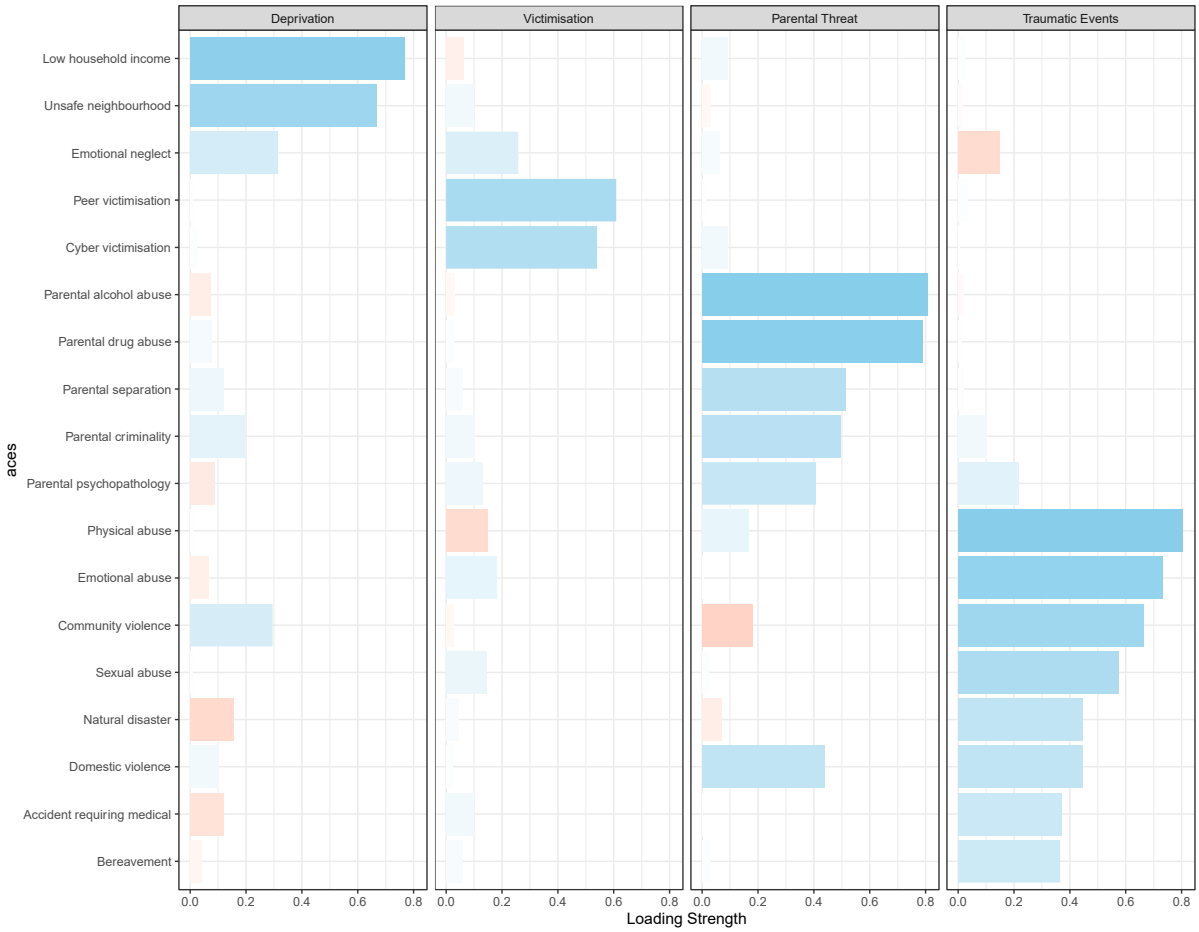
Note. RMSEA = root mean square error of approximation; RMSR = root mean square residual (RMSR); TLI = Tucker-Lewis index (TLI); BIC = Bayesian Information Criterion.

Criteria for a good fit are as follows: RMSEA < 0.06; RMSR < 0.08; TLI > 0.95.

As the likelihood of the model increases, the BIC decreases; thus, a lower BIC indicates better fit.

Plotting the factor loadings of the four-factor model for the ABCD imputed sample (**Figure 6.17**) revealed identical factors of deprivation, victimisation, parental threat, and traumatic events as the complete sample (**Figure 6.16**). Thus, the imputed sample and complete sample produced consistent results despite their differences in missingness, demonstrating the validity of the four-factor model of deprivation, victimisation, parental threat, and traumatic events.

Figure 6.17 Four-factor model for the ABCD imputed sample.



6.1.5 ACE dimensions and psychopathology in the MCS complete sample.

Next, we examined the relationships between deprivation, victimisation, parental threat, and parental discipline with internalising and externalising symptoms at age 17. Before proceeding with the regression analyses, we examined the correlations between the four factors. Certain factors were moderately correlated with each other, for example: deprivation and parental threat ($r = 0.21$), and victimisation and parental threat ($r = 0.22$). The remaining factors showed little to no correlation with each other: parental threat and parental discipline ($r = 0.13$), victimisation and parental discipline ($r = 0.11$), deprivation and victimisation ($r = 0.07$), and deprivation and parental discipline ($r = 0.01$).

Results from the unadjusted univariate regression models are reported below in text, while results from the adjusted models are presented in **Table 6.7** & **Table 6.8**.

Univariate analyses revealed that all four factors were associated with adolescent psychopathology in different ways. There was a significant association between deprivation and internalising symptoms ($\beta = 0.12$, 95% CI = 0.10 – 0.15, $p < .001$), as well as externalising symptoms ($\beta = 0.10$, 95% CI = 0.08 – 0.13, $p < .001$). After adjusting for sex and race, these associations remained significant.

There were significant associations between victimisation and internalising symptoms ($\beta = 0.23$, 95% CI = 0.21 – 0.25, $p < .001$) and externalising symptoms ($\beta = 0.22$, 95% CI = 0.20 – 0.24, $p < .001$), both of which remained significant after adjusting for covariates.

There was a small association between parental threat and internalising symptoms ($\beta = 0.10$, 95% CI = 0.08 – 0.13, $p < .001$), as well as externalising symptoms ($\beta = 0.08$, 95% CI = 0.05 – 0.10, $p < .001$). These remained significantly associated after adjusting for covariates.

There was initially no association between parental discipline and internalising symptoms ($\beta = 0.0001$, 95% CI = -0.02 – 0.02, $p = .992$), but parental discipline was associated with externalising symptoms ($\beta = 0.12$, 95% CI = 0.09 – 0.14, $p < .001$). After covariate adjustment, parental discipline was associated with both internalising and externalising symptoms.

In the multivariate adjusted model, parental threat was no longer associated with internalising symptoms ($\beta = 0.01$, 95% CI = -0.01 – 0.04, $p = .244$) or externalising symptoms ($\beta = 0.003$, 95% CI = -0.02 – 0.03, $p = .812$). Additionally, parental discipline ($\beta = 0.01$, 95% CI = -0.01 – 0.03, $p = .461$) was no longer associated with internalising symptoms.

Compared to the other three factors, victimisation appeared to be the most strongly associated with internalising symptoms ($\beta = 0.23$, 95% CI = 0.21 – 0.26, $p < .001$) and externalising symptoms ($\beta = 0.19$, 95% CI = 0.17 – 0.22, $p < .001$). Next, deprivation demonstrated increased risk for internalising symptoms ($\beta = 0.12$, 95% CI = 0.10 – 0.15, $p < .001$) and externalising symptoms ($\beta = 0.10$, 95% CI = 0.07 – 0.12, $p < .001$). After accounting for the other three factors, parental discipline only remained associated with increased risk for externalising symptoms ($\beta = 0.09$, 95% CI = 0.06 – 0.11, $p < .001$).

Table 6.7 Adjusted associations for internalising symptoms in the MCS complete sample.

	Internalising symptoms at age 17				
	Model 1: Deprivation ~ Internalising	Model 2: Victimisation ~ Internalising	Model 3: Parental Threat ~ Internalising	Model 4: Parental Discipline ~ Internalising	Model 5: Deprivation + Victimisation + Parental Threat + Parental Discipline ~ Internalising
	β (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)
ACEs					
Deprivation	0.15*** (0.12, 0.17)				0.12*** (0.10, 0.15)
Victimisation		0.25*** (0.23, 0.27)			0.23*** (0.21, 0.26)
Parental Threat			0.09*** (0.07, 0.12)		0.01 (-0.01, 0.04)
Parental Discipline				0.04*** (0.01, 0.06)	0.01 (-0.01, 0.03)
Covariates					
Sex (ref: male)					
Female	0.51*** (0.46, 0.55)	0.55*** (0.50, 0.59)	0.51*** (0.46, 0.55)	0.52*** (0.47, 0.57)	0.54*** (0.50, 0.59)
Ethnicity (ref: White)					
Black or Black British	-0.41*** (-0.57, -0.24)	-0.32*** (-0.48, -0.16)	-0.30*** (-0.47, -0.14)	-0.32*** (-0.48, -0.15)	-0.40*** (-0.56, -0.24)
Indian	-0.29*** (-0.44, -0.14)	-0.20*** (-0.35, -0.05)	-0.20*** (-0.36, -0.05)	-0.25*** (-0.40, -0.09)	-0.24*** (-0.38, -0.09)
Mixed	0.06 (-0.09, 0.22)	0.07 (-0.09, 0.22)	0.07 (-0.09, 0.23)	0.10 (-0.06, 0.26)	0.03 (-0.12, 0.19)
Other (inc. Chinese)	-0.39*** (-0.62, -0.16)	-0.23** (-0.46, -0.01)	-0.31*** (-0.54, -0.08)	-0.32*** (-0.56, -0.09)	-0.30*** (-0.53, -0.08)
Pakistani and Bangladeshi	-0.39*** (-0.51, -0.28)	-0.16*** (-0.26, -0.05)	-0.21*** (-0.32, -0.10)	-0.25*** (-0.36, -0.14)	-0.28*** (-0.39, -0.17)

Note. Predictors (deprivation, victimisation, parental threat, and parental discipline) and outcomes (internalising and externalising symptoms) were standardised.

β = standardised regression coefficient, CI = confidence interval.

*p <.05; **p <.01; ***p <.001

Table 6.8 Adjusted associations for externalising symptoms in the MCS complete sample.

	Externalising symptoms at age 17				
	Model 1: Deprivation ~ Externalising	Model 2: Victimisation ~ Externalising	Model 3: Parental Threat ~ Externalising	Model 4: Parental Discipline ~ Externalising	Model 5: Deprivation + Victimisation + Parental Threat + Parental Discipline ~ Externalising
	β (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)
ACEs					
Deprivation	0.12*** (0.09, 0.14)				0.10*** (0.07, 0.12)
Victimisation		0.21*** (0.19, 0.24)			0.19*** (0.17, 0.22)
Parental Threat			0.08*** (0.05, 0.10)		0.003 (-0.02, 0.03)
Parental Discipline				0.11*** (0.09, 0.14)	0.09*** (0.06, 0.11)
Covariates					
Sex (ref: male)					
Female	-0.16*** (-0.21, -0.11)	-0.13*** (-0.18, -0.08)	-0.16*** (-0.21, -0.11)	-0.13*** (-0.18, -0.08)	-0.11*** (-0.16, -0.06)
Ethnicity (ref: White)					
Black or Black British	-0.20** (-0.37, -0.03)	-0.13 (-0.29, 0.04)	-0.12 (-0.29, 0.05)	-0.14 (-0.31, 0.03)	-0.20** (-0.37, -0.03)
Indian	-0.06 (-0.22, 0.10)	0.01 (-0.14, 0.17)	0.01 (-0.15, 0.16)	-0.04 (-0.20, 0.11)	-0.04 (-0.19, 0.12)
Mixed	-0.002 (-0.17, 0.16)	-0.001 (-0.16, 0.16)	0.003 (-0.16, 0.17)	0.03 (-0.13, 0.19)	-0.02 (-0.18, 0.14)
Other (inc. Chinese)	-0.19 (-0.43, 0.05)	-0.06 (-0.29, 0.17)	-0.13 (-0.37, 0.11)	-0.16 (-0.39, 0.08)	-0.14 (-0.37, 0.09)
Pakistani and Bangladeshi	-0.25*** (-0.36, -0.13)	-0.05 (-0.16, 0.06)	-0.10 (-0.21, 0.02)	-0.14** (-0.25, -0.03)	-0.17*** (-0.28, -0.05)

Note. Predictors (deprivation, victimisation, parental threat, and parental discipline) and outcomes (internalising and externalising symptoms) were standardised.

β = standardised regression coefficient, CI = confidence interval.

*p <.05; **p <.01; ***p <.001

We also tested for multicollinearity by calculating the variance inflation factor (VIF) and tolerance values for the multivariate model. VIF values were all around 1 and tolerance values were much greater than 0.10 (**Table *6.9*** & **Table *6.10***), indicating that multicollinearity was very unlikely.

Table 6.9 VIF and tolerance for the multivariate model in the MCS complete sample.

ACE Dimension	VIF [95% CI]	Tolerance [95% CI]
Deprivation	1.13 [1.10, 1.16]	0.89 [0.86, 0.91]
Victimisation	1.07 [1.05, 1.11]	0.93 [0.90, 0.95]
Parental threat	1.13 [1.10, 1.16]	0.89 [0.86, 0.91]
Parental discipline	1.05 [1.03, 1.08]	0.96 [0.92, 0.97]

Table 6.10 VIF and tolerance for the multivariate model in the MCS imputed sample.

ACE Dimension	VIF [95% CI]	Tolerance [95% CI]
Deprivation	1.16 [1.14, 1.18]	0.86 [0.85, 0.87]
Victimisation	1.11 [1.09, 1.13]	0.90 [0.89, 0.91]
Parental threat	1.24 [1.22, 1.26]	0.81 [0.80, 0.82]
Parental discipline	1.13 [1.11, 1.15]	0.88 [0.87, 0.90]

6.1.6 Gender interactions in the MCS complete sample.

Notably, being female was associated with significantly increased risk for internalising symptoms (β = 0.54, 95% CI = 0.50 – 0.59, p = <.001) but decreased risk for externalising symptoms (β = -0.11, 95% CI = -0.16 – 0.06, p = <.001). Thus, we tested for interactions between sex and deprivation, victimisation, parental threat, and parental discipline. There were no significant interactions between sex and any of the four factors for externalising symptoms.

However, there was a small significant interaction between female sex and victimisation for internalising symptoms. Specifically, girls who experienced victimisation ACEs were at slightly higher risk for internalising symptoms than boys who experienced victimisation (β = 0.07, 95% CI = 0.02 – 0.11, p = <.01).

We then stratified the sample by gender and found that for boys, only deprivation (β = 0.11, 95% CI = 0.08 – 0.15, p <.001) and victimisation (β = 0.20, 95% CI = 0.17 – 0.23, p <.001) remained associated with internalising symptoms in the multivariate model. Boys who had experienced parental threat (β = -0.001, 95% CI = -0.03 – 0.03, p = .951) and parental discipline (β = -0.008, 95% CI = -0.04 – 0.02, p = .624) were not at increased risk for internalising symptoms.

For girls, only deprivation (β = 0.13, 95% CI = 0.10 – 0.17, p <.001) and victimisation (β = 0.27, 95% CI = 0.23 – 0.30, p <.001) remained associated with internalising symptoms in the multivariate model. Girls who had experienced parental threat (β = 0.03, 95% CI = -0.01 – 0.06, p = .154) and parental discipline (β = 0.03, 95% CI = -0.01 – 0.06, p = .102) were not at increased risk for internalising symptoms.

Overall, the gender stratified regression results remained consistent for boys and girls. Victimisation and deprivation significantly increased the risk for internalising symptoms, and victimisation demonstrated larger effect sizes than deprivation. As the gender interaction analyses were originally intended to be exploratory, we presented results for the total sample.

6.1.7 ACE dimensions and psychopathology in the ABCD complete sample.

Next, we examined the relationships between traumatic events, parental threat, deprivation, and victimisation with internalising and externalising symptoms at age 12-13. Before proceeding with the regression analyses, we examined the correlations between the four factors. Certain factors were moderately correlated with each other, for example: traumatic events and parental threat (r = 0.41), traumatic events and deprivation (r = 0.28), and parental threat and deprivation (r = 0.27). The remaining factors showed little to no correlation with each other: traumatic events and victimisation (r = 0.14), parental threat and victimisation (r = 0.16), and deprivation and victimisation (r = 0.08).

Results from the unadjusted univariate regression models are reported below in text, while results from the adjusted models are presented in **Table *6.11*** & **Table 6.12**.

Univariate analyses revealed that all four factors were associated with adolescent psychopathology. There was a significant association between traumatic events and internalising symptoms (β = 0.14, 95% CI = 0.11 – 0.16, p <.001), as well as externalising symptoms (β = 0.16, 95% CI = 0.13 – 0.18, p <.001). After adjusting for sex and race, these associations remained significant.

There were slightly stronger associations between parental threat and internalising symptoms (β = 0.20, 95% CI = 0.17 – 0.22, p <.001) and externalising symptoms (β = 0.22, 95% CI = 0.20 – 0.25, p <.001), both of which remained significant after adjusting for covariates.

There was a small significant association between deprivation and internalising symptoms (β = 0.04, 95% CI = 0.01 – 0.07, p <.001), with a stronger association for deprivation and externalising symptoms (β = 0.12, 95% CI = 0.09 – 0.15, p <.001). These remained significantly associated after adjusting for covariates.

Victimisation was also associated with increased risk for internalising symptoms (β = 0.17, 95% CI = 0.14 – 0.19, p <.001) and externalising symptoms (β = 0.20, 95% CI = 0.17 – 0.22, p <.001), and continued being associated after covariate adjustment.

In the multivariate adjusted model, all four factors remained independently associated with increased risk for externalising symptoms. However, for internalising symptoms, the deprivation factor was no longer significantly associated (β = -0.02, 95% CI = -0.05 – 0.02, p = .337) after controlling for traumatic events, parental threat, and victimisation. Additionally, the association between deprivation and externalising symptoms barely met the minimum significance threshold (β = 0.03, 95% CI = 0.001 – 0.06, p = .042).

Compared to the other three factors, parental threat appeared to be the most strongly associated with internalising symptoms (β = 0.16, 95% CI = 0.13 – 0.18, p <.001) and externalising symptoms (β = 0.16, 95% CI = 0.14 – 0.19, p <.001). Next, the victimisation factor demonstrated similar effect sizes with increased risk for internalising symptoms (β = 0.13, 95% CI = 0.11 – 0.16, p <.001) and externalising symptoms (β = 0.16, 95% CI = 0.14 – 0.19, p <.001). After accounting for the other three factors, traumatic events also remained associated with internalising symptoms (β = 0.07, 95% CI = 0.04 – 0.09, p <.001) and externalising symptoms (β = 0.06, 95% CI = 0.03 – 0.09, p <.001).

Table 6.11 Adjusted associations for internalising symptoms in the ABCD complete sample.

	Internalising symptoms at age 12-13				
	Model 1: Traumatic events ~ Internalising	Model 2: Parental threat ~ Internalising	Model 3: Deprivation ~ Internalising	Model 4: Victimisation ~ Internalising	Model 5: Traumatic events + Parental threat + Deprivation + Victimisation ~ Internalising
	β (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)
ACEs					
Traumatic events	0.14*** (0.11, 0.16)				0.07*** (0.04, 0.09)
Parental threat		0.20*** (0.17, 0.22)			0.16*** (0.13, 0.18)
Deprivation			0.06*** (0.03, 0.09)		-0.02 (-0.05, 0.02)
Victimisation				0.16*** (0.14, 0.19)	0.13*** (0.11, 0.16)
Covariates					
Sex (ref: male)					
Female	0.17*** (0.11, 0.22)	0.16*** (0.11, 0.22)	0.17*** (0.12, 0.22)	0.17*** (0.11, 0.22)	0.16*** (0.11, 0.21)
Ethnicity (ref: White)					
American Indian/Alaska Native	0.14 (-0.01, 0.29)	0.05 (-0.10, 0.20)	0.17** (0.02, 0.32)	0.17** (0.02, 0.32)	0.05 (-0.10, 0.20)
Asian	-0.14** (-0.25, -0.03)	-0.12** (-0.22, -0.01)	-0.15*** (-0.26, -0.04)	-0.13** (-0.24, -0.02)	-0.10 (-0.21, 0.01)
Black/African American	-0.20*** (-0.27, -0.12)	-0.22*** (-0.29, -0.14)	-0.21*** (-0.29, -0.13)	-0.15*** (-0.23, -0.07)	-0.20*** (-0.28, -0.12)
Native Hawaiian/Pacific Islander	0.07 (-0.33, 0.48)	-0.01 (-0.41, 0.39)	0.07 (-0.34, 0.48)	0.03 (-0.37, 0.44)	-0.04 (-0.43, 0.36)
Other Race	0.06 (-0.05, 0.18)	0.04 (-0.07, 0.15)	0.04 (-0.07, 0.15)	0.08 (-0.03, 0.19)	0.05 (-0.06, 0.16)

Note. Predictors (traumatic events, parental threat, deprivation, and victimisation) and outcomes (internalising and externalising symptoms) were standardised.

β = standardised regression coefficient, CI = confidence interval.

*p <.05; **p <.01; ***p <.001

Table 6.12 Adjusted associations for externalising symptoms in the ABCD complete sample.

	Externalising symptoms at age 12-13				
	Model 1: Traumatic events ~ Externalising	Model 2: Parental threat ~ Externalising	Model 3: Deprivation ~ Externalising	Model 4: Victimisation ~ Externalising	Model 5: Traumatic events + Parental threat + Deprivation + Victimisation ~ Externalising
	β (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)
ACEs					
Traumatic events	0.15*** (0.13, 0.18)				0.06*** (0.03, 0.09)
Parental threat		0.22*** (0.19, 0.25)			0.16*** (0.14, 0.19)
Deprivation			0.11*** (0.08, 0.14)		0.03* (0.001, 0.06)
Victimisation				0.19*** (0.17, 0.22)	0.16*** (0.14, 0.19)
Covariates					
Sex (ref: male)					
Female	-0.27*** (-0.32, -0.22)	-0.27*** (-0.33, -0.22)	-0.26*** (-0.31, -0.21)	-0.27*** (-0.32, -0.22)	-0.28*** (-0.32, -0.23)
Ethnicity (ref: White)					
American Indian/Alaska Native	0.18** (0.03, 0.33)	0.09 (-0.06, 0.23)	0.20** (0.05, 0.35)	0.21*** (0.06, 0.36)	0.07 (-0.08, 0.22)
Asian	-0.14*** (-0.25, -0.04)	-0.12** (-0.22, -0.01)	-0.15*** (-0.26, -0.04)	-0.13** (-0.24, -0.02)	-0.10 (-0.20, 0.01)
Black/African American	0.09** (0.01, 0.16)	0.06 (-0.01, 0.14)	0.03 (-0.05, 0.11)	0.14*** (0.06, 0.21)	0.04 (-0.03, 0.12)
Native Hawaiian/Pacific Islander	0.16 (-0.24, 0.56)	0.07 (-0.33, 0.47)	0.15 (-0.25, 0.55)	0.11 (-0.29, 0.51)	0.03 (-0.36, 0.42)
Other Race	0.04 (-0.07, 0.15)	0.02 (-0.09, 0.13)	-0.01 (-0.13, 0.10)	0.06 (-0.05, 0.17)	-0.002 (-0.11, 0.11)

Note. Predictors (traumatic events, parental threat, deprivation, and victimisation) and outcomes (internalising and externalising symptoms) were standardised.

β = standardised regression coefficient, CI = confidence interval.

*p <.05; **p <.01; ***p <.001

We also tested for multicollinearity by calculating the variance inflation factor (VIF) and tolerance values for the multivariate model. VIF values were all around 1 and tolerance values were much greater than 0.10 (**Table 6.13** & **Table *6.14***), indicating that multicollinearity was very unlikely.

Table 6.13 VIF and tolerance for the multivariate model for the ABCD complete sample.

ACE Dimension	VIF [95% CI]	Tolerance [95% CI]
Traumatic events	1.25 [1.21, 1.29]	0.80 [0.78, 0.83]
Parental threat	1.27 [1.24, 1.32]	0.79 [0.76, 0.81]
Deprivation	1.27 [1.23, 1.31]	0.79 [0.76, 0.81]
Victimisation	1.03 [1.01, 1.08]	0.97 [0.93, 0.99]

Table 6.14 VIF and tolerance for the multivariate model for the ABCD imputed sample.

ACE Dimension	VIF [95% CI]	Tolerance [95% CI]
Traumatic events	1.26 [1.24, 1.29]	0.79 [0.77, 0.81]
Parental threat	1.25 [1.22, 1.27]	0.80 [0.78, 0.82]
Deprivation	1.31 [1.29, 1.34]	0.76 [0.74, 0.78]
Victimisation	1.04 [1.03, 1.07]	0.96 [0.94, 0.97]

6.1.8 Gender interactions in the ABCD complete sample.

Notably, being female was associated with significantly increased risk for internalising symptoms (β = 0.16, 95% CI = 0.11 – 0.21, p <.001), but decreased risk for externalising symptoms (β = -0.28, 95% CI = -0.32 – -0.23, p <.001). Thus, we tested for interactions between sex and traumatic events, parental threat, deprivation, and victimisation. There were no significant interactions between sex and any of the four factors for internalising symptoms.

However, there was a small significant interaction between male sex and parental threat for externalising symptoms. Specifically, boys who experienced parental threat ACEs were at slightly higher risk for externalising symptoms than girls who experienced parental threat (β = 0.08, 95% CI = 0.02 – 0.14, p <.01).

We then stratified the sample by gender and found that for boys, only traumatic events (β = 0.07, 95% CI = 0.03 – 0.11, p <.01), parental threat (β = 0.20, 95% CI = 0.16 – 0.25, p <.001), and victimisation (β = 0.17, 95% CI = 0.13 – 0.20, p <.001) remained associated with externalising symptoms in the multivariate model. Boys who had experienced deprivation were not at increased risk for externalising symptoms (β = 0.01, 95% CI = -0.03 – 0.06, p = .590).

For girls, all four factors of traumatic events (β = 0.05, 95% CI = 0.02 – 0.09, p <.01), parental threat (β = 0.12, 95% CI = 0.09 – 0.16, p <.001), deprivation (β = 0.05, 95% CI = 0.01 – 0.09, p <.01), and victimisation (β = 0.16, 95% CI = 0.13 – 0.19, p <.001) were significantly associated with externalising symptoms in the multivariate model.

Overall, the gender stratified regression results remained consistent for boys and girls. Parental threat significantly increased the risk for externalising symptoms, and parental threat and victimisation demonstrated larger effect sizes than traumatic events and deprivation. As the gender interaction analyses were originally intended to be exploratory, we presented results for the total sample.

6.2 Supporting Information for Chapter 3.

6.2.1 Rationale and literature for deriving matching variables

Sex. Sex of the cohort member was coded as female or male, reported by parents at Sweep 1 (9 months old). Given the widely reported global gender gap in adolescent mental health (Campbell et al., 2021), we included sex as a matching variable.

Ethnicity. Ethnicity of the cohort member was reported by parents at Sweep 1 (9 months old) according to the six category Census class: White, Black or Black British, Indian, Pakistani and Bangladeshi, Mixed, and Other ethnic groups. In the Millennium Cohort Study specifically, there has been some evidence for ethnic inequalities in adolescent mental health outcomes, although findings were partially accounted for by household income and childhood adversity (Ahmad et al., 2021). Previous MCS literature has also included ethnicity as a matching variable in a propensity score analysis of the impact of sexual violence on adolescent mental health (Bentivegna & Patalay, 2022).

Birthweight. Birthweight in kilograms was reported by parents at Sweep 1 (9 months old), which we kept as a continuous variable. Low birthweight has been linked to greater risks for depression, anxiety, internalising and externalising symptoms across childhood, adolescence, and adulthood (Indredavik et al., 2010; Mathewson et al., 2017).

Gestation time. Gestation time in days was reported by parents at Sweep 1 (9 months old), which we kept as a continuous variable. Shorter gestation has been linked to psychiatric problems in adolescence (Indredavik et al., 2010).

Maternal age at birth. Maternal age at birth of the cohort member was reported by mothers at Sweep 1 (9 months old), which we kept as a continuous variable. Younger maternal age has been linked to increased risk of child maltreatment (Baldwin et al., 2020). Research suggests that both younger and advanced maternal age can influence child mental health outcomes (McGrath et al., 2014). For example, younger maternal age has been linked to increased risk for ADHD, although this association was mainly explained by genetic confounding (Chang et al., 2014). Advanced maternal age has generally been shown to be a protective factor for a broad range of mental health outcomes (Tearne, 2015).

Labour complications. Complications during labour were reported by mothers at Sweep 1 (9 months old). Mothers reported whether they had experienced complications such as breech birth, foetal distress, accidental haemorrhage, cord around neck, infection in labour, etc. If mothers had experienced any type of labour complication, we binarized this as present. Labour complications have been linked to an increased risk of psychotic episodes (Moreno et al., 2009) as well as adolescent psychiatric service use (Young et al., 2011).

Birth complications. Complications during birth or the first week were reported by mothers at Sweep 1 (9 months old). Mothers reported whether their child experienced complications such as breathing difficulties, infection, birth injury, premature birth, etc. If children had experienced any type of birth complication, we binarized this as present. There is some evidence for an association between the number of birth complications and adolescent psychiatric outcomes (Young et al., 2011).

Breastfeeding. Breastfeeding was reported by mothers at Sweep 1 (9 months old). Mothers reported when their child last had breast milk, which we recoded as a binary variable (never/less than one day = 0, answer given in days/weeks/months = 1). Breastfeeding has been shown to be a protective factor for adolescent mental health (Oddy et al., 2010), although there is a limited availability of high-quality studies showcasing this relationship (Bugaeva et al., 2023).

Pregnancy alcohol consumption. Alcohol consumption during pregnancy was reported by mothers at Sweep 1 (9 months old). Mothers reported their frequency of alcohol consumption during pregnancy (e.g., monthly, weekly, daily, never), which we recoded as a binary variable (any alcohol consumption = 1; never = 0). Prenatal alcohol exposure has been linked to a range of offspring mental health problems (Easey et al., 2019).

Pregnancy illness. Mothers reported if they had experienced any illnesses or problems during pregnancy at Sweep 1 (9 months old), which we binarized as present. Maternal illness during pregnancy has been linked to early childhood physical, socioemotional, and cognitive vulnerabilities, which may in turn increase the risk for subsequent mental disorders (Green et al., 2018).

Parent chronic illness. Parents reported if they had any longstanding chronic illness at Sweep 1 (9 months old), which we binarized as present. Parent chronic illness has been linked to an increased risk for adolescent internalising symptoms (Kaasbøll et al., 2021).

Parent smoking. Parents reported if they smoked cigarettes, cigars, or other tobacco products at Sweep 1 (9 months old), which we binarized as present. There is some evidence for an association between early second-hand smoke exposure and adolescent behavioural problems (Leung et al., 2015). We also included parent smoking as a matching variable due to evidence showing an environmentally mediated pathway through which parent smoking increases the risk for adolescent substance use (Keyes et al., 2008), which in turn is associated with adolescent mental health problems (Li et al., 2021).

Difficult infant temperament. Infant temperament was reported by parents at Sweep 1 (9 months old) using the Carey Infant Temperament Scale (Carey & McDevitt, 1978). Parents reported the frequency at which infants displayed their mood (e.g., 'happy sounds during nappy changing'), approachability (e.g., 'wary of strangers'), rhythmicity (e.g., 'sleepy at about the same time each evening'), and irritability (e.g., 'makes a fuss or cry after waking up'), which we reverse coded then summed as a continuous variable of difficult infant temperament. Research suggests a complex relationship between infant temperament and ACEs, with infant temperament being linked to subsequent ACE exposure and risk of PTSD (Wiseman et al., 2021).

Natural parents. The number and makeup of parents/carers in the household was reported by parents at Sweep 1 (9 months old), which we recoded as a binary variable (both natural parents = 1, all other parent/carer combinations = 0). There is some evidence that having both natural parents may act as a protective factor; according to the 2014 US National Health Statistics Report, children living with two biological parents were less likely to have experienced family ACEs compared to children in non-parental care (Bramlett et al., 2014).

Parent education. The highest level of parent academic qualification, measured with the National Vocational Qualification (NVQ), was reported by parents at Sweep 1 (9 months old). We recoded parent education as an ordinal variable ('Higher degree'=7; 'First degree'=6; 'Diplomas in higher education'=5; 'Other academic qualifications'=4; 'A / AS / S levels'=3; 'O level / GCSE grades A-C'=2; 'GCSE grades D-G'=1; 'None of these qualifications'=0). Low parent education level, commonly used as a proxy measure of low socioeconomic status (SES), has been linked to both ACE exposure (Baldwin et al., 2020; Martins et al., 2023; Walsh et al., 2019) and adolescent mental health problems (Fergusson et al., 2000). Previous MCS literature has also included parent education as a matching variable in a propensity score analysis of the impact of sexual violence on adolescent mental health (Bentivegna & Patalay, 2022).

Neighbourhood deprivation. Parents reported the level of neighbourhood deprivation at Sweep 1 (9 months old). Items covered neighbourhood surroundings (e.g., 'noisy neighbours'), cleanliness (e.g., 'how common are rubbish/litter in area'), and access (e.g., 'poor public transport'), which we summed as a continuous score. Neighbourhood deprivation, commonly used as a measure of low SES or poverty, has been linked to increased risk of exposure to ACEs (Lewer et al., 2020; Walsh et al., 2019) and poor adolescent mental health (Visser et al., 2021).

Parent mental health problems (pre-exposure ACE). Parents reported their mental health symptoms (e.g., 'so depressed nothing could cheer you up') in the last 30 days using the Kessler (K6) scale at Sweep 2 (age 3), which we summed as a continuous score. There is a well-established literature supporting the association between parent mental health problems and offspring mental health disorders (McLaughlin et al., 2012), and poor parent mental health and ACE exposure (Baldwin et al., 2020; Bifulco et al., 2002).

Parent substance use (pre-exposure ACE). Parents reported the frequency of their alcohol and drug use, and whether they displayed alcohol dependency (e.g., drinking first thing in the morning) at Sweep 2 (age 3), which we recoded as a binary variable. Parent substance use has been shown to significantly predict offspring mental disorders and offspring substance use in adolescence, even after controlling for other ACEs (Jääskeläinen et al., 2016).

Parental divorce (pre-exposure ACE). Parents reported if they had ever been divorced or separated at Sweep 2 (age 3), which we recoded as a binary variable. Parent divorce has been consistently linked to an increased risk of developing a variety of mental health conditions in children affected by divorce (Auersperg et al., 2019).

Bereavement (pre-exposure ACE). If either the natural mother or natural father of the cohort member had died at Sweep 2 (age 3), bereavement was binarized as present. Parentally bereaved children have been shown to be at increased risk for psychological problems (Kaplow et al., 2010).

Domestic violence (pre-exposure ACE). Parents reported whether their partner had ever used force in their relationship at Sweep 2 (age 3), which we recoded as a binary variable. Research has shown that children and adolescents living with domestic violence are at increased risk of experiencing other forms of abuse, exposure to multiple ACEs, and developing emotional and behavioural problems (Holt et al., 2008).

Peer victimisation (pre-exposure ACE). Parents reported whether their child had been picked on or bullied by other children using the Strengths and Difficulties Questionnaire at Sweep 2 (age 3), which we recoded as a binary variable (certainly true = 1; not true/somewhat true = 0). Our dimensional analysis demonstrated robust evidence for an association between peer victimisation and adolescent psychopathology in the MCS (Chow et al., 2024).

Parental discipline. Parents reported how often they used physical and verbal discipline tactics with their child (e.g., 'smacking', 'tells child off when naughty') at Sweep 3 (age 5), which we summed as a continuous score. In the Millennium Cohort Study specifically, harsh parental discipline has been linked to emotional and behavioural problems and moderated the effects of family poverty and adversity on these problems (Flouri & Midouhas, 2017).

Household income. Household income was reported using the OECD Income Weighted Quintiles at Sweep 3 (age 5), which we recoded as an ordinal variable ('Lowest quintile' = 1; 'Second quintile' = 2; 'Third quintile' = 3; 'Fourth quintile' = 4; 'Fifth quintile' = 5). Low household income has been linked to increased risk of exposure to ACEs (Baldwin et al., 2020; Lewer et al., 2020; Walsh et al., 2019) and mental health problems in childhood and adolescence (Reiss, 2013).

Child chronic illness. Parents reported if their child had any longstanding chronic illness at Sweep 3 (age 5), which we binarized as present. Compared to their healthy peers, children with chronic illness have been found to display higher internalising, externalising, and behavioural problems in adolescence (Pinquart & Shen, 2011).

ADHD diagnosis. Parents reported if their child had been diagnosed with ADHD at Sweep 3 (age 5), which we binarized as present. There is evidence that children with ADHD are at risk of higher ACE exposure compared to their peers without ADHD (Brown et al., 2017; Lugo-Candelas et al., 2021), and the literature supports an association between childhood ADHD and subsequent psychiatric disorders (Nourredine et al., 2021).

Autism diagnosis. Parents reported if their child had been diagnosed with autism at Sweep 3 (age 5), which we binarized as present. Autistic children are at greater risk of experiencing ACEs compared to non-autistic children (Hartley et al., 2024), and research has shown that co-occurring mental health conditions are highly prevalent in the autism population (Lai et al., 2019).

Cognitive ability. Children were assessed on their verbal ability and problem-solving skills using the British Ability Scales at Sweep 3 (age 5), which we summed as a continuous score. Higher cognitive ability may serve as a protective factor against mental health problems in adolescence, although this may vary by age and gender (Weeks et al., 2014).

Early behavioural difficulties. Parents reported their child's emotional and behavioural difficulties using the Total Difficulties Scale from the Strengths and Difficulties Questionnaire (SDQ) at Sweep 3 (age 5), which we summed as a continuous score. Early childhood behavioural difficulties, measured using the SDQ, have been shown to predict the diagnosis of neurodevelopmental disorders in adolescence (Ahinkorah et al., 2024).

Mother-child relationship. Mothers reported their perceptions of their relationship with their child using the Pianta Child-Parent Relationship Scale at Sweep 3 (age 5), which we summed as a continuous score (a greater score indicating a more positive relationship). Poor parent-child relationships have been shown to predict psychiatric disorders in adolescence and later adulthood (Weich et al., 2009).

Father-child relationship. Fathers reported their perceptions of their relationship with their child using the Pianta Child-Parent Relationship Scale at Sweep 3 (age 5), which we summed as a continuous score (a greater score indicating a more positive relationship). Poor parent-child relationships have been shown to predict psychiatric disorders in adolescence and later adulthood (Weich et al., 2009).

Emotion dysregulation. Parents reported their child's emotion regulation abilities (e.g., 'is easily frustrated') using the Child Social Behaviour Questionnaire at Sweep 3 (age 5), which we summed as a continuous score (a greater score indicating worse emotion dysregulation). There is evidence that emotion dysregulation predicts increases in depression and anxiety symptoms in adolescence (Masters et al., 2019), and emotion dysregulation may be a cross-disorder trait across internalising, externalising, and neurodevelopmental disorders (Bierens et al., 2023).

Sibling number. The number of siblings of the cohort member in the household was reported at Sweep 3 (age 5), which we kept as a continuous variable. Interestingly, there is some evidence from US and China cohorts that sibling number is negatively associated with adolescent mental health (Downey & Cao, 2024).

Household size. The number of people living in the household was reported at Sweep 3 (age 5), which we kept as a continuous variable. Larger family size has been linked to increased risk of child maltreatment (Baldwin et al., 2020). Household size has been linked to adolescent mental health but with mixed findings. There is some evidence from a Norwegian cohort that a large household is associated with fewer mental health problems in children, although this pattern could be attributed to having older siblings (Grinde & Tambs, 2016). In low-income contexts, living in larger households has been linked to higher adolescent achievement, but only in the context of lower quality mother-child relationships (Elliott et al., 2016).

Childhood accidents. Parents reported the number of accidents or injuries their child had experienced at Sweep 3 (age 5), which we kept as a continuous variable. Exposure to accidents or injuries has been shown to predict an increased likelihood of adolescent mental disorders (Jenness et al., 2017).

BMI. Child body mass index (BMI) was recorded at Sweep 3 (age 5), which we kept as a continuous variable. Research has shown a U-shaped association between BMI and adolescent mental health, where individuals on both ends of the BMI z score spectrum (underweight and overweight) exhibited worse mental health symptoms, consistent across sex and school grades (Chen et al., 2024).

Table 6.15 Missing data per variable before imputation in the MCS propensity score analysis.

Variable	*Complete n*	*Missing n*	*Missing %*
Parent mental health problems	15,133	3,406	18.37
Parent substance use	15,424	3,115	16.80
Parent divorce	15,472	3,067	16.54
Bereavement	15,741	2,798	15.09
Domestic violence	12,882	5,657	30.51
Emotional neglect	15,567	2,972	16.03
Physical victimisation	11,703	6,836	36.87
Emotional victimisation	11,703	6,836	36.87
Sexual victimisation	11,701	6,838	36.88
Peer victimisation	15,631	2,908	15.69
Depression and anxiety symptoms	9,637	8,902	48.02
Self-harm	9,386	9,153	49.37
Suicide attempt	9,381	9,158	49.40

6.2.2 Love plots of covariate balance before and after propensity score matching.

Figure 6.18 Covariate balance before and after matching on parent mental health problems.

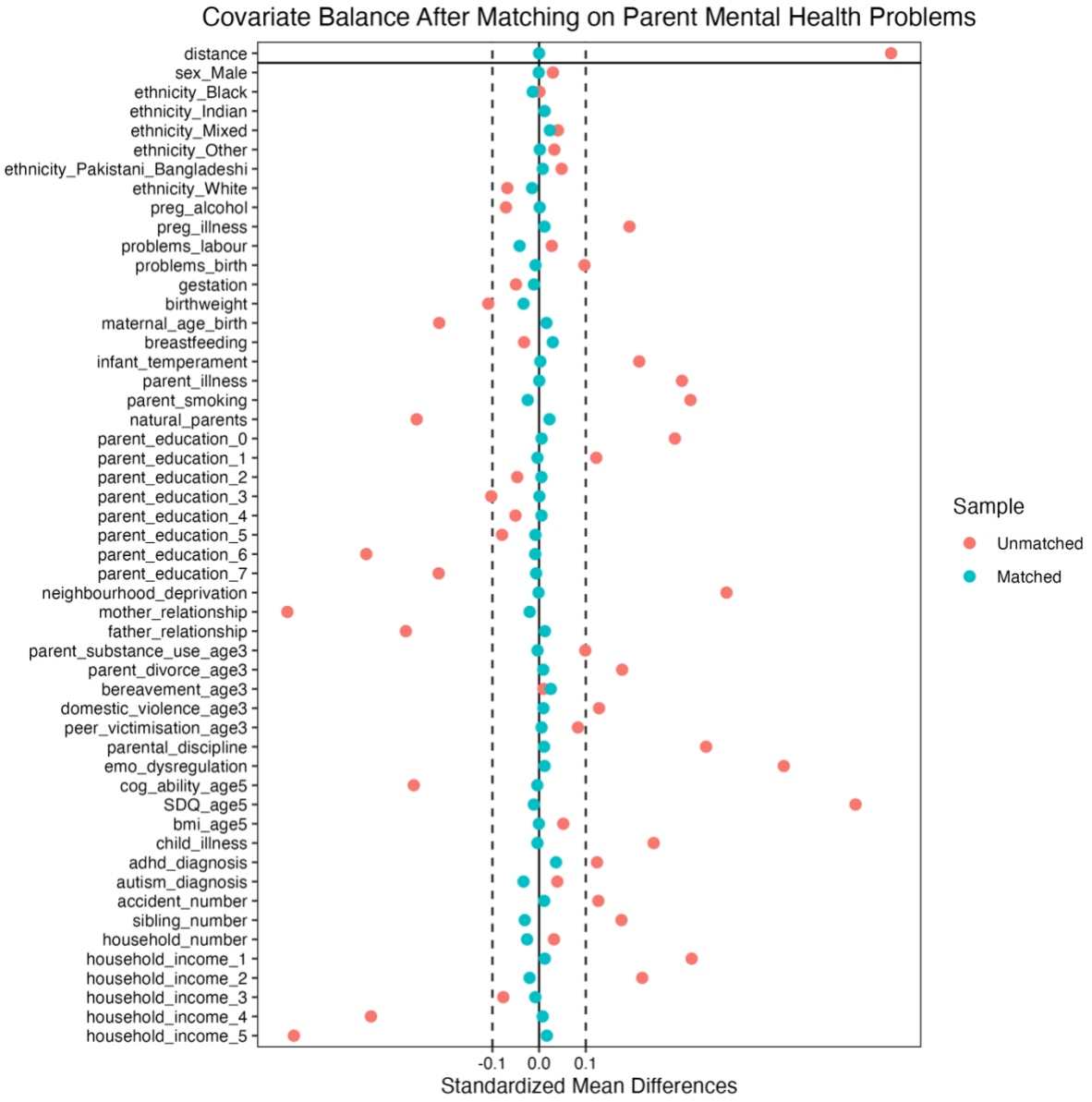


Figure 6.19 Covariate balance before and after matching on parent substance use.

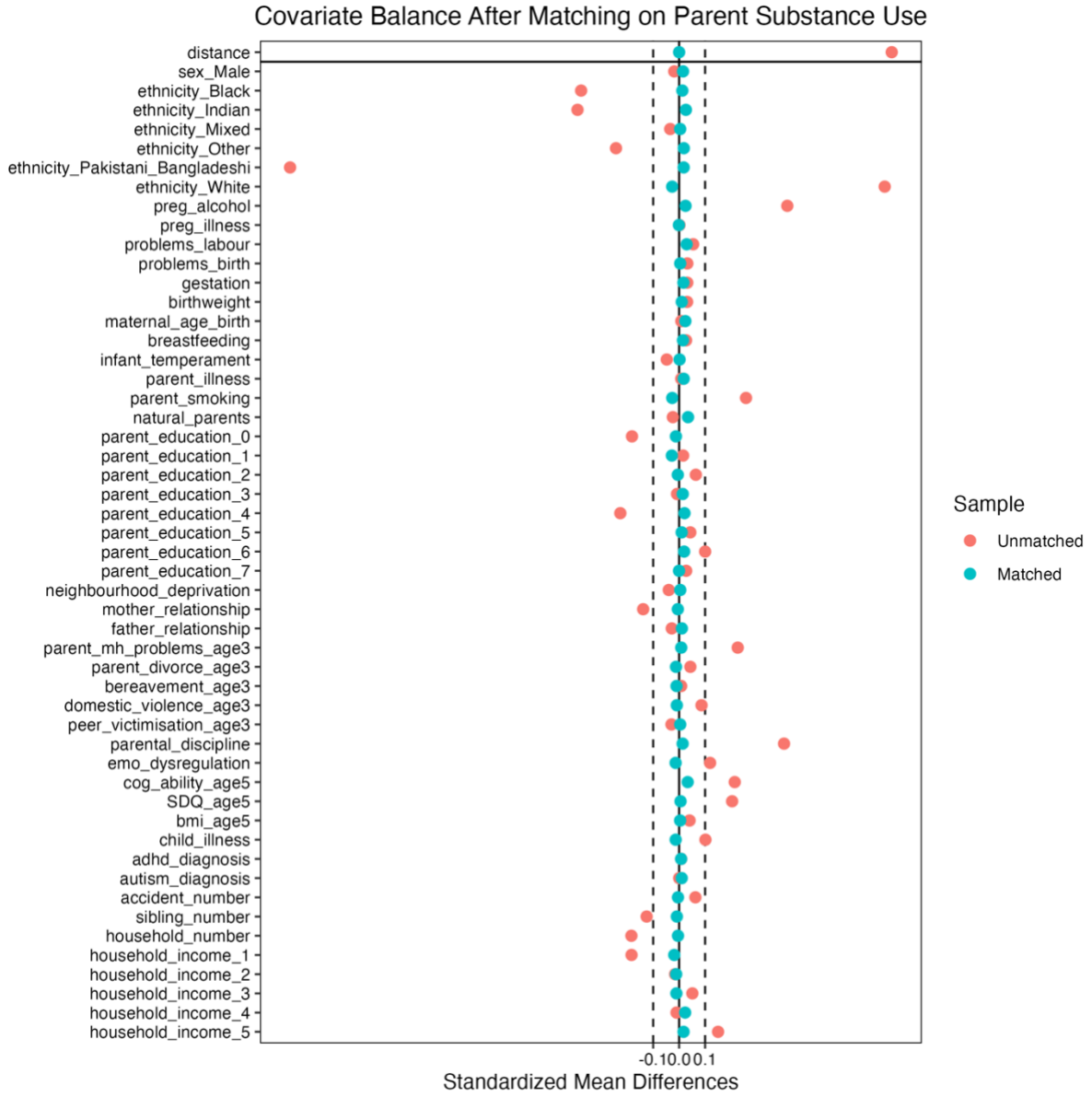


Figure 6.20 Covariate balance before and after matching on parent divorce.

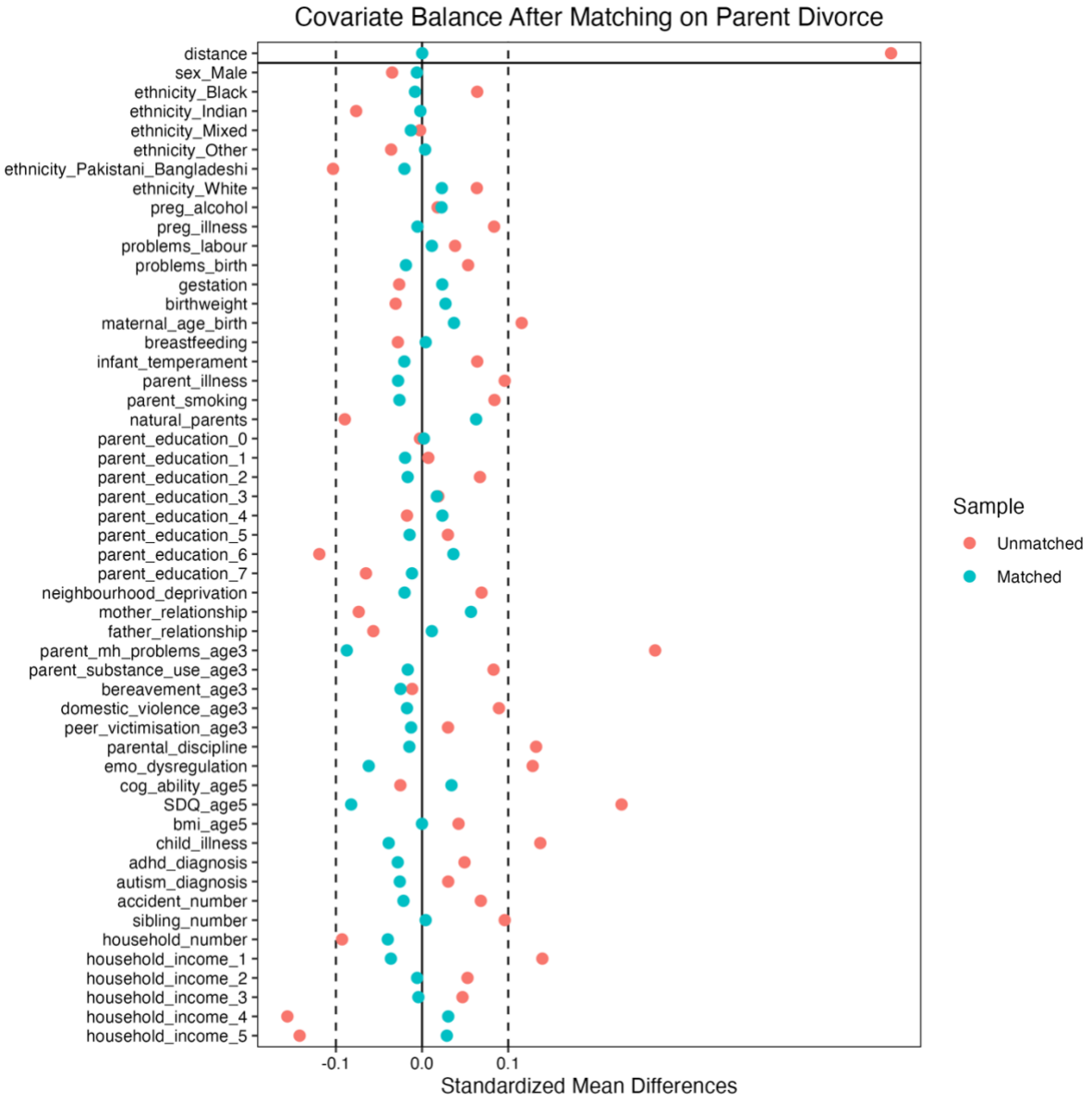


Figure 6.21 Covariate balance before and after matching on bereavement.

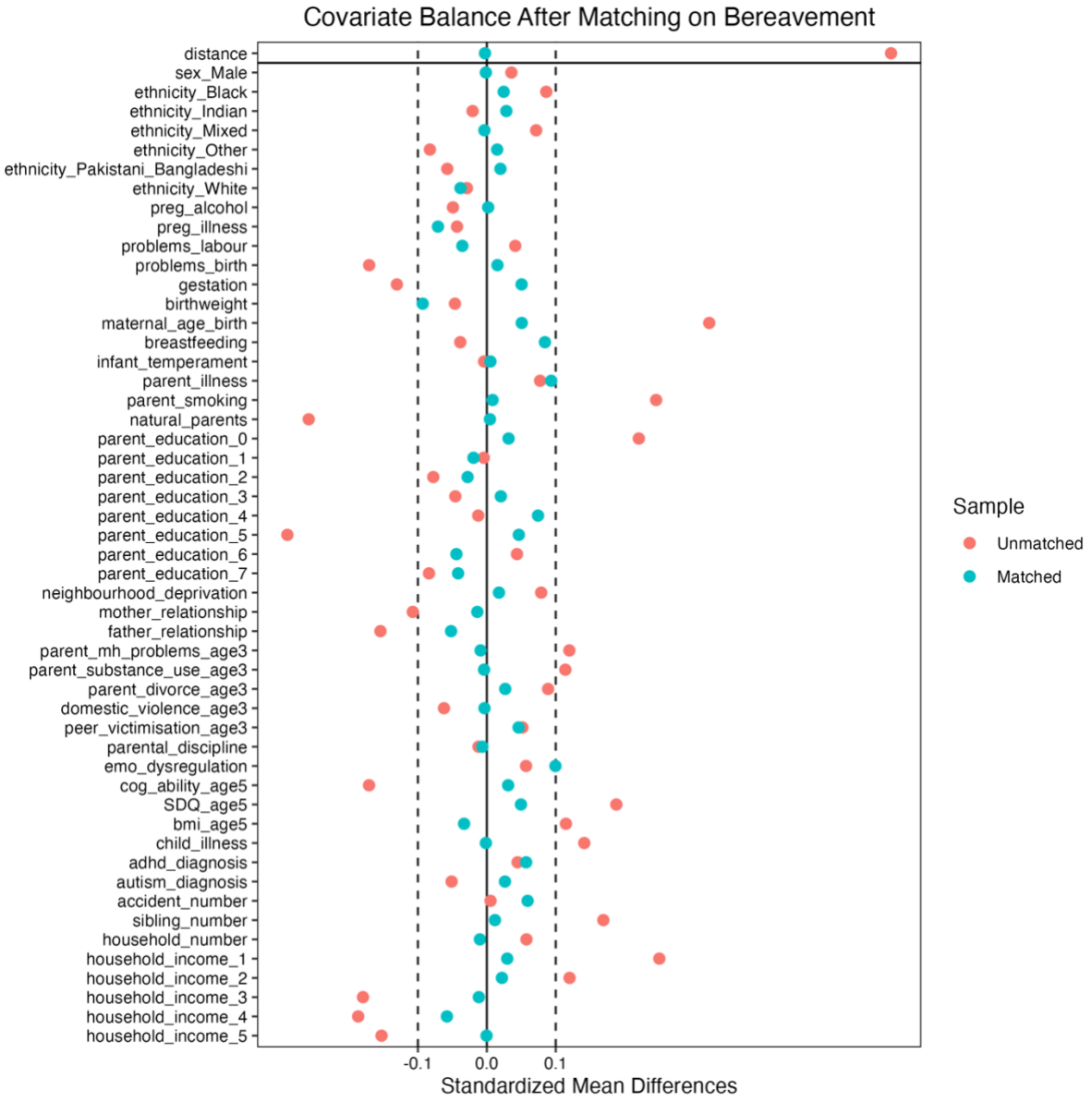


Figure 6.22 Covariate balance before and after matching on domestic violence.

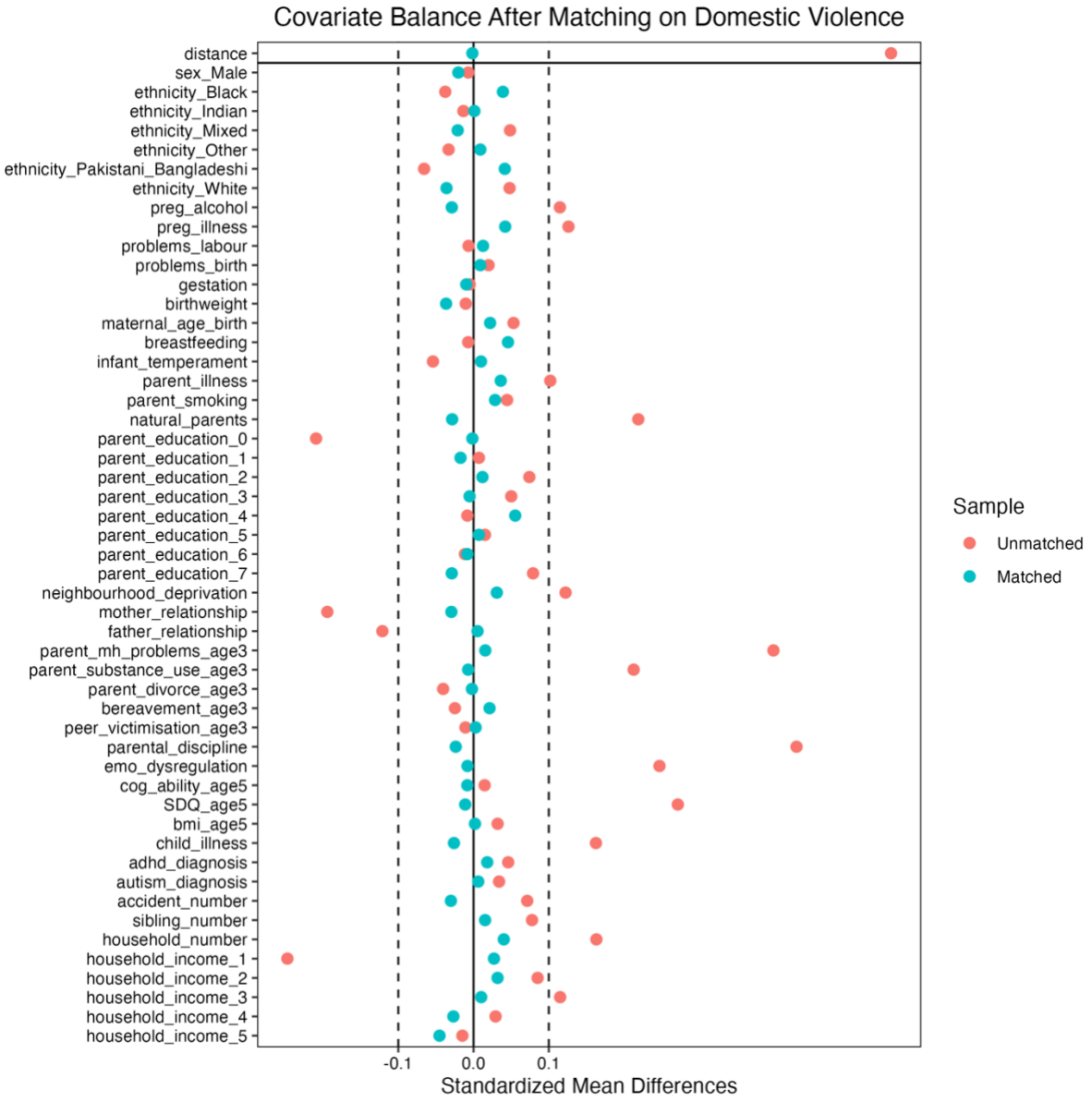


Figure 6.23 Covariate balance before and after matching on emotional neglect.

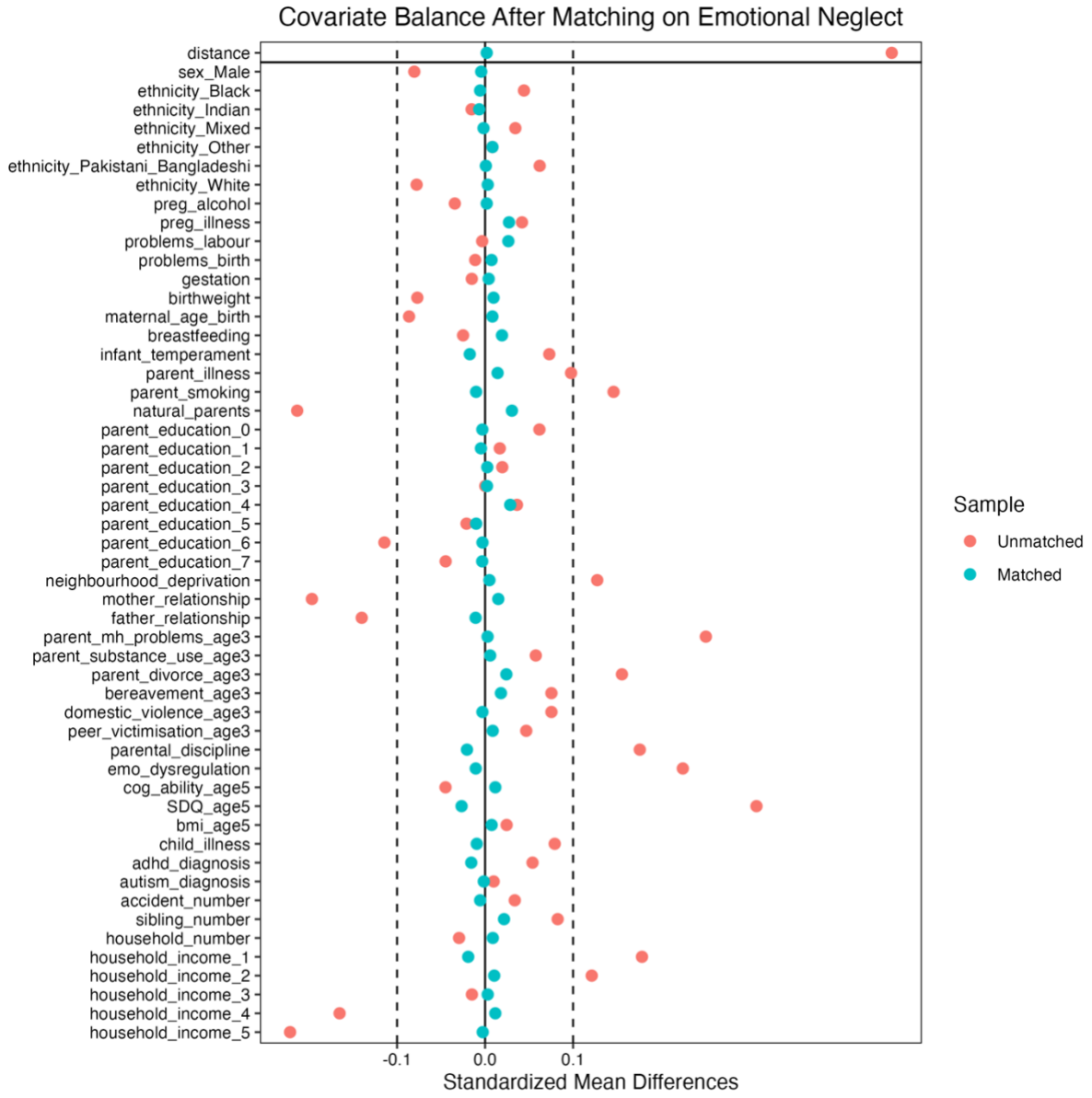


Figure 6.24 Covariate balance before and after matching on physical victimisation.

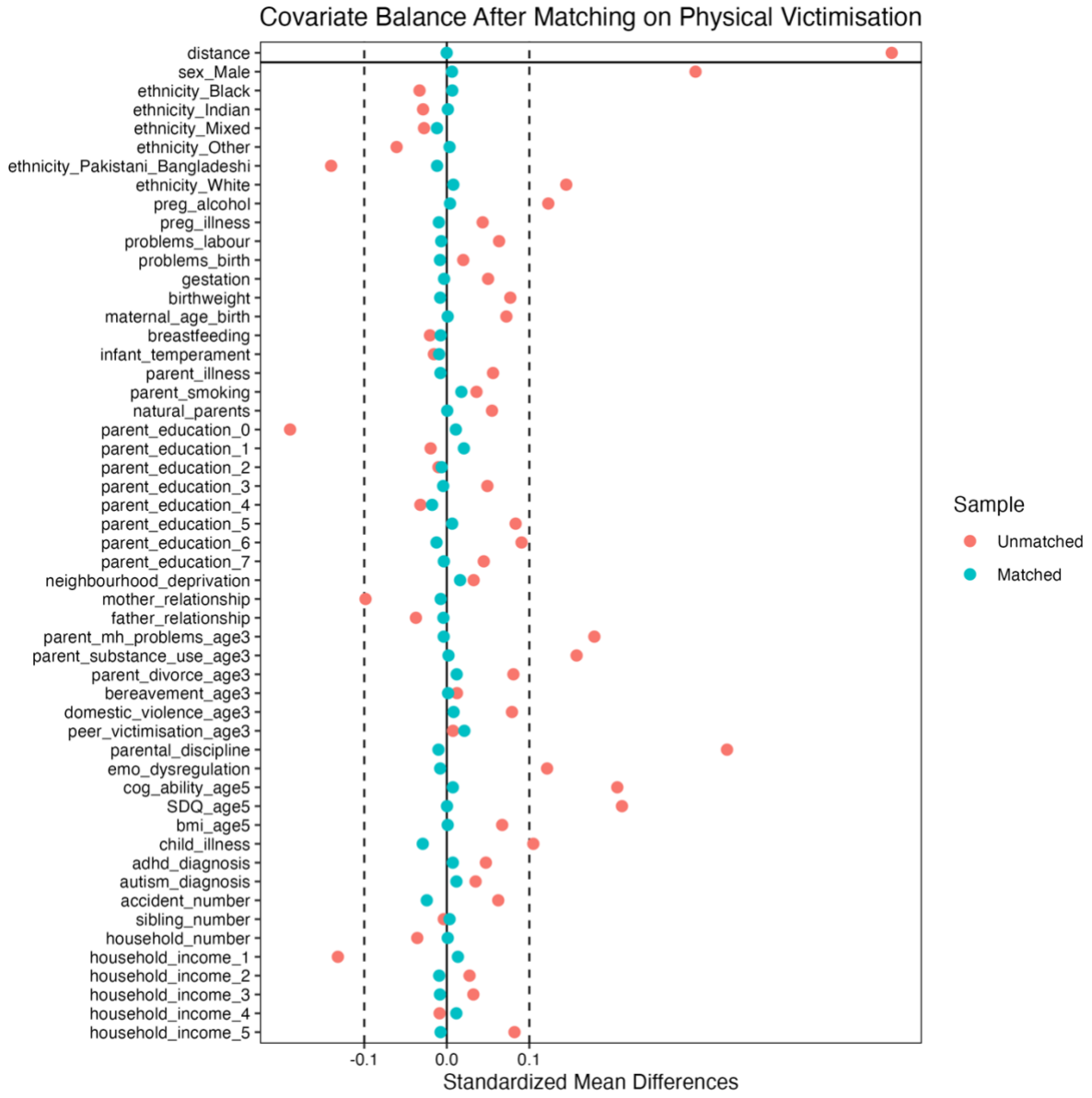


Figure 6.25 Covariate balance before and after matching on emotional victimisation.

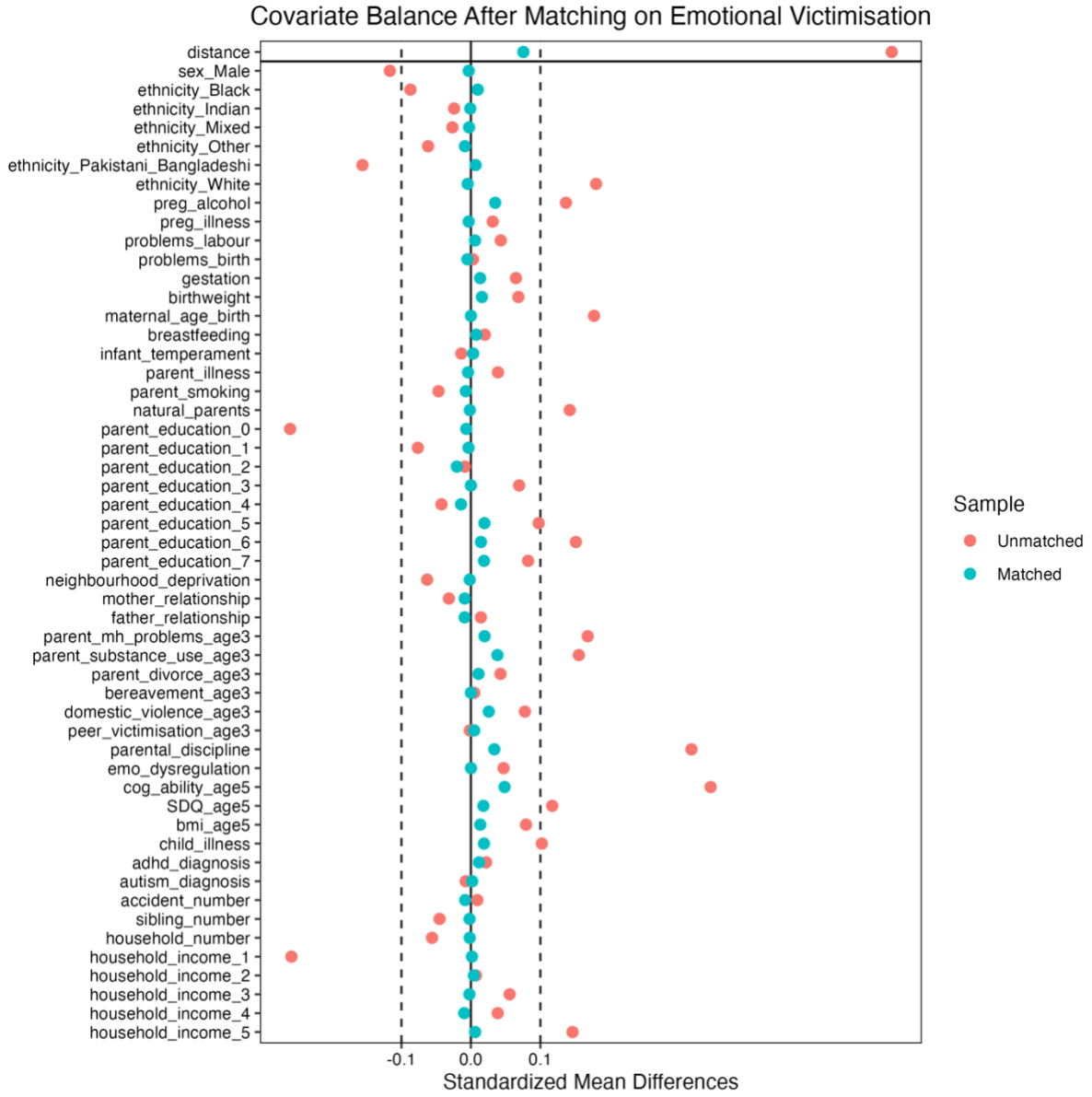


Figure 6.26 Covariate balance before and after matching on sexual victimisation.

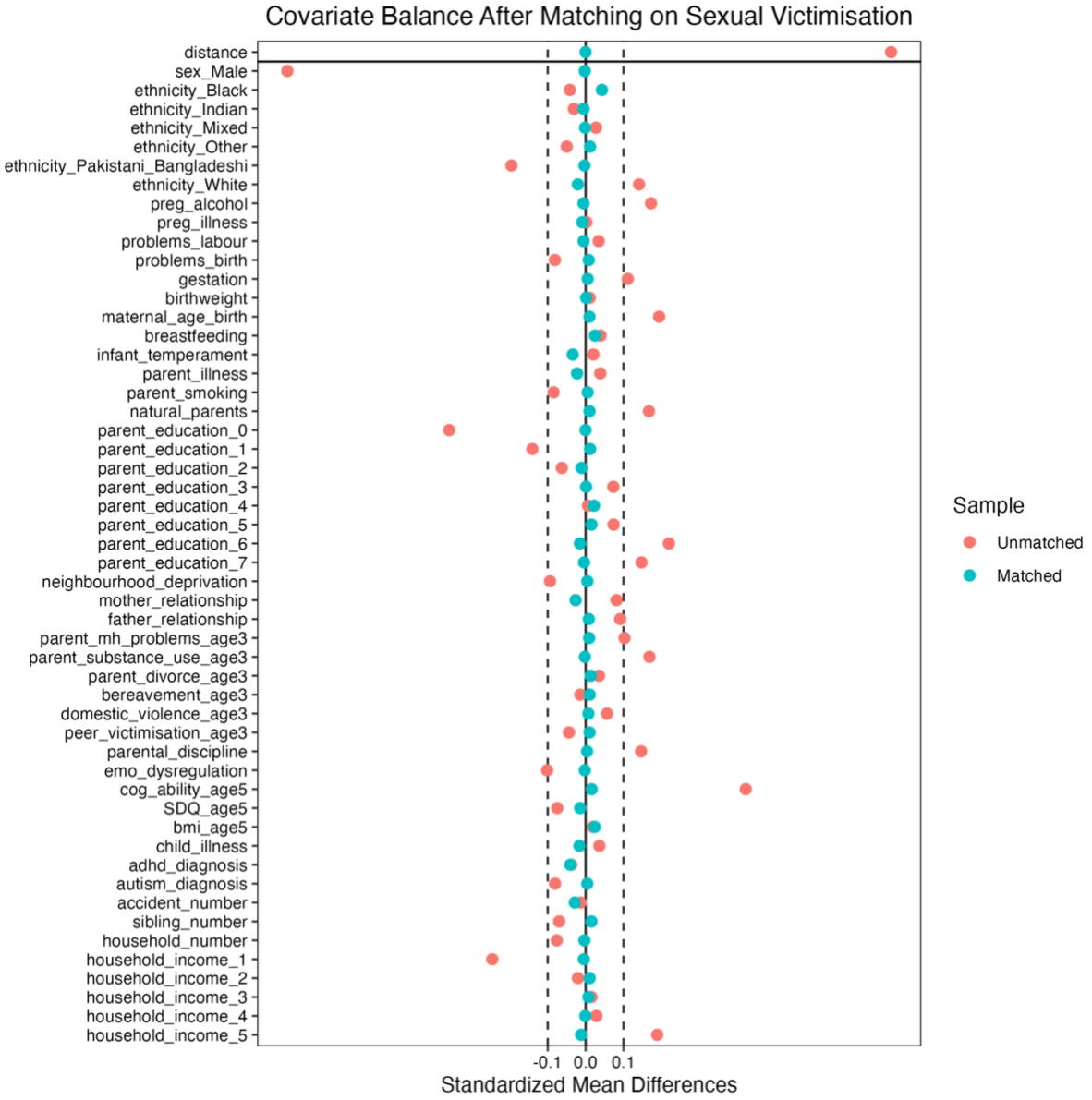
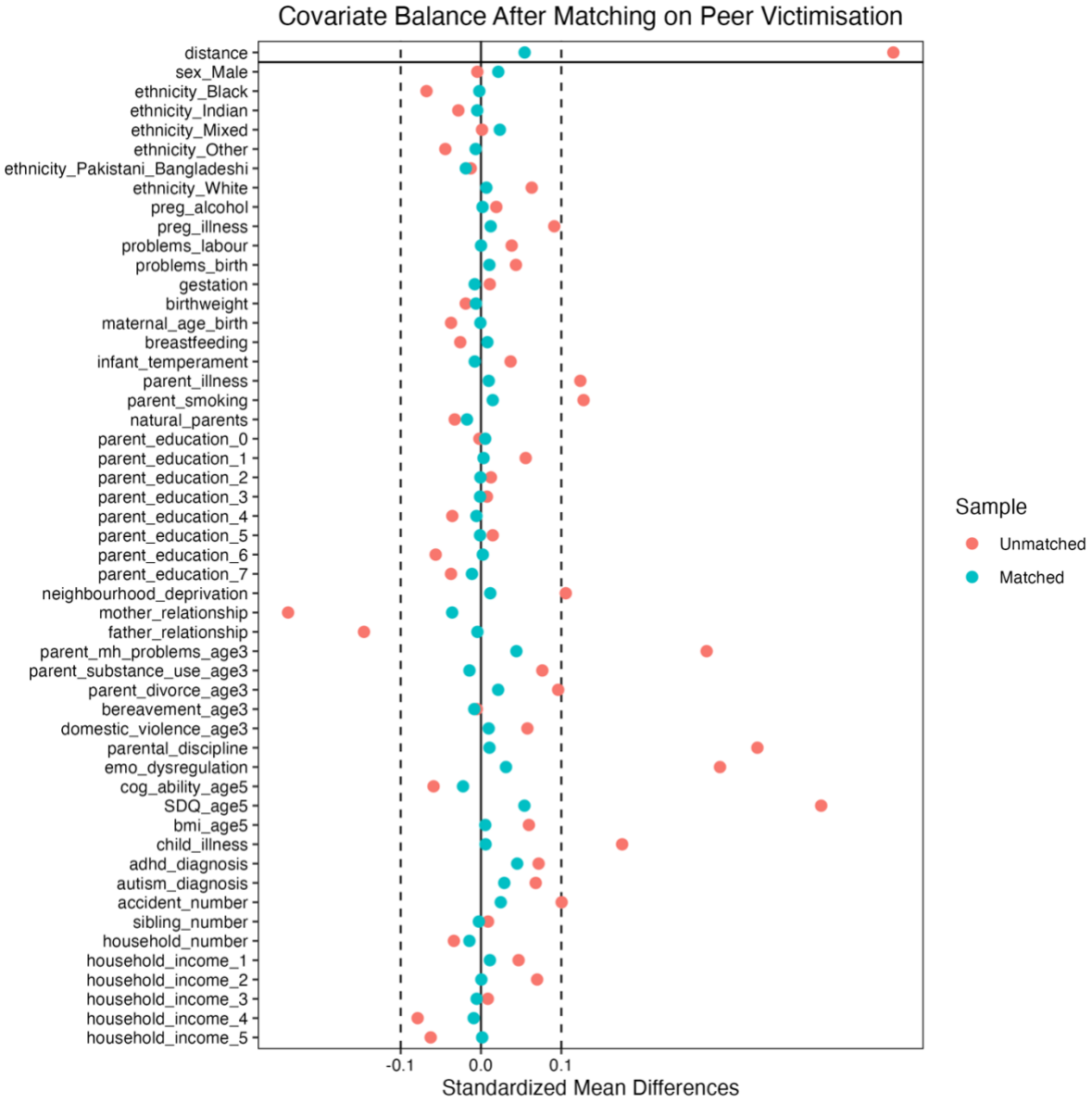


Figure 6.27 Covariate balance before and after matching on peer victimisation.



6.2.3 Propensity score matched estimates in the MCS imputed sample.

Table 6.16 Associations between ACEs and depression/anxiety in the imputed sample.

ACE	Model Adjustment	β	95% CI	p-value	Δ% in β
Parent mental health problems	Unadjusted Unmatched	0.25	[0.22, 0.28]	< .001***	
	Adjusted Unmatched	0.12	[0.09, 0.15]	< .001***	
	Unadjusted Matched	0.29	[0.26, 0.32]	< .001***	
	Adjusted Matched	0.17	[0.14, 0.19]	< .001***	↓32%
Parent substance use	Unadjusted Unmatched	0.19	[0.17, 0.21]	< .001***	
	Adjusted Unmatched	0.04	[0.02, 0.06]	< .001***	
	Unadjusted Matched	0.12	[0.10, 0.15]	< .001***	
	Adjusted Matched	0.01	[-0.01, 0.03]	0.192	↓94.7%
Parent divorce	Unadjusted Unmatched	0.14	[0.11, 0.16]	< .001***	
	Adjusted Unmatched	0.00	[-0.02, 0.02]	0.729	
	Unadjusted Matched	0.10	[0.08, 0.13]	< .001***	
	Adjusted Matched	0.00	[-0.02, 0.02]	0.803	↓100%
Bereavement	Unadjusted Unmatched	0.08	[0.01, 0.16]	0.035*	
	Adjusted Unmatched	-0.07	[-0.14, -0.01]	0.036*	
	Unadjusted Matched	0.08	[0, 0.16]	0.074	
	Adjusted Matched	-0.12	[-0.19, -0.05]	< .001***	↑50%†
Domestic violence	Unadjusted Unmatched	0.15	[0.11, 0.19]	< .001***	
	Adjusted Unmatched	0.02	[-0.02, 0.05]	0.426	
	Unadjusted Matched	0.08	[0.04, 0.13]	< .001***	
	Adjusted Matched	-0.02	[-0.06, 0.01]	0.254	↓86.7%†
Emotional neglect	Unadjusted Unmatched	0.39	[0.37, 0.41]	< .001***	
	Adjusted Unmatched	0.17	[0.15, 0.19]	< .001***	
	Unadjusted Matched	0.40	[0.38, 0.42]	< .001***	
	Adjusted Matched	0.18	[0.16, 0.2]	< .001***	↓53.8%

ACE	Model Adjustment	β	95% CI	p-value	Δ% in β
Physical victimisation	Unadjusted Unmatched	0.47	[0.45, 0.49]	< .001***	
	Adjusted Unmatched	0.07	[0.05, 0.09]	< .001***	
	Unadjusted Matched	0.43	[0.41, 0.45]	< .001***	
	Adjusted Matched	0.08	[0.06, 0.1]	< .001***	↓83%
Emotional victimisation	Unadjusted Unmatched	0.58	[0.56, 0.59]	< .001***	
	Adjusted Unmatched	0.40	[0.38, 0.42]	< .001***	
	Unadjusted Matched	0.50	[0.48, 0.51]	< .001***	
	Adjusted Matched	0.34	[0.32, 0.36]	< .001***	↓41.4%
Sexual victimisation	Unadjusted Unmatched	0.68	[0.64, 0.71]	< .001***	
	Adjusted Unmatched	0.36	[0.33, 0.39]	< .001***	
	Unadjusted Matched	0.55	[0.51, 0.58]	< .001***	
	Adjusted Matched	0.27	[0.24, 0.30]	< .001***	↓60.3%
Peer victimisation	Unadjusted Unmatched	0.36	[0.34, 0.38]	< .001***	
	Adjusted Unmatched	0.11	[0.09, 0.13]	< .001***	
	Unadjusted Matched	0.33	[0.31, 0.36]	< .001***	
	Adjusted Matched	0.10	[0.08, 0.12]	< .001***	↓72.2%

Note. β = standardised regression coefficient, CI = confidence interval.

Δ% in β = percentage change in the effect size from the Unadjusted Unmatched model to the Adjusted Matched model. ↓ represents a decrease while ↑ represents an increase. † denotes reversal in effect direction.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.17 Associations between ACEs and psychological distress in the imputed sample.

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Parent mental health problems	Unadjusted Unmatched	2.21	[1.92, 2.55]	< .001***	
	Adjusted Unmatched	1.44	[1.23, 1.69]	< .001***	
	Unadjusted Matched	2.09	[1.82, 2.41]	< .001***	
	Adjusted Matched	1.55	[1.33, 1.81]	< .001***	↓29.9%
Parent substance use	Unadjusted Unmatched	1.64	[1.46, 1.83]	< .001***	
	Adjusted Unmatched	1.02	[0.90, 1.16]	0.753	
	Unadjusted Matched	1.39	[1.25, 1.56]	< .001***	
	Adjusted Matched	1.00	[0.89, 1.13]	0.977	↓39%
Parent divorce	Unadjusted Unmatched	1.83	[1.62, 2.06]	< .001***	
	Adjusted Unmatched	1.14	[1.00, 1.30]	0.072	
	Unadjusted Matched	1.53	[1.36, 1.72]	< .001***	
	Adjusted Matched	1.13	[0.99, 1.28]	0.085	↓38.3%
Bereavement	Unadjusted Unmatched	1.48	[1.02, 2.14]	0.051	
	Adjusted Unmatched	0.80	[0.53, 1.21]	0.325	
	Unadjusted Matched	1.21	[0.83, 1.75]	0.350	
	Adjusted Matched	0.51	[0.34, 0.76]	0.002**	↓65.5%
Domestic violence	Unadjusted Unmatched	1.66	[1.35, 2.03]	< .001***	
	Adjusted Unmatched	1.10	[0.88, 1.38]	0.422	
	Unadjusted Matched	1.34	[1.10, 1.64]	0.006**	
	Adjusted Matched	0.93	[0.74, 1.16]	0.540	↓44%
Emotional neglect	Unadjusted Unmatched	4.26	[3.82, 4.75]	< .001***	
	Adjusted Unmatched	2.23	[1.97, 2.51]	< .001***	
	Unadjusted Matched	4.31	[3.86, 4.80]	< .001***	
	Adjusted Matched	2.36	[2.09, 2.66]	< .001***	↓44.6%

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Physical victimisation	Unadjusted Unmatched	4.13	[3.71, 4.61]	< .001***	
	Adjusted Unmatched	1.12	[0.98, 1.27]	0.101	
	Unadjusted Matched	3.98	[3.57, 4.43]	< .001***	
	Adjusted Matched	1.18	[1.04, 1.34]	0.014*	↓71.4%
Emotional victimisation	Unadjusted Unmatched	9.91	[8.65, 11.36]	< .001***	
	Adjusted Unmatched	4.91	[4.20, 5.74]	< .001***	
	Unadjusted Matched	8.20	[7.01, 9.59]	< .001***	
	Adjusted Matched	4.33	[3.64, 5.15]	< .001***	↓56.3%
Sexual victimisation	Unadjusted Unmatched	7.28	[6.42, 8.27]	< .001***	
	Adjusted Unmatched	3.00	[2.61, 3.44]	< .001***	
	Unadjusted Matched	5.05	[4.47, 5.71]	< .001***	
	Adjusted Matched	2.34	[2.05, 2.68]	< .001***	↓67.9%
Peer victimisation	Unadjusted Unmatched	4.39	[3.94, 4.89]	< .001***	
	Adjusted Unmatched	1.92	[1.70, 2.17]	< .001***	
	Unadjusted Matched	3.73	[3.26, 4.27]	< .001***	
	Adjusted Matched	1.84	[1.59, 2.14]	< .001***	↓58.1%

Note. OR = odds ratio, CI = confidence interval.

Δ% in OR = percentage change in the effect size from the Unadjusted Unmatched model to the Adjusted Matched model. ↓ represents a decrease while ↑ represents an increase. † denotes reversal in effect direction.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.18 Associations between ACEs and self-harm in the imputed sample.

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Parent mental health problems	Unadjusted Unmatched	1.82	[1.60, 2.07]	< .001***	
	Adjusted Unmatched	1.19	[1.03, 1.38]	0.026*	
	Unadjusted Matched	1.68	[1.48, 1.91]	< .001***	
	Adjusted Matched	1.19	[1.03, 1.38]	0.026*	↓34.6%
Parent substance use	Unadjusted Unmatched	1.78	[1.62, 1.96]	< .001***	
	Adjusted Unmatched	1.12	[1.01, 1.25]	0.047*	
	Unadjusted Matched	1.48	[1.34, 1.62]	< .001***	
	Adjusted Matched	1.06	[0.95, 1.17]	0.350	↓40.4%
Parent divorce	Unadjusted Unmatched	1.59	[1.43, 1.77]	< .001***	
	Adjusted Unmatched	0.99	[0.87, 1.11]	0.849	
	Unadjusted Matched	1.31	[1.18, 1.45]	< .001***	
	Adjusted Matched	0.92	[0.81, 1.03]	0.171	↓42.1%
Bereavement	Unadjusted Unmatched	1.46	[1.05, 2.02]	0.030*	
	Adjusted Unmatched	0.84	[0.58, 1.22]	0.397	
	Unadjusted Matched	1.49	[1.07, 2.06]	0.022*	
	Adjusted Matched	0.81	[0.56, 1.17]	0.291	↓44.5%
Domestic violence	Unadjusted Unmatched	1.55	[1.29, 1.85]	< .001***	
	Adjusted Unmatched	1.02	[0.83, 1.25]	0.869	
	Unadjusted Matched	1.18	[0.99, 1.41]	0.080	
	Adjusted Matched	0.83	[0.68, 1.01]	0.072	↓46.5%
Emotional neglect	Unadjusted Unmatched	3.62	[3.29, 3.99]	< .001***	
	Adjusted Unmatched	1.86	[1.67, 2.08]	< .001***	
	Unadjusted Matched	3.28	[2.98, 3.60]	< .001***	
	Adjusted Matched	1.68	[1.50, 1.87]	< .001***	↓53.6%

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Physical victimisation	Unadjusted Unmatched	4.93	[4.49, 5.42]	< .001***	
	Adjusted Unmatched	1.35	[1.21, 1.51]	< .001***	
	Unadjusted Matched	4.60	[4.19, 5.05]	< .001***	
	Adjusted Matched	1.42	[1.27, 1.58]	< .001***	↓71.2%
Emotional victimisation	Unadjusted Unmatched	11.49	[10.21, 12.94]	< .001***	
	Adjusted Unmatched	5.64	[4.93, 6.46]	< .001***	
	Unadjusted Matched	8.94	[7.83, 10.22]	< .001***	
	Adjusted Matched	4.64	[4.00, 5.38]	< .001***	↓59.6%
Sexual victimisation	Unadjusted Unmatched	8.32	[7.40, 9.35]	< .001***	
	Adjusted Unmatched	3.30	[2.91, 3.75]	< .001***	
	Unadjusted Matched	5.40	[4.82, 6.05]	< .001***	
	Adjusted Matched	2.29	[2.02, 2.59]	< .001***	↓72.5%
Peer victimisation	Unadjusted Unmatched	4.30	[3.92, 4.72]	< .001***	
	Adjusted Unmatched	1.85	[1.66, 2.05]	< .001***	
	Unadjusted Matched	3.72	[3.31, 4.17]	< .001***	
	Adjusted Matched	1.75	[1.53, 1.99]	< .001***	↓59.3%

Note. OR = odds ratio, CI = confidence interval.

Δ% in OR = percentage change in the effect size from the Unadjusted Unmatched model to the Adjusted Matched model. ↓ represents a decrease while ↑ represents an increase. † denotes reversal in effect direction.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.19 Associations between ACEs and suicide attempt in the imputed sample.

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Parent mental health problems	Unadjusted Unmatched	2.96	[2.46, 3.56]	< .001***	
	Adjusted Unmatched	1.82	[1.49, 2.23]	< .001***	
	Unadjusted Matched	2.18	[1.82, 2.61]	< .001***	
	Adjusted Matched	1.55	[1.27, 1.89]	< .001***	↓47.6%
Parent substance use	Unadjusted Unmatched	1.80	[1.54, 2.12]	< .001***	
	Adjusted Unmatched	1.09	[0.92, 1.29]	0.360	
	Unadjusted Matched	1.42	[1.21, 1.65]	< .001***	
	Adjusted Matched	1.01	[0.85, 1.19]	0.954	↓43.9%
Parent divorce	Unadjusted Unmatched	1.91	[1.61, 2.26]	< .001***	
	Adjusted Unmatched	1.10	[0.91, 1.32]	0.350	
	Unadjusted Matched	1.40	[1.19, 1.65]	< .001***	
	Adjusted Matched	1.01	[0.84, 1.20]	0.954	↓47.1%
Bereavement	Unadjusted Unmatched	2.41	[1.56, 3.73]	< .001***	
	Adjusted Unmatched	1.38	[0.85, 2.24]	0.216	
	Unadjusted Matched	2.11	[1.37, 3.26]	0.001**	
	Adjusted Matched	1.55	[0.95, 2.51]	0.093	↓35.7%
Domestic violence	Unadjusted Unmatched	1.89	[1.44, 2.48]	< .001***	
	Adjusted Unmatched	1.20	[0.90, 1.62]	0.247	
	Unadjusted Matched	1.30	[1.00, 1.71]	0.067	
	Adjusted Matched	0.94	[0.70, 1.26]	0.695	↓50.3%
Emotional neglect	Unadjusted Unmatched	4.78	[4.10, 5.58]	< .001***	
	Adjusted Unmatched	2.12	[1.79, 2.51]	< .001***	
	Unadjusted Matched	3.88	[3.35, 4.50]	< .001***	
	Adjusted Matched	1.86	[1.58, 2.18]	< .001***	↓61.1%

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Physical victimisation	Unadjusted Unmatched	5.44	[4.67, 6.35]	< .001***	
	Adjusted Unmatched	1.27	[1.07, 1.52]	0.008**	
	Unadjusted Matched	5.55	[4.76, 6.48]	< .001***	
	Adjusted Matched	1.45	[1.22, 1.73]	< .001***	↓73.3%
Emotional victimisation	Unadjusted Unmatched	15.77	[12.35, 20.13]	< .001***	
	Adjusted Unmatched	5.93	[4.53, 7.77]	< .001***	
	Unadjusted Matched	12.65	[9.56, 16.74]	< .001***	
	Adjusted Matched	5.02	[3.71, 6.79]	< .001***	↓68.2%
Sexual victimisation	Unadjusted Unmatched	7.95	[6.73, 9.38]	< .001***	
	Adjusted Unmatched	2.91	[2.44, 3.48]	< .001***	
	Unadjusted Matched	5.45	[4.65, 6.38]	< .001***	
	Adjusted Matched	2.14	[1.80, 2.54]	< .001***	↓73.1%
Peer victimisation	Unadjusted Unmatched	7.71	[6.46, 9.20]	< .001***	
	Adjusted Unmatched	3.04	[2.51, 3.67]	< .001***	
	Unadjusted Matched	5.88	[4.73, 7.32]	< .001***	
	Adjusted Matched	2.61	[2.07, 3.29]	< .001***	↓66.1%

Note. OR = odds ratio, CI = confidence interval.

Δ% in OR = percentage change in the effect size from the Unadjusted Unmatched model to the Adjusted Matched model. ↓ represents a decrease while ↑ represents an increase. † denotes reversal in effect direction.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

6.2.4 Propensity score matched estimates in the MCS complete sample.

Table 6.20 Associations between ACEs and depression/anxiety in the complete sample.

ACE	Model Adjustment	β	95% CI	p-value	Δ% in β
Parent mental health problems	Unadjusted Unmatched	0.36	[0.24, 0.48]	< .001***	
	Adjusted Unmatched	0.28	[0.17, 0.38]	< .001***	
	Unadjusted Matched	0.37	[0.24, 0.49]	< .001***	
	Adjusted Matched	0.31	[0.20, 0.43]	< .001***	↓13.9%
Parent substance use	Unadjusted Unmatched	0.03	[-0.03, 0.10]	0.413	
	Adjusted Unmatched	-0.02	[-0.08, 0.04]	0.658	
	Unadjusted Matched	0.02	[-0.04, 0.09]	0.584	
	Adjusted Matched	-0.03	[-0.09, 0.03]	0.385	0%†
Parent divorce	Unadjusted Unmatched	0.14	[0.06, 0.22]	0.001**	
	Adjusted Unmatched	0.03	[-0.04, 0.11]	0.482	
	Unadjusted Matched	0.13	[0.05, 0.21]	0.003**	
	Adjusted Matched	0.05	[-0.02, 0.13]	0.238	↓64.3%
Bereavement	Unadjusted Unmatched	0.00	[-0.30, 0.29]	0.980	
	Adjusted Unmatched	-0.17	[-0.44, 0.10]	0.322	
	Unadjusted Matched	0.00	[-0.30, 0.29]	0.980	
	Adjusted Matched	-0.32	[-0.59, -0.05]	0.036*	N/A
Domestic violence	Unadjusted Unmatched	0.07	[-0.05, 0.20]	0.356	
	Adjusted Unmatched	-0.05	[-0.16, 0.07]	0.531	
	Unadjusted Matched	0.05	[-0.08, 0.17]	0.566	
	Adjusted Matched	-0.04	[-0.15, 0.08]	0.591	↓42.9%†
Emotional neglect	Unadjusted Unmatched	0.48	[0.40, 0.55]	< .001***	
	Adjusted Unmatched	0.37	[0.30, 0.45]	< .001***	
	Unadjusted Matched	0.45	[0.37, 0.53]	< .001***	
	Adjusted Matched	0.35	[0.27, 0.42]	< .001***	↓27.1%

ACE	Model Adjustment	β	95% CI	p-value	Δ% in β
Physical victimisation	Unadjusted Unmatched	0.34	[0.27, 0.41]	< .001***	
	Adjusted Unmatched	0.07	[0.00, 0.13]	0.096	
	Unadjusted Matched	0.42	[0.35, 0.49]	< .001***	
	Adjusted Matched	0.14	[0.07, 0.21]	< .001***	↓58.8%
Emotional victimisation	Unadjusted Unmatched	0.55	[0.48, 0.61]	< .001***	
	Adjusted Unmatched	0.36	[0.29, 0.42]	< .001***	
	Unadjusted Matched	0.55	[0.49, 0.62]	< .001***	
	Adjusted Matched	0.39	[0.33, 0.46]	< .001***	↓29.1%
Sexual victimisation	Unadjusted Unmatched	0.68	[0.60, 0.76]	< .001***	
	Adjusted Unmatched	0.51	[0.43, 0.59]	< .001***	
	Unadjusted Matched	0.57	[0.48, 0.65]	< .001***	
	Adjusted Matched	0.36	[0.28, 0.45]	< .001***	↓47.1%
Peer victimisation	Unadjusted Unmatched	0.43	[0.37, 0.50]	< .001***	
	Adjusted Unmatched	0.25	[0.18, 0.31]	< .001***	
	Unadjusted Matched	0.44	[0.37, 0.50]	< .001***	
	Adjusted Matched	0.25	[0.19, 0.31]	< .001***	↓41.9%

Note. β = standardised regression coefficient, CI = confidence interval.

Δ% in β = percentage change in the effect size from the Unadjusted Unmatched model to the Adjusted Matched model. ↓ represents a decrease while ↑ represents an increase. † denotes reversal in effect direction.

NA = Δ% in β is not computed when Unadjusted Unmatched effect size = 0.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.21 Associations between ACEs and psychological distress in the complete sample.

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Parent mental health problems	Unadjusted Unmatched	2.00	[1.49, 2.68]	< .001***	
	Adjusted Unmatched	1.74	[1.27, 2.39]	0.001**	
	Unadjusted Matched	1.93	[1.44, 2.60]	< .001***	
	Adjusted Matched	1.95	[1.41, 2.69]	< .001***	↓2.5%
Parent substance use	Unadjusted Unmatched	1.06	[0.87, 1.29]	0.658	
	Adjusted Unmatched	0.94	[0.76, 1.17]	0.658	
	Unadjusted Matched	1.12	[0.92, 1.37]	0.348	
	Adjusted Matched	0.99	[0.80, 1.23]	0.958	↓6.6%
Parent divorce	Unadjusted Unmatched	1.38	[1.11, 1.72]	0.007**	
	Adjusted Unmatched	1.08	[0.85, 1.38]	0.587	
	Unadjusted Matched	1.14	[0.92, 1.42]	0.327	
	Adjusted Matched	0.97	[0.77, 1.23]	0.872	↓29.7%
Bereavement	Unadjusted Unmatched	0.98	[0.41, 2.33]	0.980	
	Adjusted Unmatched	0.67	[0.27, 1.65]	0.481	
	Unadjusted Matched	0.94	[0.39, 2.24]	0.931	
	Adjusted Matched	0.54	[0.22, 1.34]	0.263	↓44.9%
Domestic violence	Unadjusted Unmatched	1.29	[0.91, 1.82]	0.221	
	Adjusted Unmatched	1.01	[0.70, 1.46]	0.980	
	Unadjusted Matched	1.25	[0.89, 1.76]	0.290	
	Adjusted Matched	1.03	[0.71, 1.50]	0.914	↓20.2%
Emotional neglect	Unadjusted Unmatched	2.93	[2.39, 3.59]	< .001***	
	Adjusted Unmatched	2.57	[2.07, 3.19]	< .001***	
	Unadjusted Matched	2.58	[2.11, 3.15]	< .001***	
	Adjusted Matched	2.34	[1.88, 2.89]	< .001***	↓20.1%

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Physical victimisation	Unadjusted Unmatched	1.95	[1.61, 2.36]	< .001***	
	Adjusted Unmatched	1.23	[1.00, 1.53]	0.087	
	Unadjusted Matched	2.40	[1.97, 2.93]	< .001***	
	Adjusted Matched	1.45	[1.16, 1.82]	0.002**	↓25.6%
Emotional victimisation	Unadjusted Unmatched	2.61	[2.07, 3.31]	< .001***	
	Adjusted Unmatched	1.67	[1.29, 2.16]	< .001***	
	Unadjusted Matched	2.53	[2.00, 3.19]	< .001***	
	Adjusted Matched	1.76	[1.36, 2.27]	< .001***	↓32.6%
Sexual victimisation	Unadjusted Unmatched	3.36	[2.72, 4.16]	< .001***	
	Adjusted Unmatched	2.65	[2.12, 3.33]	< .001***	
	Unadjusted Matched	2.40	[1.95, 2.96]	< .001***	
	Adjusted Matched	1.81	[1.45, 2.26]	< .001***	↓46.1%
Peer victimisation	Unadjusted Unmatched	2.35	[1.94, 2.84]	< .001***	
	Adjusted Unmatched	1.71	[1.39, 2.10]	< .001***	
	Unadjusted Matched	2.43	[2.00, 2.94]	< .001***	
	Adjusted Matched	1.84	[1.49, 2.26]	< .001***	↓21.7%

Note. OR = odds ratio, CI = confidence interval.

Δ% in OR = percentage change in the effect size from the Unadjusted Unmatched model to the Adjusted Matched model. ↓ represents a decrease while ↑ represents an increase. † denotes reversal in effect direction.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.22 Associations between ACEs and self-harm in the complete sample.

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Parent mental health problems	Unadjusted Unmatched	1.60	[1.22, 2.10]	0.001**	
	Adjusted Unmatched	1.47	[1.10, 1.98]	0.016*	
	Unadjusted Matched	1.53	[1.17, 2.00]	0.004**	
	Adjusted Matched	1.52	[1.13, 2.03]	0.008**	↓5%
Parent substance use	Unadjusted Unmatched	0.97	[0.82, 1.15]	0.801	
	Adjusted Unmatched	0.86	[0.72, 1.03]	0.158	
	Unadjusted Matched	0.93	[0.79, 1.10]	0.482	
	Adjusted Matched	0.81	[0.67, 0.97]	0.033*	↓16.5%
Parent divorce	Unadjusted Unmatched	1.25	[1.03, 1.51]	0.038*	
	Adjusted Unmatched	1.06	[0.86, 1.30]	0.667	
	Unadjusted Matched	1.07	[0.88, 1.29]	0.577	
	Adjusted Matched	0.89	[0.72, 1.09]	0.356	↓28.8%
Bereavement	Unadjusted Unmatched	1.34	[0.68, 2.65]	0.482	
	Adjusted Unmatched	1.16	[0.57, 2.39]	0.743	
	Unadjusted Matched	1.44	[0.73, 2.83]	0.382	
	Adjusted Matched	1.04	[0.50, 2.17]	0.953	↓22.4%
Domestic violence	Unadjusted Unmatched	1.03	[0.75, 1.40]	0.918	
	Adjusted Unmatched	0.82	[0.59, 1.15]	0.338	
	Unadjusted Matched	1.01	[0.74, 1.37]	0.980	
	Adjusted Matched	0.83	[0.59, 1.16]	0.362	↓19.4%
Emotional neglect	Unadjusted Unmatched	2.13	[1.78, 2.56]	< .001***	
	Adjusted Unmatched	1.81	[1.48, 2.21]	< .001***	
	Unadjusted Matched	2.05	[1.71, 2.46]	< .001***	
	Adjusted Matched	1.77	[1.46, 2.16]	< .001***	↓16.9%

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Physical victimisation	Unadjusted Unmatched	2.26	[1.92, 2.66]	< .001***	
	Adjusted Unmatched	1.44	[1.20, 1.73]	< .001***	
	Unadjusted Matched	2.84	[2.40, 3.36]	< .001***	
	Adjusted Matched	1.75	[1.45, 2.11]	< .001***	↓22.6%
Emotional victimisation	Unadjusted Unmatched	3.20	[2.62, 3.90]	< .001***	
	Adjusted Unmatched	2.04	[1.64, 2.53]	< .001***	
	Unadjusted Matched	3.00	[2.47, 3.64]	< .001***	
	Adjusted Matched	2.09	[1.69, 2.58]	< .001***	↓34.7%
Sexual victimisation	Unadjusted Unmatched	4.04	[3.34, 4.90]	< .001***	
	Adjusted Unmatched	3.18	[2.60, 3.89]	< .001***	
	Unadjusted Matched	3.17	[2.63, 3.84]	< .001***	
	Adjusted Matched	2.38	[1.94, 2.92]	< .001***	↓41.1%
Peer victimisation	Unadjusted Unmatched	2.32	[1.98, 2.71]	< .001***	
	Adjusted Unmatched	1.62	[1.36, 1.93]	< .001***	
	Unadjusted Matched	2.49	[2.12, 2.92]	< .001***	
	Adjusted Matched	1.81	[1.52, 2.15]	< .001***	↓22%

Note. OR = odds ratio, CI = confidence interval.

Δ% in OR = percentage change in the effect size from the Unadjusted Unmatched model to the Adjusted Matched model. ↓ represents a decrease while ↑ represents an increase. † denotes reversal in effect direction.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.23 Associations between ACEs and suicide attempt in the complete sample.

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Parent mental health problems	Unadjusted Unmatched	2.67	[1.82, 3.91]	< .001***	
	Adjusted Unmatched	2.11	[1.40, 3.19]	< .001***	
	Unadjusted Matched	1.90	[1.31, 2.77]	0.001**	
	Adjusted Matched	1.79	[1.19, 2.71]	0.009**	↓33%
Parent substance use	Unadjusted Unmatched	1.14	[0.85, 1.53]	0.478	
	Adjusted Unmatched	0.96	[0.70, 1.31]	0.854	
	Unadjusted Matched	1.13	[0.85, 1.52]	0.482	
	Adjusted Matched	0.98	[0.72, 1.34]	0.953	↓14%
Parent divorce	Unadjusted Unmatched	1.62	[1.18, 2.21]	0.005**	
	Adjusted Unmatched	1.20	[0.86, 1.68]	0.378	
	Unadjusted Matched	1.34	[0.99, 1.82]	0.093	
	Adjusted Matched	1.10	[0.80, 1.51]	0.648	↓32.1%
Bereavement	Unadjusted Unmatched	1.67	[0.59, 4.72]	0.423	
	Adjusted Unmatched	1.41	[0.47, 4.18]	0.614	
	Unadjusted Matched	2.19	[0.77, 6.23]	0.207	
	Adjusted Matched	1.80	[0.59, 5.46]	0.385	↑7.8%
Domestic violence	Unadjusted Unmatched	2.01	[1.30, 3.10]	0.003**	
	Adjusted Unmatched	1.54	[0.97, 2.46]	0.104	
	Unadjusted Matched	1.62	[1.05, 2.49]	0.044*	
	Adjusted Matched	1.35	[0.85, 2.13]	0.290	↓32.8%
Emotional neglect	Unadjusted Unmatched	3.19	[2.39, 4.24]	< .001***	
	Adjusted Unmatched	2.49	[1.83, 3.38]	< .001***	
	Unadjusted Matched	2.87	[2.16, 3.80]	< .001***	
	Adjusted Matched	2.44	[1.80, 3.31]	< .001***	↓23.5%

ACE	Model Adjustment	OR	95% CI	p-value	Δ% in OR
Physical victimisation	Unadjusted Unmatched	2.51	[1.90, 3.31]	< .001***	
	Adjusted Unmatched	1.34	[0.98, 1.82]	0.096	
	Unadjusted Matched	2.65	[2.00, 3.51]	< .001***	
	Adjusted Matched	1.21	[0.88, 1.66]	0.332	↓51.8%
Emotional victimisation	Unadjusted Unmatched	4.16	[2.73, 6.36]	< .001***	
	Adjusted Unmatched	2.15	[1.36, 3.40]	0.002**	
	Unadjusted Matched	6.89	[4.07, 11.67]	< .001***	
	Adjusted Matched	4.14	[2.38, 7.19]	< .001***	↓0.5%
Sexual victimisation	Unadjusted Unmatched	4.09	[3.05, 5.47]	< .001***	
	Adjusted Unmatched	2.96	[2.18, 4.03]	< .001***	
	Unadjusted Matched	3.87	[2.90, 5.16]	< .001***	
	Adjusted Matched	2.44	[1.79, 3.32]	< .001***	↓40.3%
Peer victimisation	Unadjusted Unmatched	3.90	[2.87, 5.30]	< .001***	
	Adjusted Unmatched	2.61	[1.88, 3.62]	< .001***	
	Unadjusted Matched	3.94	[2.90, 5.36]	< .001***	
	Adjusted Matched	2.76	[1.99, 3.84]	< .001***	↓29.2%

Note. OR = odds ratio, CI = confidence interval.

Δ% in OR = percentage change in the effect size from the Unadjusted Unmatched model to the Adjusted Matched model. ↓ represents a decrease while ↑ represents an increase. † denotes reversal in effect direction.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

6.3 Supporting Information for Chapter 4.

6.3.1 Quality control (QC) and processing of genetic data

To derive polygenic scores (PGS) for depression, anxiety, and suicide attempt, I followed the best practice guidelines for QC (Choi et al., 2020; Marees et al., 2018; Mills et al., 2020) which are summarised in **Table *6.24*** below. Before computing polygenic scores, the base dataset (the GWAS summary statistics on which the PGS calculation is based) and target dataset (the genotype data of individuals in whom PGS are calculated – in this case, the MCS cohort) must first undergo rigorous quality control (QC). QC is crucial to generating reliable polygenic scores because raw genotype data are inherently flawed, due to processing issues such as poor quality of DNA samples, poor DNA hybridisation to the array, poorly performing genotype probes, sample mix-ups or contamination (Marees et al., 2018).

The genome build is a standardised 'reference genome' created from multiple individuals that serves as a representative genome model. The GWAS summary statistics were provided on the GRCh37/hg19 genome build, while the target MCS dataset was on the GRCh38/hg38 build. To ensure compatibility, I converted the genomic coordinates of the summary statistics from hg19 to hg38 using the LiftOver tool. Specifically, I used the 'snp_modifyBuild' function from the R package 'bigsnpr', which acts as a LiftOver wrap up. Variants that could not be successfully mapped to the new build were excluded. For the anxiety GWAS, which used chr:pos identifiers (chromosome base position identifiers), SNP locations were converted to reference SNP cluster IDs (rsIDs) using the 'colochelpR' package in R, referencing dbSNP build 144.

Table 6.24 Summary of QC procedures conducted prior to deriving polygenic scores.

QC procedure	Recommendation	Method
Duplicate SNPs	Ensure there are no duplicated SNPs in either the base or target datasets, to avoid PGS software crashing or errors in results.	Removed duplicated SNPs with the **duplicated()** function in R or the **uniq -d** command in bash.
Ambiguous SNPs	Remove all ambiguous SNPs to avoid systematic errors. If the base and target datasets were generated using different genotyping chips and the chromosome strand (+/-) used for either dataset is unknown, then it is not possible to pair up the alleles of ambiguous SNPs across the datasets (e.g., SNPs with A/T or G/C pairs).	Used the **awk** command in **bash** to remove ambiguous SNPs with A/T, T/A, G/C, or C/G pairs.
Missing SNPs and missing individuals	Exclude SNPs that are missing in a large proportion of the subjects and individuals with high rates of genotype missingness, with a recommended threshold of 0.01.	Performed SNP and individual filtering (with the PLINK commands **--geno** and **--mind**).

Sex discrepancy	Check for discrepancies between the recorded sex and the genetic sex based on X chromosome homozygosity rates. If there are many discrepancies, this could indicate sample mix-ups. **Homozygosity rate:** the proportion of genetic loci at which an individual carries two identical (homozygous) alleles.	Males should have an X chromosome homozygosity estimate >0.8 and females should have a value <0.2. Subjects with sex discrepancies were deleted based on the genotype information in the dataset (PLINK command **--check-sex**).
Minor allele frequency (MAF)	Include only SNPs above the set MAF threshold. The recommended threshold for a regular GWAS is between 0.01 and 0.05 (Marees et al., 2018). **Minor allele frequency:** the frequency of the least often occurring allele.	Selected autosomal SNPs only (chromosomes 1 to 22, excluding sex chromosomes X and Y). Removed SNPs with low MAF (PLINK command **--maf**), MAF <0.01.
Hardy-Weinberg equilibrium (HWE)	Exclude markers which deviate from HWE, as they commonly indicate genotyping error. **Hardy-Weinberg equilibrium:** assuming an infinitely large population with no selection, mutation, or migration, the genotype and allele frequencies remain constant over generations.	Removed SNPs with a HWE p-value <1e-6 (PLINK command **--hwe**).
Heterozygosity	Exclude individuals with high or low heterozygosity rates, as they can indicate sample contamination or inbreeding. **Heterozygosity rate:** the proportion of genetic loci at which an individual carries two different (heterozygous) alleles.	Removed individuals who deviated ±3 standard deviations from the sample's heterozygosity rate mean.
Relatedness	Closely related individuals in the target data may lead to overfitted results, limiting the generalisability of results. Individuals with a first or second degree relative in the sample (pi-hat > 0.125) should be removed.	Pruned independent SNPs (PLINK command **--indep-pairwise**) and limited to autosomal chromosomes only, then removed closely related individuals (PLINK command **--king-cutoff**).
Population stratification	Because allele frequencies can differ between subpopulations (e.g., individuals with different ethnic background), population stratification can lead to false positives or mask true associations. To account for population stratification, analyses should be stratified by ancestry. **Principal Component Analysis (PCA)** is recommended to identify and adjust for ancestry differences among individuals.	Pruned independent SNPs and limited to autosomal chromosomes only, then generated principal components (PCs) to account for population stratification (PLINK command **--pca 10**). It is recommended to use the first 10 PCs as covariates (Mills et al., 2020).

6.3.2 Linkage disequilibrium (LD) and pruning to account for LD

In the process of computing polygenic scores, it is important to account for linkage disequilibrium (LD), i.e., the non-random association between alleles at different loci in a population (Marees et al., 2018). LD arises due to limited genetic recombination, where SNPs that are in LD are more likely to be inherited together, especially if they are in physical proximity on a chromosome. As LD creates a correlation structure across SNPs, a non-causal SNP may still show an association with a phenotypic trait if it is in LD with a causal SNP; thus, LD poses a challenge in identifying the contribution of causal genetic variants (Choi et al., 2020; Mills et al., 2020).

To account for LD, SNPs should be 'pruned' to retain a set of independent SNPs for the subsequent analysis (e.g., principal component analysis), and 'clumped' to retain the SNPs most strongly associated with the phenotypic trait in GWAS results (Choi et al., 2020; Marees et al., 2018; Mills et al., 2020).

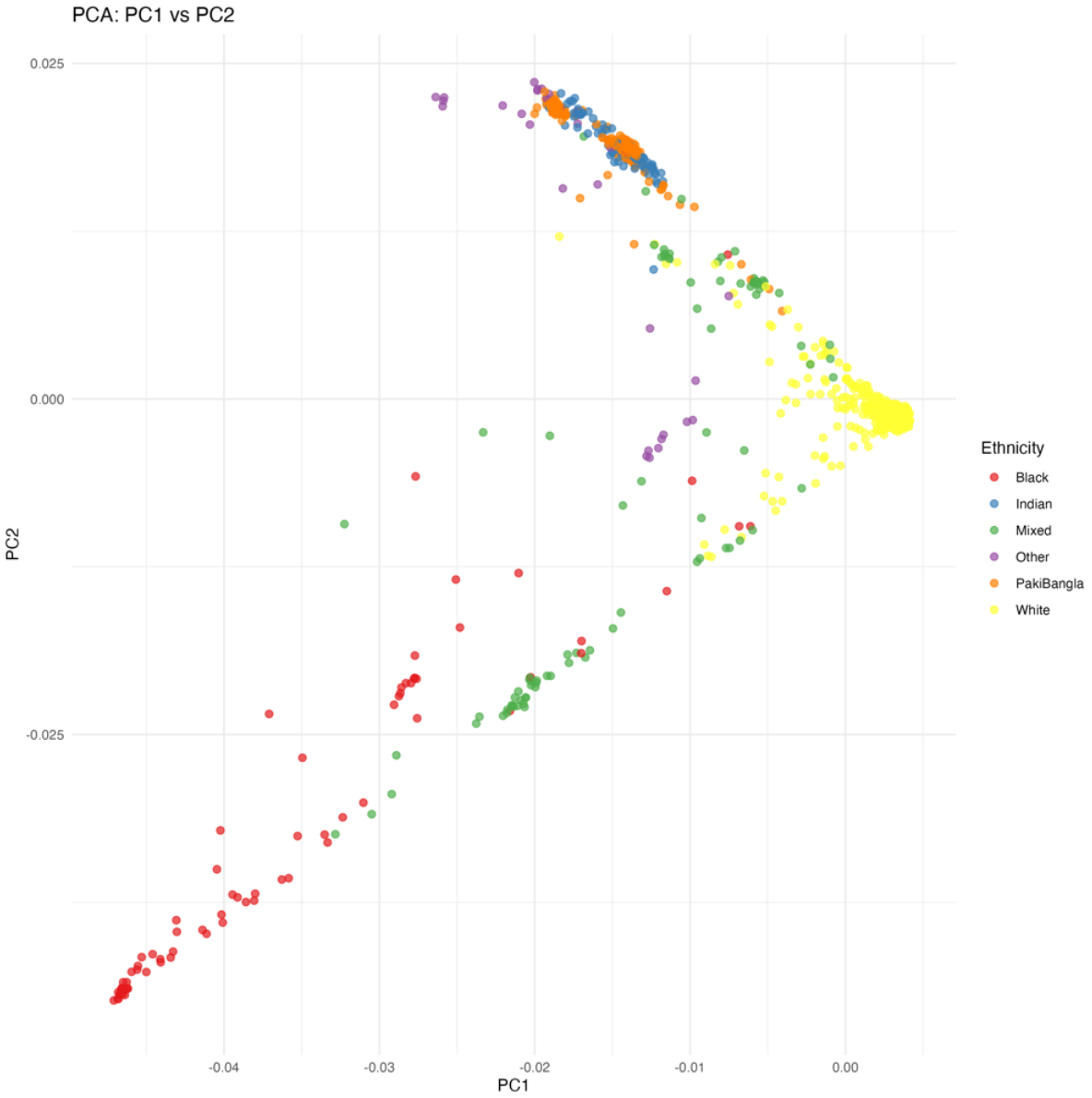
Pruning is a technique that uses the strength of LD (measured as the squared correlation coefficient between SNPs, r^2) within a sliding window across the genome (measured in kilobases, kb) to retain only independent SNPs that are minimally correlated, by removing those exceeding a specified LD threshold (Marees et al., 2018; Mills et al., 2020). In PLINK, I conducted LD pruning using a 200 kb sliding window, shifting the window by 50 SNPs at each step, and removed SNPs in high LD ($r^2 > 0.25$) according to recommended guidelines (Choi et al., 2020).

6.3.3 Principal component analysis (PCA) to account for population stratification

After pruning, I conducted principal component analysis (PCA) on the independent SNPs using PLINK. Principal component analysis (PCA) is a dimension reduction technique used to transform high-dimensional SNP genotype data into a smaller set of uncorrelated variables known as principal components (PCs), which capture the most significant patterns of variation across the genome (Price et al., 2006; Mills et al., 2020). First, the genotype data is arranged as a matrix with individuals as rows and SNPs as columns. PCA computes a covariance matrix to measure how much each individual's genetic variation differs across SNPs. From this covariance matrix, PCA derives PCs, also known as 'eigenvectors', which represent the directions of maximum variance in the data. The corresponding 'eigenvalues' capture how much variance each PC explains. The original genotype data is then projected onto the PCs, essentially reducing the number of variables whilst preserving the most important patterns, or 'axes' of genetic variation. Each PC captures the maximum possible variance in descending order (e.g., PC1 captures the most variance, followed by PC2, then PC3, et cetera). When applied to genotype data, PCA identifies the major axes of genetic differentiation among individuals (Mills et al., 2020). It enables the visualisation of how individuals cluster based on their genetic variation, often reflecting the major subpopulations within a dataset. Notably, the PCs do not directly represent ancestry or population structure; rather, they *infer* ancestry by capturing the largest sources of genotype variance, which often correspond to ancestry differences (Price et al., 2006).

The PCA scatterplot in **Figure 6.28** shows how individuals in the MCS cluster together based on genetic similarity, coloured by participant self-reported ethnicity to label each subpopulation. The first PC1 (which explains the most variation out of all the PCs) likely captures the major ancestry differences in the dataset, which is often European vs. African ancestry in human genetic studies (Mills et al., 2020). This is supported by the distinct separation of the red cluster (Black individuals) from the yellow cluster (White individuals) on opposite ends of PC1. The second PC2 (which explains less variation than PC1, but still more variation than the subsequent PCs) might reflect secondary genetic differences within South Asian populations, such as the blue cluster (Indian individuals) versus the orange cluster (Pakistani and Bangladeshi individuals). Alternatively, PC2 might reflect the differences between the green group of 'Mixed' ethnicity individuals. As expected, the 'Mixed' ethnicity individuals are spread between the other groups as they possess ancestry from multiple populations, demonstrating 'admixture', i.e., when two or more previously isolated and genetically differentiated populations interbreed to produce new genetic lineages (Mills et al., 2020). Finally, individuals in the purple 'Other' ethnicity category are scattered across the plot, possibly indicating individuals from diverse ancestry backgrounds who do not fit into a single cluster.

Figure 6.28 Pairwise scatterplot of PC1 and PC2 from genome-wide PCA in the MCS.



To account for population stratification, I extracted the first 10 PCs from the PCA to be used as covariates in the outcome regression models. Population stratification is the presence of multiple subpopulations (e.g., individuals with different ancestry groups) in a study (Marees et al., 2018; Mills et al., 2020). Because allele frequencies tend to differ between subpopulations (e.g., one ancestry might have more A alleles at a particular SNP compared to another ancestry), these genetic differences can then create spurious associations with phenotypic traits in GWAS, resulting in false positives if population stratification is not accounted for (Mills et al., 2020).

Population stratification explained with a directed acyclic graph (DAG)

A textbook example of population stratification is the 'chopsticks gene' thought experiment (Hamer & Sirota, 2000). In this hypothetical study, the authors described the case of a fictional ethnogeneticist who discovers the 'Successful Use of Selected Hand Instruments' (SUSHI) gene, a genetic variant that is significantly correlated with chopstick use, accounting for nearly half of the variance. This finding is later debunked as SUSHI is revealed to be a histocompatibility antigen gene that just happens to have different allele frequencies in Asian and Caucasian subpopulations (i.e., population stratification), who naturally differ in chopstick use for cultural rather than genetic reasons.

Population stratification can also be explained as a case of backdoor path confounding, which can be illustrated using the same DAG from **Chapter 1, Figure *1.1***, A ← C → B. In this scenario, the variables are represented as follows: SUSHI gene ← population stratification → chopstick use. Because population stratification is a common cause (i.e., confounder) of both the SUSHI gene and chopstick use, this backdoor path (if left unblocked) creates a spurious association between the SUSHI gene and chopstick use, even though the causal path A → B does not actually exist. To remove this spurious association, one can block this backdoor path (i.e., condition on the confounder) by accounting for population stratification, which can be achieved through adjusting for PCs derived from PCA. Including PCs as covariates in GWAS regression models helps to control for ancestry differences, thereby reducing the risk of spurious associations arising from population stratification (Choi et al., 2020; Price et al., 2006; Mills et al., 2020).

6.3.4 Deriving polygenic scores for depression, anxiety, and suicide attempt

Clumping and thresholding (C+T) to derive polygenic scores

Polygenic scores (PGS) for depression, anxiety, and suicide attempt were derived using the clumping and thresholding (C+T) method. This approach removes correlated SNPs (clumping) and filters out SNPs that are weakly associated with the phenotype of interest (thresholding). First, to account for linkage disequilibrium (LD), I used PLINK to 'clump' the summary statistics by retaining the SNP with the lowest *p*-value in each LD block, using an r^2 threshold of 0.1 and a 250kb window. Unlike pruning, which randomly selects one SNP per LD block without considering association strength, clumping preferentially retains the most strongly associated SNP, thereby improving the predictive accuracy of the PGS (Choi et al., 2020; Mills et al., 2020).

Next, the clumped SNPs were filtered based on their GWAS association *p*-value, and SNPs with *p*-values exceeding a pre-specified threshold were removed. This step addresses a key challenge in deriving polygenic scores: the trade-off between predictive signal and noise. Stricter *p*-value thresholds (e.g., the genome-wide significance level of $p < 5e\text{-}8$) retain fewer SNPs that are more strongly associated with the trait, reducing false positives but limiting predictive power for highly polygenic traits. Conversely, more lenient thresholds (e.g., $p < 0.05$) include a broader set of SNPs with weaker associations, which can increase predictive signal but also risks introducing noise from non-causal variants, e.g., proxy SNPs that are linked to causal variants due to LD (Mills et al., 2020).

Five-fold cross-validation to optimise the *p*-value threshold

As the optimal *p*-value threshold for a given trait and target sample is unknown *a priori*, it must be empirically determined. However, testing multiple thresholds and selecting the best performing one on the full dataset can lead to overfitting, yielding an inflated estimate of performance that may not generalise to independent data (Allegrini et al., 2022). To address this, k-fold cross-validation is the recommended data-driven approach to determine the optimal *p*-value threshold for deriving PGS (Allegrini et al., 2022; Choi et al., 2020). By iteratively splitting the sample into training and testing folds, k-fold cross-validation ensures that the selection process of the optimal threshold is performed in an out-of-sample manner, yielding a more robust and generalisable PGS while minimising the risk of overfitting.

Thus, I applied a five-fold cross-validation (CV) approach as follows. First, the MCS dataset was subset to individuals of European genetic ancestry to align with the ancestry of the source GWAS. This European ancestry subsample was randomly split into five equal-sized folds. For each fold in turn, the remaining four folds (80%) served as the training set, and the held-out fold (20%) served as the test set. Within each training set, a series of PGS were generated using LD-clumped SNPs ($r^2 < 0.1$, 250kb window) filtered through ten systematically adjusted *p*-value thresholds (ranging from $p < 1e\text{-}8$ to $p < 0.1$).

The predictive accuracy of each of the ten PGS was then assessed within each training set to avoid information leakage and prevent overfitting during the tuning process. For the depression and anxiety PGS, this was quantified as the incremental R^2 from a linear model predicting the continuous depression and anxiety score at age 17, over and above a base model adjusted for sex and the 10 principal components (PCs). For the binary suicide attempt outcome, predictive accuracy was quantified using McFadden's pseudo-R^2.

In each of the five folds, the *p*-value threshold yielding the highest R^2 in the training set was identified as the optimal threshold for that fold. After repeating this process for all five folds, the final optimal threshold for each trait was determined by selecting the modal (i.e., most frequently chosen) best threshold from across the five folds. Finally, this cross-validated optimal threshold was used to generate the final PGS for each participant in the full MCS sample.

As a sensitivity analysis, the CV procedure was repeated within the non-European ancestry subsample to assess the robustness of the selected thresholds. Results were broadly consistent across the two ancestry groups. For example, while the optimal threshold for the suicide attempt PGS in the non-European sample was $p < 0.10$ (**Figure 6.34**), $p < 0.05$ was the next best performing threshold in 3 out of 5 folds and was therefore selected for consistency with the optimal threshold in the European sample ($p < 0.05$, **Figure 6.33**).

Overall, the optimal thresholds identified were: depression $p < 0.05$ (**Figure 6.29**, **Figure 6.30**); anxiety $p < 0.01$ (**Figure 6.31**, **Figure 6.32**); suicide attempt $p < 0.05$ (**Figure 6.33**, **Figure 6.34**). All final PGS were standardised (mean = 0, standard deviation = 1) for use in subsequent analyses and confirmed to be normally distributed (**Figure 6.35**, **Figure 6.36**, **Figure 6.37**, **Figure 6.38**, **Figure 6.39**, **Figure 6.40**).

Figure 6.29 Depression PGS R^2 per threshold in each CV fold (European subset).

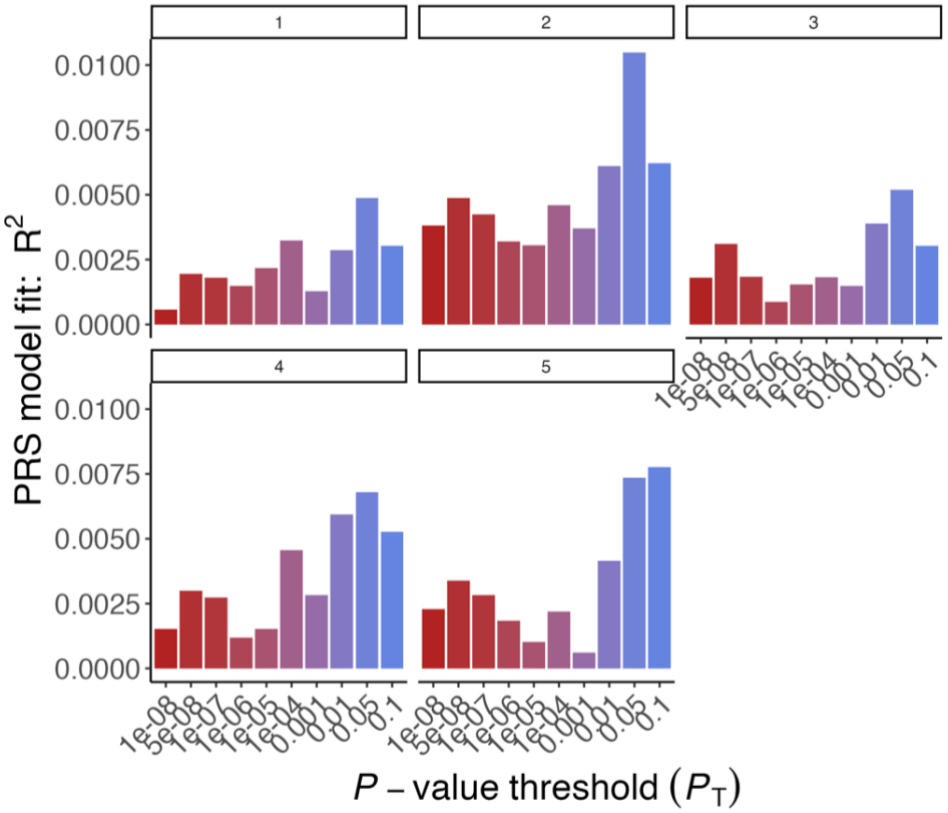


Figure 6.30 Depression PGS R^2 per threshold in each CV fold (non-European subset).

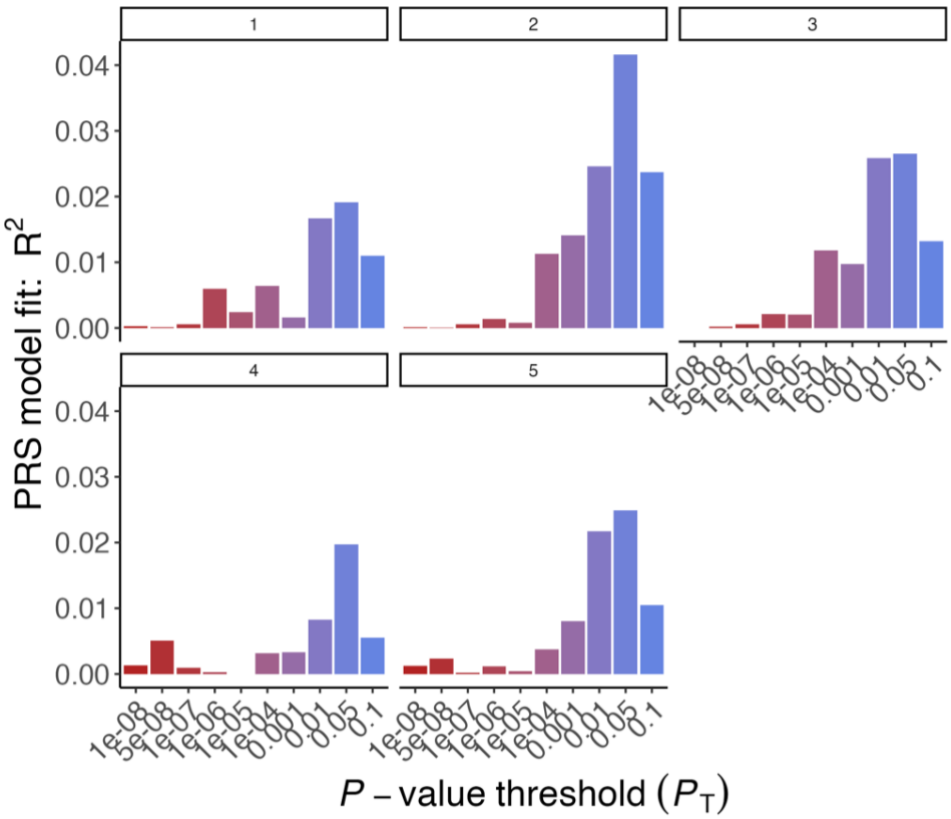


Figure 6.31 Anxiety PGS R^2 per threshold in each CV fold (European subset).

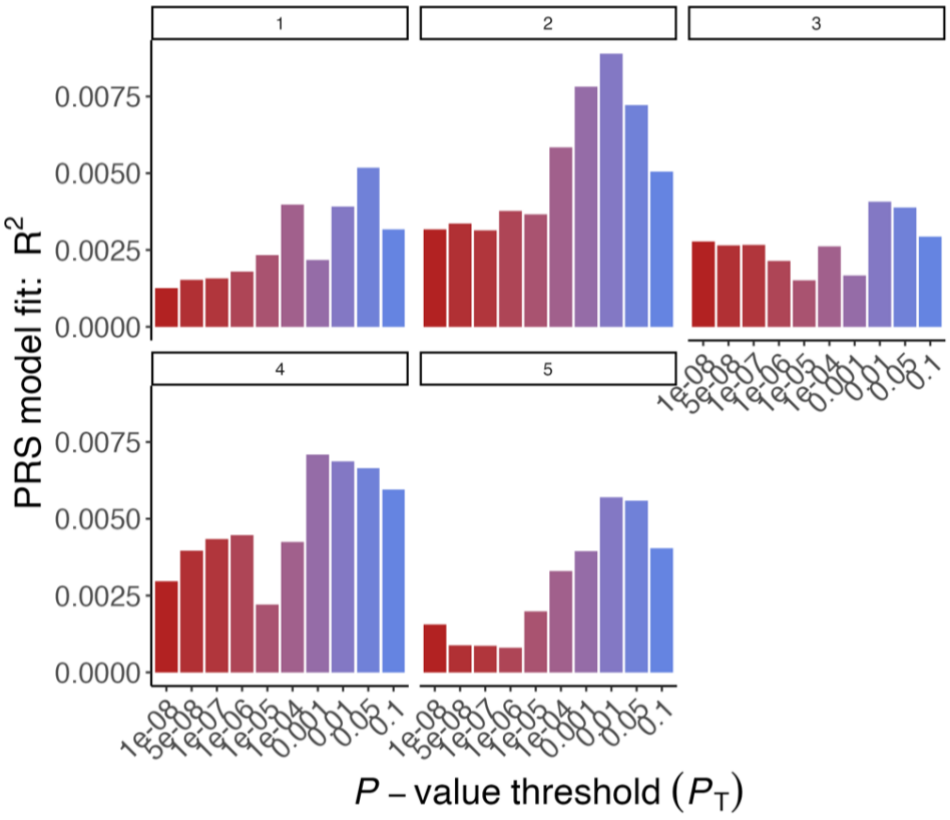


Figure 6.32 Anxiety PGS R^2 per threshold in each CV fold (non-European subset).

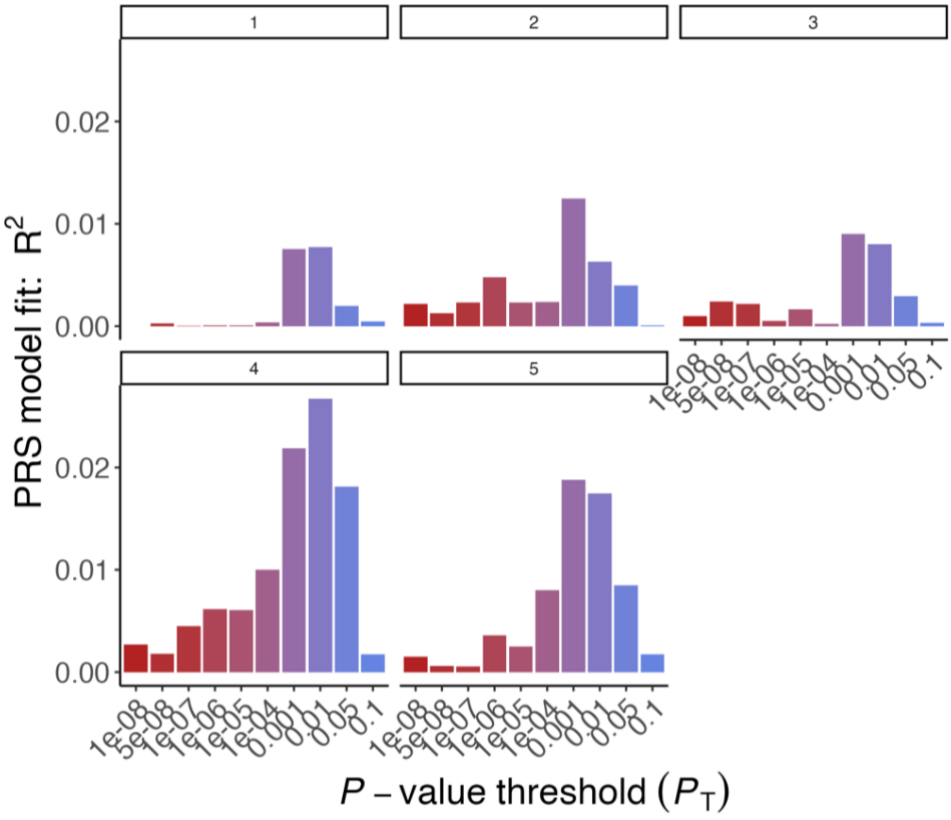


Figure 6.33 Suicide attempt PGS R^2 per threshold in each CV fold (European subset).

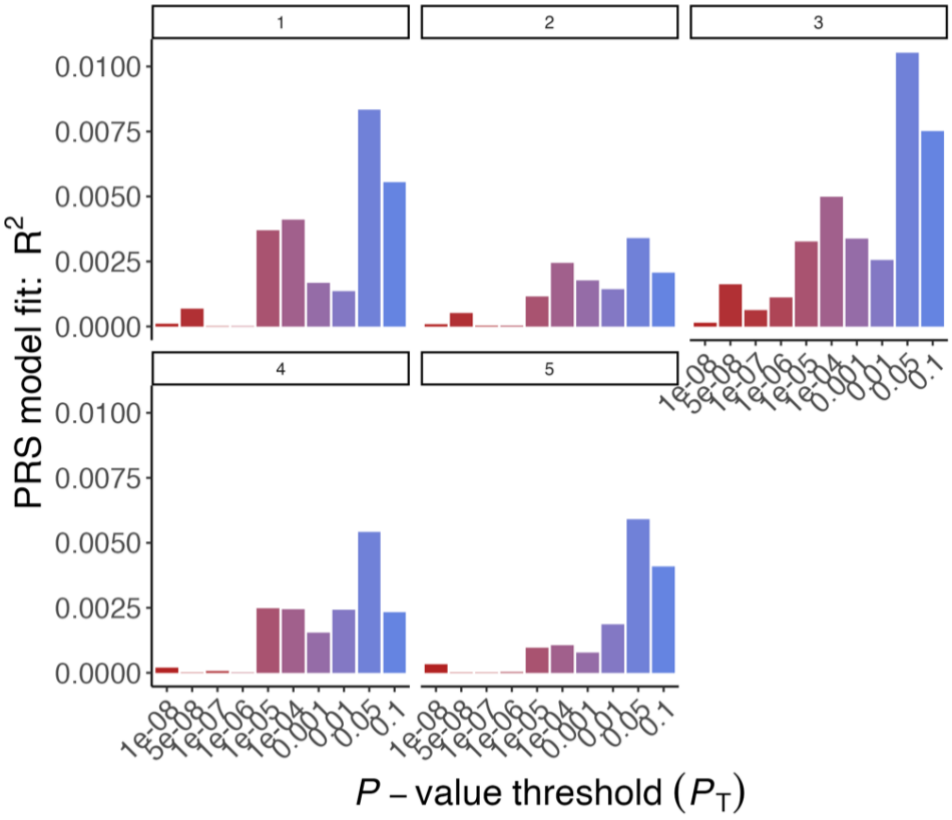


Figure 6.34 Suicide attempt PGS R^2 per threshold in each CV fold (non-European subset).

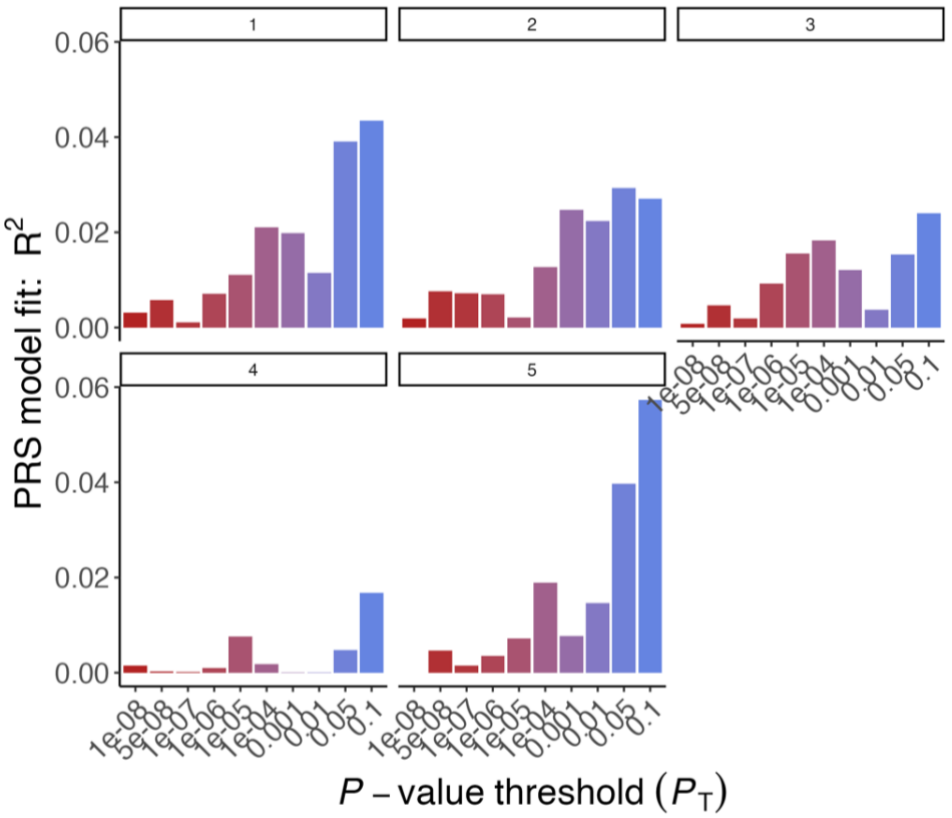


Figure 6.35 Normal distribution of standardised depression PGS in the MCS cohort.

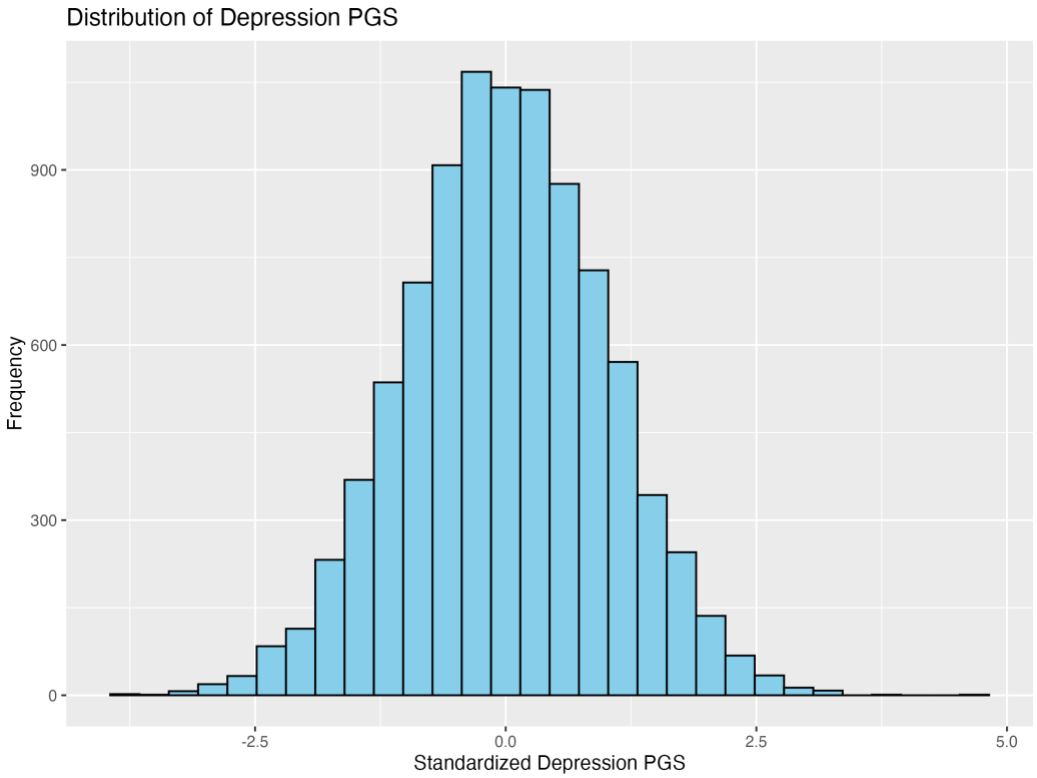


Figure 6.36 Normal distribution of standardised anxiety PGS in the MCS cohort.

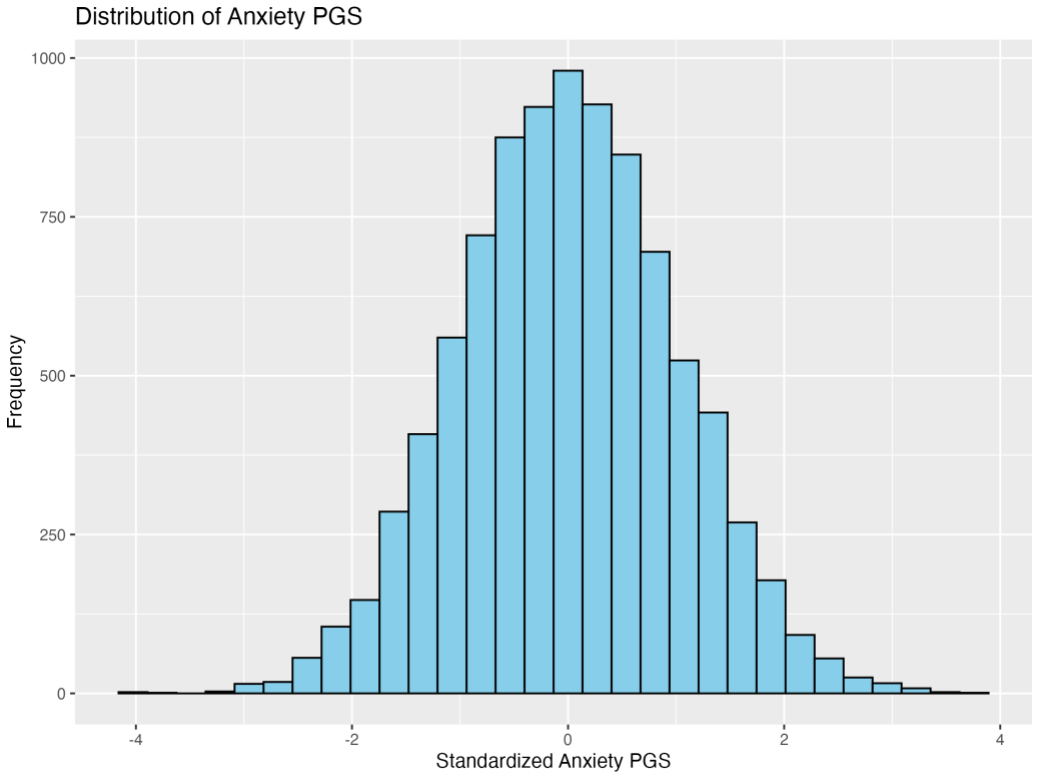


Figure 6.37 Normal distribution of standardised suicide attempt PGS in the MCS cohort.

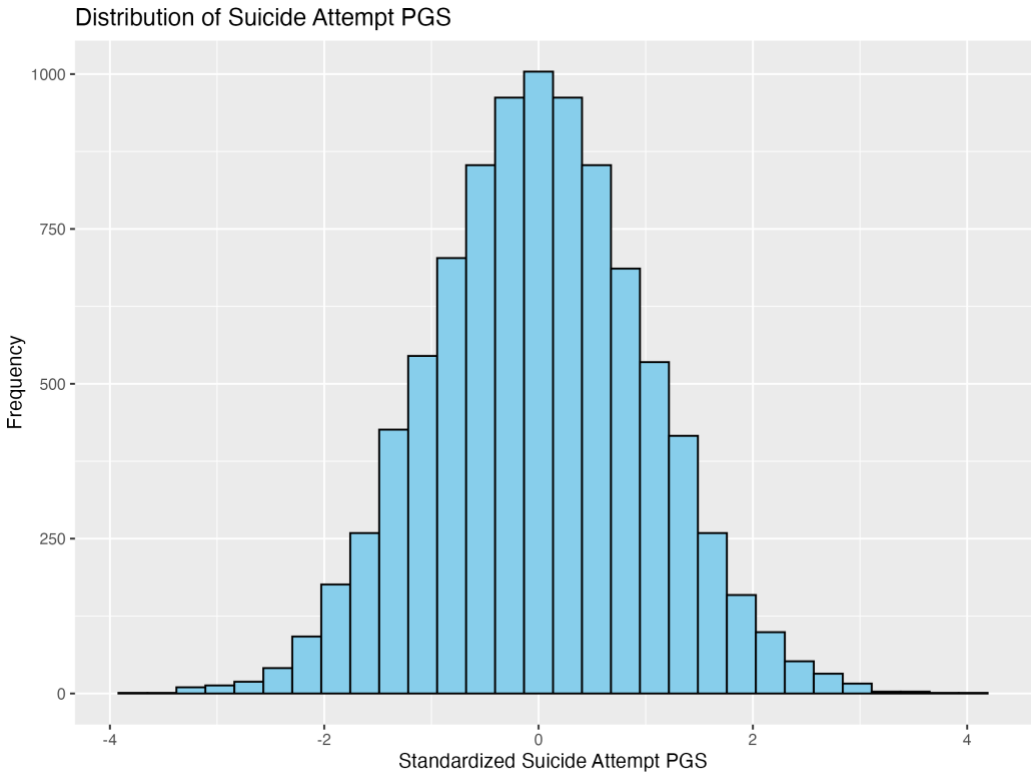


Figure 6.38 Normal distribution of standardised education PGS in the MCS cohort.

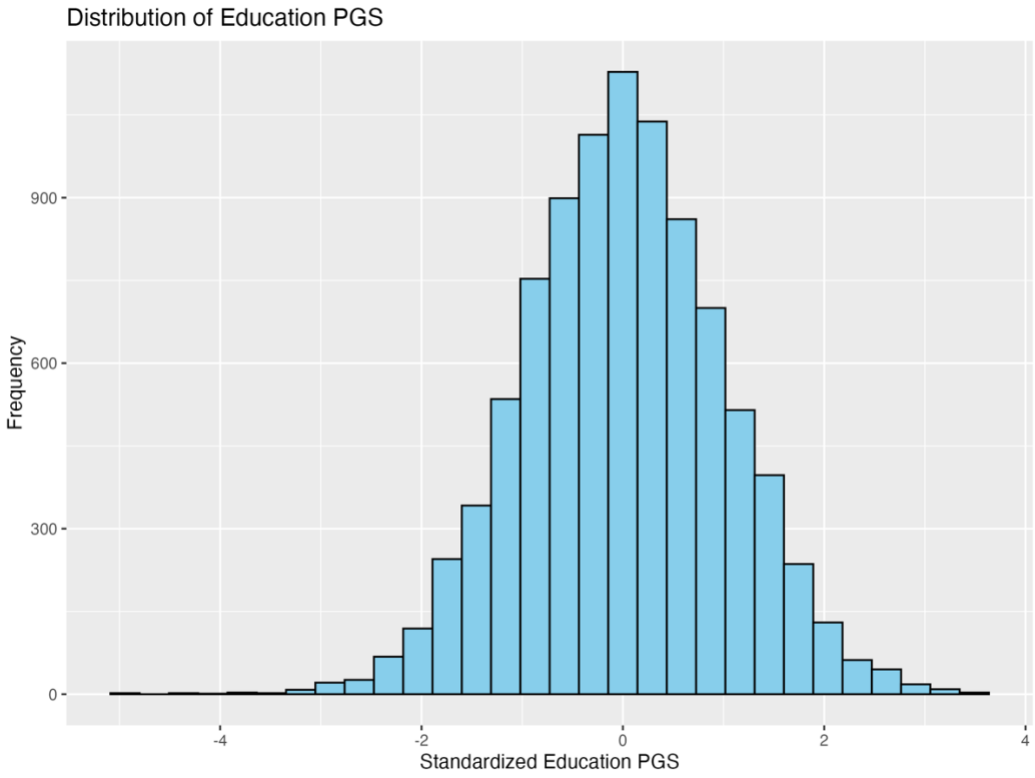


Figure 6.39 Normal distribution of standardised intelligence PGS in the MCS cohort.

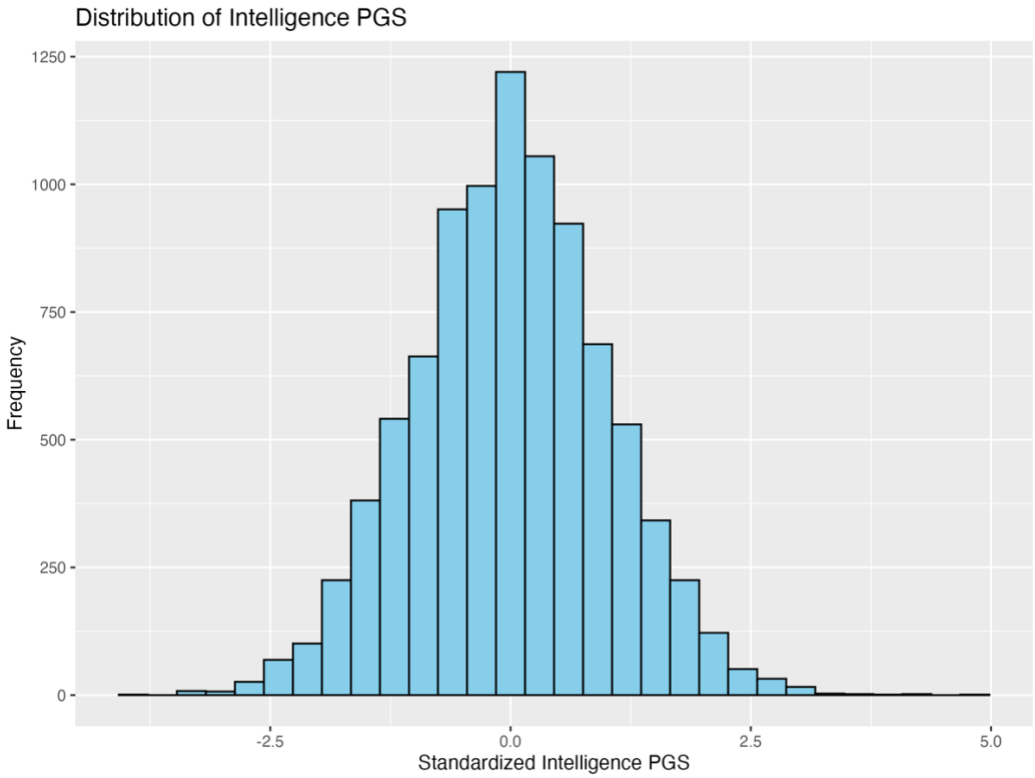
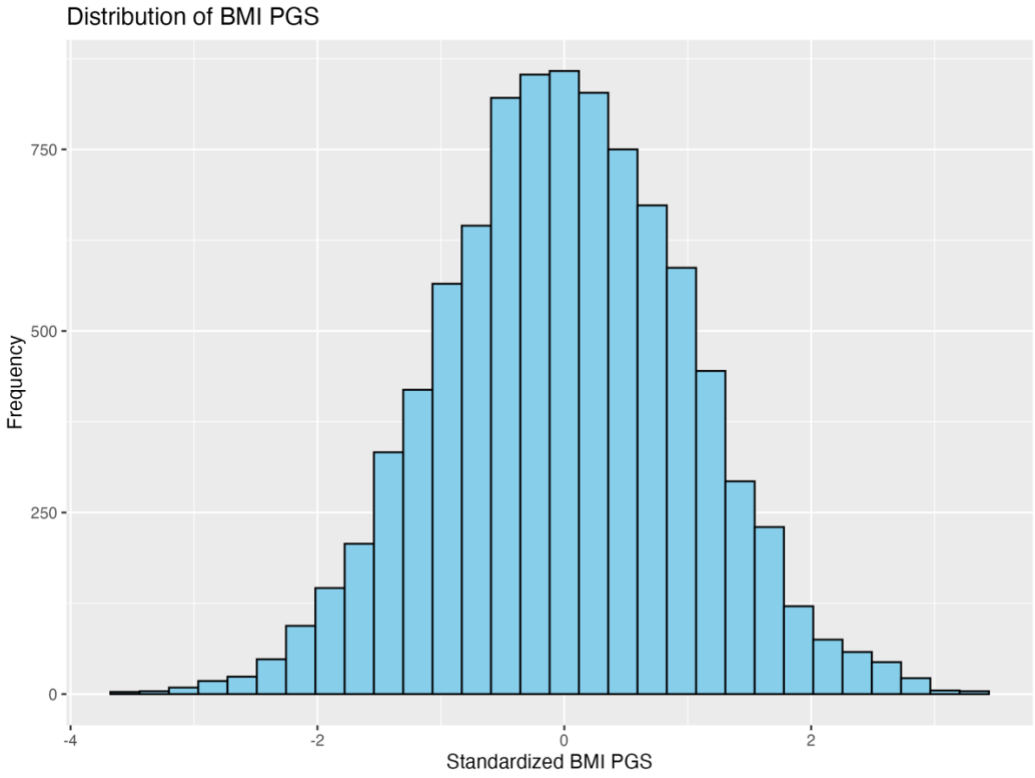


Figure 6.40 Normal distribution of standardised BMI PGS in the MCS cohort.



6.3.5 Gene-environment correlation (rGE) regression tables

Table 6.25 Single-PGS models of associations between PGS and ACEs.

ACE	PGS	OR [95% CI]	p-value
Parent mental health problems	Depression PGS	1.24 [1.13, 1.36]	< .001***
	Anxiety PGS	1.13 [1.03, 1.24]	0.028*
	Suicide Attempt PGS	1.19 [1.08, 1.30]	0.002**
	Education PGS	0.73 [0.66, 0.80]	< .001***
	Intelligence PGS	0.81 [0.73, 0.89]	< .001***
	BMI PGS	1.06 [0.97, 1.16]	0.358
Parent substance use	Depression PGS	1.01 [0.96, 1.07]	0.739
	Anxiety PGS	1.02 [0.97, 1.08]	0.527
	Suicide Attempt PGS	1.04 [0.98, 1.10]	0.346
	Education PGS	0.93 [0.88, 0.99]	0.034*
	Intelligence PGS	0.97 [0.92, 1.03]	0.437
	BMI PGS	0.99 [0.94, 1.05]	0.887
Parent divorce	Depression PGS	1.10 [1.02, 1.19]	0.025*
	Anxiety PGS	1.05 [0.97, 1.13]	0.353
	Suicide Attempt PGS	1.05 [0.97, 1.13]	0.367
	Education PGS	0.85 [0.79, 0.92]	< .001***
	Intelligence PGS	0.92 [0.85, 0.99]	0.073
	BMI PGS	1.00 [0.92, 1.07]	0.949
Bereavement	Depression PGS	1.13 [0.90, 1.42]	0.437
	Anxiety PGS	1.11 [0.88, 1.40]	0.482
	Suicide Attempt PGS	1.03 [0.82, 1.29]	0.879
	Education PGS	0.83 [0.66, 1.06]	0.251
	Intelligence PGS	0.94 [0.74, 1.18]	0.676
	BMI PGS	1.07 [0.85, 1.35]	0.674

ACE	PGS	OR [95% CI]	p-value
Domestic violence	Depression PGS	1.16 [1.02, 1.30]	0.042*
	Anxiety PGS	1.00 [0.89, 1.13]	0.978
	Suicide Attempt PGS	1.09 [0.97, 1.23]	0.278
	Education PGS	0.84 [0.75, 0.95]	0.017*
	Intelligence PGS	0.98 [0.87, 1.11]	0.814
	BMI PGS	0.93 [0.83, 1.05]	0.367
Emotional neglect	Depression PGS	1.23 [1.15, 1.32]	< .001***
	Anxiety PGS	1.23 [1.15, 1.32]	< .001***
	Suicide Attempt PGS	1.17 [1.09, 1.25]	< .001***
	Education PGS	0.78 [0.72, 0.83]	< .001***
	Intelligence PGS	0.90 [0.84, 0.96]	0.006**
	BMI PGS	1.02 [0.95, 1.09]	0.676
Physical victimisation	Depression PGS	1.12 [1.05, 1.20]	0.002**
	Anxiety PGS	1.12 [1.05, 1.19]	0.003**
	Suicide Attempt PGS	1.17 [1.10, 1.25]	< .001***
	Education PGS	0.91 [0.85, 0.97]	0.016*
	Intelligence PGS	0.95 [0.89, 1.02]	0.278
	BMI PGS	0.95 [0.89, 1.02]	0.251
Emotional victimisation	Depression PGS	1.04 [0.99, 1.09]	0.185
	Anxiety PGS	1.07 [1.02, 1.12]	0.010**
	Suicide Attempt PGS	1.02 [0.97, 1.07]	0.527
	Education PGS	1.00 [0.95, 1.05]	0.978
	Intelligence PGS	0.98 [0.93, 1.02]	0.482
	BMI PGS	0.98 [0.94, 1.03]	0.610

ACE	PGS	OR [95% CI]	p-value
Sexual victimisation	Depression PGS	1.20 [1.06, 1.36]	0.013*
	Anxiety PGS	1.19 [1.05, 1.34]	0.016*
	Suicide Attempt PGS	1.12 [0.99, 1.27]	0.148
	Education PGS	0.93 [0.82, 1.05]	0.387
	Intelligence PGS	1.04 [0.92, 1.17]	0.676
	BMI PGS	0.94 [0.83, 1.06]	0.457
Peer victimisation	Depression PGS	1.19 [1.13, 1.27]	< .001***
	Anxiety PGS	1.12 [1.06, 1.19]	< .001***
	Suicide Attempt PGS	1.14 [1.08, 1.21]	< .001***
	Education PGS	0.74 [0.70, 0.78]	< .001***
	Intelligence PGS	0.85 [0.80, 0.90]	< .001***
	BMI PGS	0.98 [0.93, 1.04]	0.683

Note. OR = odds ratio, CI = confidence interval. All models were adjusted for sex, ethnicity, and the ten genetic principal components (PCs). All PGS were standardised.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.26 Multi-PGS models of associations between PGS and ACEs.

ACE	PGS	OR [95% CI]	p-value
Parent mental health problems	Depression PGS	1.16 [1.03, 1.30]	0.087
	Anxiety PGS	1.00 [0.90, 1.12]	0.950
	Suicide Attempt PGS	1.08 [0.97, 1.20]	0.438
	Education PGS	0.78 [0.70, 0.87]	< .001***
	Intelligence PGS	0.89 [0.81, 0.99]	0.140
	BMI PGS	1.06 [0.96, 1.16]	0.509
Parent substance use	Depression PGS	0.98 [0.92, 1.05]	0.828
	Anxiety PGS	1.02 [0.95, 1.08]	0.828
	Suicide Attempt PGS	1.03 [0.97, 1.10]	0.601
	Education PGS	0.93 [0.88, 0.99]	0.144
	Intelligence PGS	1.00 [0.94, 1.06]	0.950
	BMI PGS	0.99 [0.94, 1.05]	0.916
Parent divorce	Depression PGS	1.09 [1.00, 1.20]	0.215
	Anxiety PGS	1.00 [0.91, 1.09]	0.950
	Suicide Attempt PGS	0.99 [0.91, 1.08]	0.916
	Education PGS	0.87 [0.80, 0.94]	0.011*
	Intelligence PGS	0.97 [0.90, 1.06]	0.792
	BMI PGS	0.99 [0.92, 1.07]	0.929
Bereavement	Depression PGS	1.10 [0.83, 1.45]	0.792
	Anxiety PGS	1.07 [0.82, 1.39]	0.828
	Suicide Attempt PGS	0.95 [0.73, 1.23]	0.842
	Education PGS	0.84 [0.65, 1.09]	0.438
	Intelligence PGS	1.00 [0.78, 1.29]	0.972
	BMI PGS	1.07 [0.85, 1.35]	0.813

ACE	PGS	OR [95% CI]	p-value
Domestic violence	Depression PGS	1.18 [1.02, 1.36]	0.140
	Anxiety PGS	0.91 [0.79, 1.04]	0.416
	Suicide Attempt PGS	1.03 [0.90, 1.18]	0.828
	Education PGS	0.84 [0.73, 0.96]	0.070
	Intelligence PGS	1.05 [0.92, 1.20]	0.792
	BMI PGS	0.92 [0.82, 1.04]	0.467
Emotional neglect	Depression PGS	1.10 [1.02, 1.20]	0.099
	Anxiety PGS	1.14 [1.06, 1.23]	0.011*
	Suicide Attempt PGS	1.05 [0.97, 1.13]	0.509
	Education PGS	0.80 [0.74, 0.86]	< .001***
	Intelligence PGS	0.99 [0.92, 1.06]	0.893
	BMI PGS	1.02 [0.95, 1.09]	0.828
Physical victimisation	Depression PGS	1.03 [0.95, 1.11]	0.792
	Anxiety PGS	1.06 [0.98, 1.14]	0.416
	Suicide Attempt PGS	1.13 [1.05, 1.22]	0.013*
	Education PGS	0.93 [0.87, 1.00]	0.215
	Intelligence PGS	0.99 [0.92, 1.06]	0.893
	BMI PGS	0.95 [0.89, 1.02]	0.416
Emotional victimisation	Depression PGS	1.01 [0.96, 1.07]	0.842
	Anxiety PGS	1.07 [1.01, 1.12]	0.087
	Suicide Attempt PGS	0.99 [0.94, 1.05]	0.916
	Education PGS	1.01 [0.96, 1.07]	0.828
	Intelligence PGS	0.98 [0.93, 1.03]	0.685
	BMI PGS	0.98 [0.94, 1.03]	0.792

ACE	PGS	OR [95% CI]	p-value
Sexual victimisation	Depression PGS	1.12 [0.96, 1.30]	0.416
	Anxiety PGS	1.11 [0.97, 1.28]	0.416
	Suicide Attempt PGS	1.03 [0.89, 1.18]	0.842
	Education PGS	0.93 [0.81, 1.06]	0.521
	Intelligence PGS	1.08 [0.95, 1.23]	0.509
	BMI PGS	0.94 [0.83, 1.06]	0.589
Peer victimisation	Depression PGS	1.12 [1.05, 1.21]	0.013*
	Anxiety PGS	1.02 [0.96, 1.09]	0.792
	Suicide Attempt PGS	1.05 [0.98, 1.12]	0.416
	Education PGS	0.77 [0.72, 0.82]	< .001***
	Intelligence PGS	0.94 [0.88, 1.00]	0.215
	BMI PGS	0.98 [0.93, 1.04]	0.792

Note. OR = odds ratio, CI = confidence interval. All models were adjusted for sex, ethnicity, and the ten genetic principal components (PCs). All PGS were standardised.

Note on interpretation. The 95% CIs were calculated for each individual model. However, the *p*-values have been adjusted for all 60 statistical tests performed using the Benjamini-Hochberg (FDR) procedure. This necessary correction makes the significance threshold more stringent. Therefore, some associations may have a 95% CI that does not include the null value (i.e., 1.0 for an odds ratio) but are correctly interpreted as non-significant based on the more conservative FDR-adjusted *p*-value.

6.3.6 PGS-psychopathology regression tables

Table 6.27 Single-PGS models of associations between PGS and psychopathology.

Psychopathology Outcome	PGS	Estimate (β or OR)	95% CI	p-value
Depression & Anxiety Symptoms	Depression PGS	0.03	[0.01, 0.05]	0.011*
	Anxiety PGS	0.03	[0.01, 0.05]	0.003**
	Suicide Attempt PGS	0.02	[0.00, 0.04]	0.072
	Education PGS	-0.04	[-0.06, -0.02]	<.001***
	Intelligence PGS	-0.01	[-0.03, 0.01]	0.527
	BMI PGS	0.01	[-0.01, 0.03]	0.476
High Psychological Distress	Depression PGS	1.23	[1.09, 1.39]	0.002**
	Anxiety PGS	1.18	[1.05, 1.33]	0.014*
	Suicide Attempt PGS	1.15	[1.02, 1.30]	0.039*
	Education PGS	0.77	[0.68, 0.87]	<.001***
	Intelligence PGS	0.93	[0.83, 1.05]	0.314
	BMI PGS	0.97	[0.86, 1.10]	0.640
Self-Harm	Depression PGS	1.19	[1.08, 1.31]	0.002**
	Anxiety PGS	1.17	[1.06, 1.28]	0.004**
	Suicide Attempt PGS	1.21	[1.10, 1.33]	<.001***
	Education PGS	0.83	[0.75, 0.91]	<.001***
	Intelligence PGS	0.95	[0.86, 1.04]	0.314
	BMI PGS	0.91	[0.83, 1.00]	0.084
Suicide Attempt	Depression PGS	1.18	[1.01, 1.39]	0.065
	Anxiety PGS	1.20	[1.02, 1.41]	0.043*
	Suicide Attempt PGS	1.31	[1.11, 1.53]	0.003**
	Education PGS	0.74	[0.63, 0.87]	0.002**
	Intelligence PGS	0.86	[0.73, 1.00]	0.081
	BMI PGS	0.87	[0.74, 1.02]	0.114

Table 6.28 Multi-PGS models of associations between PGS and psychopathology.

Psychopathology Outcome	PGS	Estimate (β or OR)	95% CI	p-value
Depression & Anxiety Symptoms	Depression PGS	0.01	[-0.01, 0.04]	0.528
	Anxiety PGS	0.02	[0.00, 0.05]	0.140
	Suicide Attempt PGS	0.00	[-0.02, 0.03]	0.766
	Education PGS	-0.04	[-0.07, -0.02]	0.002**
	Intelligence PGS	0.01	[-0.01, 0.03]	0.510
	BMI PGS	0.01	[-0.01, 0.03]	0.661
High Psychological Distress	Depression PGS	1.14	[0.99, 1.33]	0.202
	Anxiety PGS	1.08	[0.94, 1.24]	0.510
	Suicide Attempt PGS	1.04	[0.91, 1.19]	0.691
	Education PGS	0.77	[0.68, 0.88]	0.002**
	Intelligence PGS	1.04	[0.91, 1.18]	0.691
	BMI PGS	0.97	[0.86, 1.09]	0.691
Self-Harm	Depression PGS	1.07	[0.95, 1.21]	0.491
	Anxiety PGS	1.07	[0.96, 1.20]	0.433
	Suicide Attempt PGS	1.13	[1.02, 1.26]	0.091
	Education PGS	0.84	[0.76, 0.94]	0.011*
	Intelligence PGS	1.02	[0.92, 1.14]	0.703
	BMI PGS	0.91	[0.83, 1.00]	0.164
Suicide Attempt	Depression PGS	1.00	[0.82, 1.22]	0.979
	Anxiety PGS	1.10	[0.92, 1.32]	0.510
	Suicide Attempt PGS	1.23	[1.03, 1.47]	0.091
	Education PGS	0.78	[0.65, 0.93]	0.031*
	Intelligence PGS	0.96	[0.80, 1.13]	0.691
	BMI PGS	0.87	[0.74, 1.02]	0.220

6.3.7 GAPS analysis regression tables

Table 6.29 GAPS estimates of ACEs on depression and anxiety symptoms.

ACE	Propensity Score Model	β	95% CI	p-value
Parent mental health problems	PGS-only Matching	-0.14	[-0.23, -0.05]	0.004**
	Phenotype-only Matching	-0.17	[-0.25, -0.09]	<.001***
	GAPS Matching	-0.07	[-0.15, 0.00]	0.091
Parent substance use	PGS-only Matching	0.01	[-0.04, 0.05]	0.820
	Phenotype-only Matching	-0.00	[-0.04, 0.03]	0.878
	GAPS Matching	-0.01	[-0.05, 0.02]	0.557
Parent divorce	PGS-only Matching	-0.03	[-0.09, 0.03]	0.444
	Phenotype-only Matching	-0.01	[-0.06, 0.04]	0.665
	GAPS Matching	0.01	[-0.03, 0.06]	0.660
Bereavement	PGS-only Matching	-0.23	[-0.49, 0.02]	0.106
	Phenotype-only Matching	-0.19	[-0.47, 0.09]	0.262
	GAPS Matching	-0.07	[-0.35, 0.20]	0.665
Domestic violence	PGS-only Matching	-0.05	[-0.15, 0.06]	0.508
	Phenotype-only Matching	-0.02	[-0.10, 0.06]	0.672
	GAPS Matching	-0.02	[-0.11, 0.06]	0.660
Emotional neglect	PGS-only Matching	0.33	[0.27, 0.39]	<.001***
	Phenotype-only Matching	0.14	[0.06, 0.22]	<.001***
	GAPS Matching	0.22	[0.15, 0.30]	<.001***
Physical victimisation	PGS-only Matching	0.09	[0.03, 0.16]	0.008**
	Phenotype-only Matching	0.25	[0.18, 0.31]	<.001***
	GAPS Matching	0.14	[0.07, 0.21]	<.001***
Emotional victimisation	PGS-only Matching	0.54	[0.49, 0.58]	<.001***
	Phenotype-only Matching	0.17	[0.13, 0.22]	<.001***
	GAPS Matching	0.15	[0.10, 0.20]	<.001***

ACE	Propensity Score Model	β	95% CI	p-value
Sexual victimisation	PGS-only Matching	0.92	[0.80, 1.04]	<.001***
	Phenotype-only Matching	0.25	[0.10, 0.41]	0.003**
	GAPS Matching	0.32	[0.16, 0.47]	<.001***
Peer victimisation	PGS-only Matching	0.57	[0.52, 0.62]	<.001***
	Phenotype-only Matching	0.23	[0.16, 0.29]	<.001***
	GAPS Matching	0.30	[0.24, 0.37]	<.001***

Note. β = standardised regression coefficient, CI = confidence interval.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.30 GAPS estimates of ACEs on high psychological distress.

ACE	Propensity Score Model	OR	95% CI	p-value
Parent mental health problems	PGS-only Matching	0.06	[0.00, 0.91]	0.002**
	Phenotype-only Matching	0.11	[0.01, 1.58]	0.042*
	GAPS Matching	0.15	[0.01, 1.97]	0.106
Parent substance use	PGS-only Matching	0.04	[0.00, 0.61]	<.001***
	Phenotype-only Matching	0.10	[0.01, 1.20]	0.022*
	GAPS Matching	0.07	[0.01, 0.85]	0.003**
Parent divorce	PGS-only Matching	0.08	[0.01, 0.91]	0.004**
	Phenotype-only Matching	0.23	[0.02, 2.97]	0.262
	GAPS Matching	0.22	[0.02, 2.95]	0.242
Bereavement	PGS-only Matching	0.25	[0.08, 0.77]	0.024*
	Phenotype-only Matching	0.94	[0.44, 2.01]	0.878
	GAPS Matching	1.24	[0.58, 2.65]	0.660
Domestic violence	PGS-only Matching	0.06	[0.00, 0.98]	0.005**
	Phenotype-only Matching	0.41	[0.03, 6.25]	0.557
	GAPS Matching	0.23	[0.01, 3.71]	0.287
Emotional neglect	PGS-only Matching	2.49	[1.87, 3.32]	<.001***
	Phenotype-only Matching	1.63	[1.30, 2.03]	<.001***
	GAPS Matching	2.24	[1.79, 2.81]	<.001***
Physical victimisation	PGS-only Matching	0.97	[0.69, 1.37]	0.878
	Phenotype-only Matching	1.79	[1.40, 2.29]	<.001***
	GAPS Matching	1.44	[1.14, 1.82]	0.006**
Emotional victimisation	PGS-only Matching	16.91	[9.87, 28.98]	<.001***
	Phenotype-only Matching	9.78	[6.77, 14.13]	<.001***
	GAPS Matching	5.71	[4.28, 7.60]	<.001***

Sexual victimisation	PGS-only Matching	1.71	[1.20, 2.43]	0.006**
	Phenotype-only Matching	1.77	[1.34, 2.34]	<.001***
	GAPS Matching	1.89	[1.43, 2.50]	<.001***
Peer victimisation	PGS-only Matching	4.39	[3.20, 6.02]	<.001***
	Phenotype-only Matching	1.90	[1.52, 2.36]	<.001***
	GAPS Matching	2.31	[1.85, 2.87]	<.001***

Note. OR = odds ratio, CI = confidence interval.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.31 GAPS estimates of ACEs on self-harm.

ACE	Propensity Score Model	OR	95% CI	p-value
Parent mental health problems	PGS-only Matching	0.12	[0.02, 0.62]	0.001**
	Phenotype-only Matching	0.11	[0.02, 0.54]	<.001***
	GAPS Matching	0.15	[0.03, 0.77]	0.006**
Parent substance use	PGS-only Matching	0.10	[0.03, 0.34]	<.001***
	Phenotype-only Matching	0.33	[0.10, 1.09]	0.067
	GAPS Matching	0.38	[0.11, 1.27]	0.133
Parent divorce	PGS-only Matching	0.13	[0.03, 0.60]	<.001***
	Phenotype-only Matching	0.30	[0.06, 1.51]	0.142
	GAPS Matching	0.37	[0.08, 1.78]	0.242
Bereavement	PGS-only Matching	1.79	[0.84, 3.84]	0.218
	Phenotype-only Matching	0.92	[0.49, 1.74]	0.827
	GAPS Matching	1.44	[0.78, 2.68]	0.342
Domestic violence	PGS-only Matching	0.39	[0.08, 1.90]	0.259
	Phenotype-only Matching	0.78	[0.15, 4.03]	0.813
	GAPS Matching	0.57	[0.11, 3.03]	0.567
Emotional neglect	PGS-only Matching	2.10	[1.66, 2.66]	<.001***
	Phenotype-only Matching	1.63	[1.35, 1.98]	<.001***
	GAPS Matching	2.01	[1.66, 2.45]	<.001***
Physical victimisation	PGS-only Matching	1.49	[1.13, 1.97]	0.010**
	Phenotype-only Matching	2.58	[2.11, 3.14]	<.001***
	GAPS Matching	2.25	[1.86, 2.74]	<.001***
Emotional victimisation	PGS-only Matching	9.29	[6.51, 13.25]	<.001***
	Phenotype-only Matching	6.79	[5.26, 8.75]	<.001***
	GAPS Matching	5.08	[4.05, 6.37]	<.001***

Sexual victimisation	PGS-only Matching	5.71	[4.08, 7.97]	<.001***
	Phenotype-only Matching	1.50	[1.15, 1.96]	0.005**
	GAPS Matching	1.46	[1.11, 1.91]	0.012*
Peer victimisation	PGS-only Matching	3.89	[3.07, 4.93]	<.001***
	Phenotype-only Matching	2.34	[1.94, 2.82]	<.001***
	GAPS Matching	2.35	[1.94, 2.83]	<.001***

Note. OR = odds ratio, CI = confidence interval.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

Table 6.32 GAPS estimates of ACEs on suicide attempt.

ACE	Propensity Score Model	OR	95% CI	p-value
Parent mental health problems	PGS-only Matching	0.66	[0.14, 3.18]	0.665
	Phenotype-only Matching	0.52	[0.11, 2.46]	0.491
	GAPS Matching	0.51	[0.11, 2.43]	0.479
Parent substance use	PGS-only Matching	0.08	[0.01, 1.08]	0.007**
	Phenotype-only Matching	0.20	[0.02, 2.15]	0.188
	GAPS Matching	0.20	[0.02, 2.18]	0.204
Parent divorce	PGS-only Matching	0.24	[0.02, 3.21]	0.299
	Phenotype-only Matching	0.27	[0.02, 3.50]	0.372
	GAPS Matching	0.24	[0.02, 3.01]	0.272
Bereavement	PGS-only Matching	1.16	[0.39, 3.44]	0.820
	Phenotype-only Matching	0.79	[0.31, 2.00]	0.665
	GAPS Matching	0.62	[0.25, 1.55]	0.369
Domestic violence	PGS-only Matching	0.39	[0.03, 5.57]	0.535
	Phenotype-only Matching	0.68	[0.05, 10.03]	0.819
	GAPS Matching	0.48	[0.03, 7.21]	0.660
Emotional neglect	PGS-only Matching	2.88	[2.03, 4.09]	<.001***
	Phenotype-only Matching	1.89	[1.43, 2.48]	<.001***
	GAPS Matching	2.51	[1.91, 3.32]	<.001***
Physical victimisation	PGS-only Matching	1.26	[0.84, 1.89]	0.365
	Phenotype-only Matching	1.93	[1.43, 2.61]	<.001***
	GAPS Matching	1.89	[1.42, 2.52]	<.001***
Emotional victimisation	PGS-only Matching	19.99	[8.59, 46.52]	<.001***
	Phenotype-only Matching	5.88	[3.83, 9.03]	<.001***
	GAPS Matching	4.64	[3.22, 6.69]	<.001***

Sexual victimisation	PGS-only Matching	2.38	[1.47, 3.85]	0.001**
	Phenotype-only Matching	1.13	[0.81, 1.58]	0.557
	GAPS Matching	1.47	[1.05, 2.04]	0.046*
Peer victimisation	PGS-only Matching	3.60	[2.45, 5.30]	<.001***
	Phenotype-only Matching	1.93	[1.46, 2.55]	<.001***
	GAPS Matching	2.43	[1.83, 3.21]	<.001***

Note. OR = odds ratio, CI = confidence interval.

*p <.05; **p <.01; ***p <.001; p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method.

6.3.8 Sensitivity analysis and post-hoc balance diagnostics

In the PGS-only matching models, bereavement (*OR* = 0.25) and domestic violence (*OR* = 0.06) were associated with lower odds of psychological distress (**Figure 4.7**). These associations are unlikely to reflect true protective effects and are more plausibly explained as statistical artefacts. One potential explanation is suppression effects or collider bias, where adjusting for a large set of covariates (particularly in the presence of multiple co-occurring ACEs) can inadvertently reverse the observed relationship between an exposure and outcome. It is also possible that some ACEs (e.g., bereavement) may be positively correlated with unmeasured protective factors (e.g., increased social support), generating protective associations with mental health when not fully accounted for. After conditioning on the PGS-only propensity scores, the sample of exposed versus unexposed individuals may have become imbalanced or underpowered for certain low-frequency ACEs (e.g., domestic violence), resulting in imprecise estimates.

The PGS-only matching specification produced inflated and unstable estimates, particularly for the more potent ACEs like emotional victimisation. Post-hoc balance diagnostics confirmed that the instability of estimates in the PGS-only models was a consequence of insufficient balance on phenotypic confounders, i.e., with standardised mean differences (SMD) > 0.1. As shown in **Appendix Table *6.33***, while the PGS-only model successfully balanced the six polygenic scores (SMD < 0.1), it left the matched groups severely imbalanced on numerous phenotypic confounders, such as maternal age at birth (SMD = 1.09), birthweight (SMD = 0.56), and mother-child relationship quality (SMD = 0.60). The resulting poor balance in the PGS-only matched dataset likely led to the inflated estimates. As shown in **Figure 4.*9***, the PGS-only model produced extremely wide CIs for emotional victimisation (*OR* = 19.99, 95% CI [8.59, 46.52], p < .001). In contrast, both the phenotype-only (*OR* = 5.88) and GAPS (*OR* = 4.64) models produced substantially smaller and more precise estimates for the same association.

Overall, the inverse associations and inflated risk estimates in the PGS-only models were consistently attenuated to more plausible or non-significant effects in the final GAPS models, supporting the interpretation that these were likely spurious associations which were then correctly attenuated by the robust GAPS approach. This pattern provides direct evidence for the value of the GAPS approach. Without accounting for environmental confounding, the PGS-only model produced unreliable estimates; in contrast, by simultaneously adjusting for both genetic and phenotypic confounders, the GAPS model created a more robustly balanced sample, leading to more stable, conservative, and ultimately more precise estimates.

Table 6.33 Covariate balance for emotional victimisation (PGS-only matching).

Covariate	Std. Mean Diff (Unmatched)	Std. Mean Diff (Matched)	Balance Status
Depression PGS	0.041	0.001	Balanced, <0.1
Anxiety PGS	0.068	0.009	Balanced, <0.1
Suicide Attempt PGS	0.020	0.014	Balanced, <0.1
BMI PGS	-0.017	0.008	Balanced, <0.1
Intelligence PGS	-0.018	-0.001	Balanced, <0.1
Education PGS	-0.001	-0.018	Balanced, <0.1
Sex (Male)	0.083	0.101	Not Balanced, >0.1
Ethnicity (Black)	0.000	0.000	Balanced, <0.1
Ethnicity (Mixed)	0.001	0.001	Balanced, <0.1
Ethnicity (Pakistani & Bangladeshi)	0.000	0.000	Balanced, <0.1
Ethnicity (White)	-0.001	-0.001	Balanced, <0.1
Pregnancy alcohol consumption	-0.061	-0.077	Balanced, <0.1
Pregnancy illness	-0.014	-0.022	Balanced, <0.1
Labour complications	-0.031	-0.033	Balanced, <0.1
Birth complications	-0.026	-0.027	Balanced, <0.1
Gestation time	0.366	0.370	Not Balanced, >0.1

Covariate	Std. Mean Diff (Unmatched)	Std. Mean Diff (Matched)	Balance Status
Birthweight	0.529	0.559	Not Balanced, >0.1
Maternal age at birth	1.109	1.085	Not Balanced, >0.1
Breastfeeding	0.013	0.016	Balanced, <0.1
Difficult infant temperament	-0.332	-0.293	Not Balanced, >0.1
Parent chronic illness	-0.018	-0.017	Balanced, <0.1
Parent smoking	-0.044	-0.027	Balanced, <0.1
Natural parents	0.012	0.008	Balanced, <0.1
Parent education	0.014	-0.020	Balanced, <0.1
Neighbourhood deprivation	0.356	0.382	Not Balanced, >0.1
Mother-child relationship	0.610	0.602	Not Balanced, >0.1
Father-child relationship	0.089	0.066	Balanced, <0.1
Parent mental health problems (age 3)	0.326	0.361	Not Balanced, >0.1
Parent substance use (age 3)	0.002	-0.004	Balanced, <0.1
Parent divorce (age 3)	0.004	0.008	Balanced, <0.1
Bereavement (age 3)	0.001	0.001	Balanced, <0.1
Domestic violence (age 3)	-0.001	-0.001	Balanced, <0.1
Peer victimisation (age 3)	-0.003	-0.003	Balanced, <0.1
Parental discipline	0.026	0.019	Balanced, <0.1
Emotional dysregulation	0.097	0.106	Not Balanced, >0.1
Cognitive ability	0.075	0.054	Balanced, <0.1
SDQ behavioural difficulties	0.456	0.491	Not Balanced, >0.1
BMI (age 5)	0.075	0.040	Balanced, <0.1
Child chronic illness	0.031	0.043	Balanced, <0.1
ADHD diagnosis	0.000	-0.001	Balanced, <0.1
Autism diagnosis	-0.001	-0.002	Balanced, <0.1

Covariate	Std. Mean Diff (Unmatched)	Std. Mean Diff (Matched)	Balance Status
Number of childhood accidents	0.200	0.185	Not Balanced, >0.1
Sibling number	0.039	0.085	Balanced, <0.1
Household size	0.038	0.075	Balanced, <0.1
Household income	-0.008	-0.052	Balanced, <0.1

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