Testing the role of relative age within school year on mental health in children with neurodevelopmental vulnerability

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Thesis Summary

Testing the role of relative age within school year on mental health in children with neurodevelopmental vulnerability

It is important to understand the risk factors that lead some young people to develop mental health problems. The effects of potentially modifiable causal risk factors such as relative age in the school year, and their relationship with other known factors such as neurodevelopmental disorders on mental health problems throughout development were relatively unexplored epidemiologically.

First, associations were examined between relative age and risk of mental health problems in childhood, adolescence, and young adulthood, in a longitudinal population cohort (ALSPAC), using general and specific measurements of mental health and depression. Young relative age was associated with poorer parent-rated general mental health in the school years (measurements taken between 7-16 years) but not before (age 4) or after (age 25). Relative age was not associated with symptoms of depression.

Second, to investigate whether those with neurodevelopmental difficulties are particularly affected by relative age effects, the design was extended to test parent-rated ADHD traits before school entry, and genetic risk of ADHD as moderators of associations between relative age and mental health. Relative age and ADHD risk contributed towards mental health problem risk, but there was no evidence of interactions between relative age and ADHD risk on mental health problems.

Third, associations between relative age and adult (16-25 years) mental health disorder diagnoses and other related adverse clinical outcomes were investigated in cases (individuals with ADHD/ASD diagnosed in childhood) and in controls using data from a whole population electronic healthcare records cohort (SAIL databank). Relative age showed associations with outcomes in controls, but less so for cases, and there was no evidence of interactions between relative age and neurodevelopmental disorders. Relative age was associated with ADHD diagnosis.

The thesis considers the implications of these findings for policy and practice, and highlights directions for future research.

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Chapter 1: Introduction

1.1 Chapter synopsis

Up to one in every eight children are diagnosed with a mental health disorder. One potentially modifiable risk factor is relative age within school year. The youngest children in the school year perform worse than their older peers in education, and they are at increased risk of bullying, low self-esteem, and a diagnosis of mental health disorders. However, more information is needed on the effects of relative age on mental health. It is unknown if any effects vary by developmental stage, and it is also not clear if these effects persist beyond the school years. Research is also needed into whether neurodevelopmentally vulnerable children, defined here as those with, or at increased risk of, neurodevelopmental disorders, who are known to be at increased risk of developing other mental health disorders (emotional disorders, and behavioural disorders), are more affected by relative age effects. These are the research questions that the present thesis aims to address. This chapter will first outline, in section 1.2 (Mental health problems in children and young people), common emotional, behavioural, and neurodevelopmental disorders in childhood and adolescence, their co-occurrences, developmental course, dimensional and categorical approaches to mental health, and highlight the importance of prevention of and early intervention for mental health problems. The next section, 1.3 (Aetiology of mental health problems), will explain that, to find suitable potentially modifiable causal risk factors of mental health it is important to consider their aetiology; this section will describe the genetic and environmental risk and protective factors for mental health problems in youth, including those posed by the school environment. The following section, 1.4 (School entry, age in school year and mental health) will define relative age within the school year and summarise

research into educational, social, and mental health outcomes. The chapter will subsequently describe the difficulties faced by observational and epidemiological research in identifying truly causal risk factors of mental health, and the opportunities that age within school year may provide for causal inference (1.5: Age within school year – opportunities for causal inference). The section that follows (1.6: Limitations of previous research and knowledge gaps) will outline key knowledge gaps and limitations of prior research into the effects of relative age in the school year and mental health. Finally, in section 1.7 (The present thesis; summary, aims and hypotheses), the rationale of the thesis will be summarised, and the aims and hypotheses provided.

1.2 Mental Health problems in children and young people

Child and adolescent mental health problems are common, global, and have the potential to severely impact on the individual's quality of life (World Health Organization, 2018). Current surveys of mental health in children and young people in England report that approximately one in eight (12.8%) children and adolescents aged between five to nineteen years meet diagnostic criteria for at least one mental health disorder (Sadler et al., 2018). There is considerable evidence for an increase in depression prevalence over time, especially in adolescent girls, according to surveys of mental health in children and young people taken between 1999-2017 (Collishaw, 2015; Green, McGinnity, Meltzer, Ford, & Goodman, 2005; Sadler et al., 2018) and longitudinal population cohorts (Armitage et al., 2023). Individuals of any age can develop a mental health disorder, however, individuals are especially vulnerable in adolescence; approximately half of mental health disorders onset in the early adolescent period (by fourteen years of age), and reviews have identified that the peak age of onset of mental health disorders is in the early to mid-twenties

(Kessler et al., 2007). Crucially, however, many of the symptoms of depression that initially onset in adolescence go untreated and undiagnosed, and many adults diagnosed with mental health disorders retrospectively recall that their first feelings or episodes of mental health disorders occurred in adolescence (Kessler et al., 2007).

1.2.1 Common mental health problems in childhood and adolescence

Mental health problems are highly heterogenous in children and adolescents. Various mental health symptoms and disorders are catalogued in diagnostic guidelines such as the Diagnostic and Statistical Manual of Mental Health (DSM-5, American Psychological Association (APA), 2013) and the International Classification of Diseases (World Health Organization (WHO), 2019). The outcomes investigated in the present thesis are child, adolescent, and young adult mental health problems. The most common are emotional (e.g., depression, and anxiety), behavioural (e.g., conduct disorders, oppositional defiant disorder (ODD) and neurodevelopmental disorders (e.g., attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD)). As described in section 1.2.2, mental health disorders also very often co-occur. As explained in section 1.2.4, each of these disorders lie on a spectrum of severity, with similar aetiology for symptom scales as for categorical disorders. It is necessary to investigate and understand mental health problems and their impact to prevent their impacts, and where prevention is unattainable, measures to mitigate mental health effects should be considered. This is because mental health problems account for 7% of all ill-health in the UK, and they have a considerable impact on various areas of life, throughout the life course (Maughan & Collishaw, 2015; McDaid et al., 2022). Mental health problems can impact on academic or work performance (Breslau et al., 2009; Lopez-Lopez et al.,

2019; Riglin, Petrides, Frederickson, & Rice, 2014; Sellers et al., 2019), relationships with family and friends (Arseneault, Bowes, & Shakoor, 2010; Patalay & Fitzsimons, 2018) and they can affect social functioning (Mikami, Miller, & Lerner, 2019; Saris, Aghajani, van der Werff, van der Wee, & Penninx, 2017), resulting in a lower quality of life. Mental health problems also impact on the economy, which is especially important during the present cost of living crisis; a recent economic report estimated that mental health and neurodevelopmental problems cost the UK over £118 billion per year, amounting to approximately 5% of the UK's gross domestic product (GDP; McDaid et al., 2022). Further deleterious consequences of mental health problems are described in section 1.2.5.

This section will outline some common examples of these disorders. Since DSM criteria are more frequently used to define mental health disorders in research, the present thesis will use the definition of mental health disorders in the DSM, unless otherwise specified. This list is not exhaustive; there are many additional mental health disorders to those outlined in this subsection, but those that are most relevant to this thesis are described below.

1.2.1.1 Emotional Disorders

Emotional disorders are characterised by depressive, anxiety, and psychosomatic symptoms. Depression and anxiety are sometimes combined into a single group as internalising disorders, because distress is directed within the person themselves (Riglin et al., 2014). Depression is defined in the Diagnostic and Statistical Manual of Mental Health (DSM-5, APA, 2013) primarily as a persistent feeling of sadness and hopelessness, and a loss of interest or pleasure in activities (anhedonia). Further symptoms include observable increases or decreases in appetite, and weight (gain or loss), changes in sleep (hypersomnia or insomnia), in addition to difficulties in

thinking, concentrating, feelings of guilt or worthlessness, and suicidal ideation. Depression can also feature psychomotor symptoms such as changes in bodily movements, as well as changes in speech volume and prosody, which are observable by other people. For a person to be clinically diagnosed with depression, they must have at least five of any depressive symptoms in the manual, with at least one being a primary symptom, i.e., depressed mood or anhedonia, over a period of at least two weeks. Moreover, these symptoms must cause significant distress and impairments in daily functioning, whether in social, occupational, or educational contexts, and symptoms must also not be the result of co-occurring substance abuse or other pre-existing medical conditions. Children and adolescents with depression may have a more irritable rather than a 'flat' or depressive mood (APA, 2013).

Anxiety as an emotion is the state of fear, worry, or apprehensive expectation and is an emotional state experienced by most people in many different situations because they play a functional role in living, for example responding to a threat or adverse change in the environment (Beesdo, Knappe, & Pine, 2009). However, anxiety disorders differ in that the anxiety experienced in these disorders is persistent, causes significant emotional distress and impacts on the individual's functioning, and in that feelings of perceived threat are incommensurate with the actual threat (DSM-5, APA, 2013). To meet clinical criteria for generalised anxiety disorder, patients must have general worries and anxious feelings, in addition to at least three of the following symptoms: restlessness, fatigue, concentration difficulties, irritability, muscle tension, or sleep difficulties (APA, 2013). To try to prevent these feelings of threat as well as reduce associated symptoms, people may resort to avoidance behaviours, such as refusing to enter a situation where this threat may be encountered, for example, children and adolescents may refuse to attend school

because of their anxieties related to the school setting, such as exams, academic stress, bullying from peers, or crowding (Kearney, 2008). Anxiety consists of several specific conditions; general anxiety disorders are pathological but unspecific worries. There are more specific forms of anxiety; social anxiety refers to fears encountered in social situations, such as the fear of meeting strangers (APA, 2013), separation anxiety is the fear caused by being separated from certain people or animals (APA, 2013), and specific phobias are defined as fears of objects or events that do not realistically pose a threat. For example, house spiders in the United Kingdom do not pose a direct threat to individuals, but the fear response of an individual with arachnophobia (i.e., the pathological fear of spiders) would be far exceeding that of someone who does not have that phobia.

1.2.1.2 Behavioural Disorders

If emotional disorders are considered as a person's distress being generally directed inwardly, then behavioural disorders (sometimes known as ‘externalising disorders’ (MacKinnon, Kingsbury, Mahedy, Evans, & Colman, 2018)) are the polar opposite, that is to say that feelings and distress are directed externally towards others. Examples of behavioural disorders include oppositional defiant disorder (ODD) and conduct disorder.

Oppositional Defiant Disorder (ODD) is a type of behavioural disorder that is characterised by patterns of angry or irritable moods, non-compliant behaviours with peers and authority figures, and vindictiveness (spitefulness) over a period of at least six months (APA, 2013). As with emotional disorders above, behavioural disorders including ODD must cause some degree of impairment in social, academic, or occupational functioning, but ODD behaviours should not occur in the presence of an emotional disorder (APA, 2013).

A more severe form of behavioural disorder, conduct disorders are characterised by behaviours that violate social norms and the rights of other people or animals (APA, 2013). Examples of these disruptive behaviours include aggression to others such as bullying and cruelty (to people or animals), theft, property destruction, and deliberate violations of rules. In the context of school, this can include truancy and vandalism (APA, 2013). Distinctions are made between those with conduct disorders with an onset in childhood or adolescence, and distinctions are also made between those who also display limited prosocial emotions, including a lack of remorse or empathy, as well as the severity of the nature of these conduct problems (APA, 2013).

1.2.1.3 Neurodevelopmental Disorders

Neurodevelopmental disorders are another group of disorders that can influence mental health. There are several neurodevelopmental disorders that frequently co-occur with each other, but the two most important neurodevelopmental disorders to the thesis are attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). For the purposes of the thesis, neurodevelopmental disorders are considered as subtypes of mental health disorders, but there are distinct differences between emotional disorders, behavioural disorders, and neurodevelopmental disorders in their developmental courses; these differences are outlined in more detail in section 1.2.3.

ADHD is the most commonly diagnosed neurodevelopmental disorder with an estimated global prevalence of 2.2%, 3.4% or 7.2% depending on data sources (Fayyad et al., 2017; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015; Thomas, Sanders, Doust, Beller, & Glasziou, 2015). ADHD is defined as age-inappropriate and maladaptive levels of inattention, hyperactivity, and impulsive behaviours. Inattention symptoms include a lack of attention to detail and difficulties sustaining

attention and task effort (APA, 2013). Hyperactive and impulsive symptoms of ADHD include developmentally inappropriate fidgeting, difficulties playing quietly, poor turn-taking, and interrupting or intruding others' conversations (APA, 2013).

Autistic Spectrum Disorders (ASD) refer to the spectra of neurodevelopmental disorders that are currently diagnosed based on deficits in social interaction and communication in addition to restricted and repetitive behaviours and interests (APA, 2013). Classifying ASD as a singular neurodevelopmental disorder with a wide spectrum of impairments is a notable change from the DSM-IV which categorised subtypes of disorders with ASD behavioural characteristics, such as Asperger Syndrome, and pervasive developmental disorder (APA, 2000). Nonetheless, many of the key behavioural features of ASD remain the same. The first key feature of ASD is that individuals are categorised as impaired in their ability to reciprocate socially and emotionally. Some examples of this are impaired abilities to sustain a conversation, and difficulties in sharing interests and emotions (APA, 2013). Alongside impaired verbal social communication problems, people with autism frequently differ in nonverbal communication, such as facial expression differences as well as abnormal eye contact and body language (APA, 2013). Furthermore, verbal, and nonverbal communication differences in autistic people lead to difficulties in developing and sustaining mutual relationships, and an increased likelihood of facing rejection and social isolation (APA, 2013). ASD is also characterised by restricted and repetitive behaviours and interests; these can take many different forms including repeated motor movements ('stimming,' pacing etc), repeated speech, ritualised behaviours and routines that cause emotional distress if changed or disrupted, and sensory hyposensitivity/hypersensitivity (APA, 2013). A recent

prevalence cohort study of ASD of over 7 million school-aged children in England estimated that the prevalence of ASD is 1.76% (Roman-Urrestarazu et al., 2021).

1.2.2 Co-occurrence of mental health problems in young people

There is often considerable overlap between common mental health disorders, and many mental health disorders are co-morbid, i.e., more than one disorder can be present in an individual at the same time (Thapar & Cooper, 2016). For example, depression frequently co-occurs with anxiety disorders, with an estimated co-morbidity of up to 75% in some studies (Garber & Weersing, 2010). Additional examples include the co-morbidity between ADHD and conduct disorders (Jensen & Steinhausen, 2015) and co-morbidity between ADHD and ASD (Leitner, 2014). Co-morbidity of mental health disorders is clinically relevant because the psychosocial, academic, behavioural and adaptive outcomes of individuals with co-occurring disorders tend to be considerably worse than individuals diagnosed with a single disorder (Garber & Weersing, 2010; Rao & Landa, 2014; Sikora, Vora, Coury, & Rosenberg, 2012). Crucial to the present thesis is that research has consistently found that neurodevelopmental disorders are highly co-morbid and predictive of mental health disorders such as anxiety and depression (Addicoat, Thapar, Riglin, Thapar, & Collishaw, 2019; Hendren, Haft, Black, White, & Hoeft, 2018; Purcell, Scott-Roberts, & Kirby, 2015; Rai et al., 2018; Thapar & Cooper, 2016; Topal, Demir Samurcu, Taskiran, Tufan, & Semerci, 2018). This association has been observed to be stable across much of the lifespan (Addicoat et al., 2019), providing evidence of a stable relationship between childhood neurodevelopmental problems and adult emotional problems in the general population. This overlap between mental health disorders has led researchers to identify common genetic and environmental factors

and clinical correlates between these disorders, which will be described in section 1.3 of the thesis.

1.2.3 Developmental course of mental health disorders in childhood, adolescence, and into young adulthood

Prior to adolescence, emotional and behavioural disorder prevalence are relatively low (Beesdo et al., 2009; Sadler et al., 2018; Thapar, Collishaw, Pine, & Thapar, 2012). However, during adolescence, diagnoses of emotional and behavioural disorders increase (Sadler et al., 2018; Thapar et al., 2012), and the peak levels of emotional disorder diagnoses are in the early-to-mid-twenties (Kessler et al., 2007). There is a strong degree of continuity and recurrence of emotional disorder symptoms from childhood and adolescence through to adulthood (Dunn, 2006). Unlike emotional disorders, which can show patterns of relapse and remittance (Dunn, 2006; Thapar et al., 2012), neurodevelopmental disorders are usually considered to be persistent and symptoms tend to be stable over the life course and they tend to onset far earlier in life, often in early childhood (Thapar, Cooper, & Rutter, 2017), however, recent evidence from the Multimodal Treatment study of ADHD (MTA) indicates that ADHD symptoms fluctuate over time in the majority of individuals who received a childhood diagnosis of ADHD (Sibley et al., 2021).

However, there are several differences of note between adolescent and adulthood presentations and treatment responses to mental health disorders and researchers have argued that this may explain why many cases of mental health disorders in adolescence go untreated (Rice, Riglin, Lomax, et al., 2019; Thapar et al., 2012). For example, in children and adolescents, irritability can qualify as a mood symptom in emotional disorders, or emotion dysregulation in behavioural disorders (Thapar et al., 2012; Whelan, Stringaris, Maughan, & Barker, 2013), which also frequently occur

in children with neurodevelopmental disorders (Eyre et al., 2019; Eyre et al., 2017). This may lead to emotional disorder symptoms being missed in children and adolescents with co-occurring behavioural or neurodevelopmental disorders because irritability, mood volatility and fluctuations may be mistaken for behavioural disorders; temper tantrums and anger outbursts are core symptoms of some of these disorders (Thapar et al., 2012; Whelan et al., 2013). Recent research, moreover, has found that psychosomatic symptoms of depression including changes in appetite and weight, as well as decreased energy and sleep levels, were more commonly found in adolescents with depression than those in adults (Rice, Riglin, Lomax, et al., 2019). Conversely, concentration problems and anhedonia were found to be more typical symptoms of adulthood depression (Rice, Riglin, Lomax, et al., 2019). This is supported by findings that sleep issues such as changes in sleep or disrupted sleep patterns are more frequently encountered in young children at risk of emotional disorders (Whalen, Gilbert, Barch, Luby, & Belden, 2017). Depression in adolescence may also be overlooked if behaviours commonly seen in other disorders are the main cause of concern, including, but not limited to substance use, school refusal, anxiety, and behaviour problems (Thapar et al., 2012). Research has identified that genetic liability to childhood neurodevelopmental difficulties such as ADHD strongly influences the likelihood of showing depression symptoms in adolescence, but only in early adolescence (Rice, Riglin, Thapar, et al., 2019). This led the researchers to conclude that early onset depression may include different underlying causes to later onset forms of depressive disorder (Rice, Riglin, Thapar, et al., 2019). This is important considering that psychosocial, socioeconomic and physical outcomes for earlier onset depression, including depression severity, employment status, medical and psychiatric morbidity, and substance abuse, are

particularly poor (Lopez-Lopez et al., 2019; Thapar et al., 2012; Wilson, Hicks, Foster, McGue, & Iacono, 2015).

1.2.4 Dimensional and categorical perspectives of mental health problems

Prevalence estimates of mental health disorders may widely vary, depending on different methods that researchers have used to assess behaviour. For example, participants may have been recruited from clinics, or from the general population, or the researchers may have used categorical or dimensional approaches to measuring mental health. A categorical approach to assessment relies on diagnostic criteria to determine the presence or absence of a condition or a set of symptoms considered as abnormal, or disruptive, such as those that constitute official diagnoses contained within the DSM-5 or ICD-11 (APA, 2013; WHO, 2019). However, a dimensional approach places these same behaviours on a continuum of frequency and/or severity. The differences, and the relative advantages of categorical and dimensional perspectives of mental health problems will be described in this subsection.

1.2.4.1 Categorical approaches to mental health - advantages

A categorical approach is useful when administering certain medical treatments that are specific to individuals with specific mental health problems, such as the use of stimulant and non-stimulant medication for ADHD, and antidepressants for depression. These medications are often prescribed to children diagnosed with these disorders with the intention of mitigating symptoms and therefore facilitating academic and psychological functioning. However, while stimulant and non-stimulant medications may reduce ADHD symptoms (Cortese et al., 2018), these medications have not been shown to work on traits that are specific to other neurodevelopmental disorders, such as ASD (Sturman, Deckx, & van Driel, 2017). In the case of

neurodevelopmental disorders with co-morbid ADHD, for example ASD and ADHD, stimulant medications alleviate the ADHD symptoms, but not ASD symptoms (Sturman et al., 2017). There are other reasons for using or requiring a diagnosis besides medication prescription, such as accessing other support or services (e.g. in schools) and, although this is not universal, a diagnosis may help individuals feel that they understand their behaviour/difficulties and reduce stigma and lead to a sense of belonging (Cage, Di Monaco, & Newell, 2018; Corden, Brewer, & Cage, 2021; O'Connor, Burke, & Rooney, 2020).

1.2.4.2 Dimensional approaches to mental health - advantages

Mental health problems defined dimensionally (e.g., using symptom scales) exhibit the same patterns of aetiology, risk factors, co-occurrence, and outcomes as when considered as categorical disorders but do not identify a binary threshold of the presence of a certain number of symptoms to designate presence or absence of disorder. In research a dimensional approach can be helpful as it increases statistical power, and because it avoids 'lumping' together of individuals who lie below or above an arbitrary threshold (Thapar et al., 2017). Furthermore, dimensional approaches to mental health typically provide more information to clinicians and researchers on the individual's mental health traits compared to categorical approaches; therefore, dimensional models allow for clinicians to implement interventions and treatment plans that are more specifically tailored to that individual's needs (van Heugten-van der Kloet & van Heugten, 2015). Dimensional approaches are also beneficial to researchers, as they allow for better identification of subclinical traits occurring in the general population (van Heugten-van der Kloet & van Heugten, 2015), and they facilitate tracking developmental trajectories in mental health (Rice, Riglin, Thapar, et al., 2019).

Diagnostic guidelines are beneficial to clinical practice, where clinicians must make categorical decisions on whether a mental health disorder is present, whether to prescribe treatment or refer to specialists. Categorical approaches are also helpful when communicating the features of mental health disorders concisely (Frances, First, & Pincus, 1995; Thapar et al., 2017). In the present thesis, data from research-based and healthcare-based longitudinal cohorts, using both categorical and dimensional perspectives of mental health will be used, however, a dimensional approach to mental health will mostly be applied to conceptualise mental health.

1.2.4.3 The importance of prevention, early intervention, and support of mental health problems

The prevention (if achievable) and early intervention and support of mental health problems in children and adolescents is especially crucial considering their impact on education, employment, quality of life, and early mortality, and the Global Burden of Disease studies demonstrate that mental health disorders are some of the most common causes of years lived with disabilities (Vos et al., 2017).

Active prevention and timely interventions of mental health problems in young people are important because they lead to better prognoses in affected individuals as they develop from adolescence to adulthood (Brent et al., 2015; Thapar, Eyre, Patel, & Brent, 2022). The degree to which people recover from emotional disorders, or are prevented from relapse, has been demonstrated to be influenced by their duration of an untreated illness (Bukh, Andersen, & Kessing, 2016). Research has shown that emotional disorder symptoms were decreased in fourteen-year-old adolescents who had been in contact with mental health services a year prior, in comparison to adolescents who had not sought help (Neufeld, Dunn, Jones, Croudace, & Goodyer, 2017). The same study also reported that those who remained untreated at fourteen

years were seven times more likely to report clinically diagnosed emotional disorders at seventeen years (Neufield et al., 2017).

Some types of mental health disorders, such as emotional disorders can be treated by a variety of readily available psychological and pharmacological treatment options including cognitive behavioural therapy, and antidepressant medications (Miller & Campo, 2021; Thapar et al., 2012). However, there are no panaceas to treating mental health disorders as some people respond better to mental health disorder treatments than others. This is especially the case if mental health disorders onset early; studies have shown that standard pharmacological and psychological treatment options for emotional disorders in adults, such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Cognitive Behavioural Therapy (CBT), appear to have smaller effect sizes in younger populations (Cipriani et al., 2016; Rice, Riglin, Lomax, et al., 2019; Thapar et al., 2012; Weisz et al., 2017). Current NHS advice recommends that SSRIs should not be given to young people to treat mild manifestations of emotional disorders, and that SSRIs should only be prescribed to young people in combination with other therapies such as CBT (NHS, 2022).

However, many mental health disorders go untreated and undiagnosed (Potter et al., 2012). Potter et al (2012) identified that in a survey of 333 children of depressed parents recruited from GP surgeries across South Wales, over two thirds of the 79 children who met diagnostic criteria for mental health disorders were not known to health, educational, or social services, nor were their parents seeking help by proxy for these disorders. For those in contact with some support, children were more likely to contact non-medical service providers such as teachers and special educational needs (SEN) services rather than primary care or medical mental health services (Potter et al., 2012). This finding implies that the school environment plays an

especially vital role for help-seeking and subsequent intervention for mental health problems, and the importance the school environment plays will be discussed in the section later in this chapter on school environment (section 1.3.4).

Perhaps exacerbated by the fact that most children with mental health problems do not receive support or treatment, deleterious consequences and impacts of mental health problems often continue forward in development; early onset mental health disorders are associated with a wide range of adverse, long-term outcomes in adolescence and in adulthood. These include educational, occupational and health outcomes. Mental health problems in childhood and adolescence are associated with poor education attainment. Riglin, Petrides, Frederickson and Rice (2014) meta-analysed school grades and psychiatric problems in adolescence and found that emotional disorders pose significant problems for education attainment, measured as school grades, and school failure (i.e. failure to complete mandatory education) in late adolescence (Riglin et al., 2014).

The effects of mental health problems on educational attainment strongly predicts future career or further education pathways. Furthermore, trajectory studies of child and adolescent mental health disorders show associations with socioeconomic outcomes in adulthood; Lopez-Lopez et al (2019) found that individuals with persistent levels of depression in childhood, as well as those with symptoms in young adulthood, were significantly more likely to be Not in Education, Employment or Training (NEET status) at 24 years. Moreover, the same study found that individuals with persistent depression in childhood were more likely to be NEET irrespective of whether depression symptoms improved (Lopez-Lopez et al., 2019). Additional research shows that individuals with neurodevelopmental disorders are less likely to enter higher education, more likely to be unemployed or in unskilled

work, be on disability pensions, and earn less than individuals without neurodevelopmental disorders (Kuriyan et al., 2013; Lallukka, Mittendorfer-Rutz, Ervasti, Alexanderson, & Virtanen, 2020). Furthermore, young people with mental health problems are considerably more likely to develop other deleterious long-term outcomes such as cardiovascular disease, (Hare, Toukhsati, Johansson, & Jaarsma, 2014; Leppert et al., 2021). Moreover, mental health problems are associated with a wide range of behaviours that can exacerbate the risk of physical health problems. These include alcohol, smoking, and substance misuse (Biederman et al., 2012; Breslau, Miller, Joanie Chung, & Schweitzer, 2011; Costello, Erkanli, Federman, & Angold, 1999; Danzo, Connell, & Stormshak, 2017; Langley et al., 2023; Taylor et al., 2014), low physical activity, high sedentary behaviour (Kandola, Lewis, Osborn, Stubbs, & Hayes, 2020), as well as obesity (Leppert et al., 2021; Muhlig, Antel, Focker, & Hebebrand, 2016). More urgent consequences of mental health disorders in adolescents are self-harm, suicide attempts and completion (Bilsen, 2018; Chen, Chen, & Gau, 2019; Fitzgerald, Dalsgaard, Nordentoft, & Erlangsen, 2019; Hirvikoski et al., 2019; John et al., 2020; Maddox, Trubanova, & White, 2017); with suicide, according to recent surveys, being the leading cause of death for individuals in England and Wales aged between ten and nineteen years (ONS, 2019). Therefore, identifying modifiable risk factors to reduce the incidence of mental health problems (anxiety and depression) in childhood and adolescence are priorities for research.

It is thus imperative for research to identify biological and environmental risk factors and protective mechanisms of mental health disorders for young people. (Murphy, Sarris, & Byrne, 2017) Moreover, it is imperative that research prioritises risk factors that are potentially modifiable and exert a causal influence on mental health symptoms.

1.3 Aetiology of mental health problems

The present thesis will consider the extent to which children with, or are at higher risk of, mental health problems may be particularly vulnerable in the context of being of young age within school year. This section will outline the aetiology of mental health problems, starting with genetic risk, moving to environmental risk and protective factors from family background and extra-familial relationships, and then highlighting the school environment as an especially relevant environment to this thesis.

1.3.1 Genetic risk

Mental health problems have some degree of heritability; it is widely known that they run in families (Thapar et al., 2012). Familial risk of mental health problems is also environmentally transmitted (Thapar et al., 2012). Parental depression has consistently been shown to be an especially strong risk factor for depression in children and adolescents; children of depressed parents are three to four times more likely to develop depression than children who were born to parents with no mental health problems (Thapar et al., 2012; Weissman et al., 2016). Furthermore, successful treatment of parental mental health disorders leads to improved psychological functioning in their children (Gunlicks & Weissman, 2008). Weissman et al (2016) moreover found that family history of depression strongly influences life-course mental health trajectories.

The relative contribution of genetic and environmental risk factors towards mental health problem risk have been estimated using natural experiments such as twin studies. Polderman et al (2015) meta-analysed over two thousand papers on twin studies of emotional and behavioural disorders. The researchers found a moderate genetic component to depression and anxiety in adults, and that the relative contribution of genetic effects towards explaining the variance in depression and

anxiety traits were considerably higher both in child and in adolescent populations, compared to adult populations (Polderman et al., 2015). This suggests that genetic factors play a more significant role in childhood and adolescent mental health problems, but then environmental contributions become more important as the young person develops. However, other research suggests genetic innovation of some mental health problems, i.e., the heritability of depression increases from childhood into adolescence and new genetic influences begin to manifest during this period of development (Kendler, Gardner, & Lichtenstein, 2008; Rice, 2014).

Genetic influence estimates of common neurodevelopmental conditions such as ADHD and ASD are higher than emotional disorders (Faraone & Larsson, 2019; Sandin et al., 2017). The most recent Psychiatric Genomics Consortium (PGC) paper found that there are many common genetic variants involved (7.3k) that can explain 90% of the trait heritability of ADHD (Demontis et al., 2023). This suggests that additive genetic effects are the main underpinning causes of these neurodevelopmental disorders. High heritability estimates have led researchers to search for the genetic factors associated with these conditions, but, like emotional disorders, it is widely acknowledged that there is no single gene that is accountable for any one neurodevelopmental disorder phenotype (Cardoso et al., 2019; Faraone & Larsson, 2019). Rather, neurodevelopmental disorders are likely to involve multiple genetic effects with both rare and common genetic variants contributing to the disorder phenotype (Cardoso et al., 2019; Faraone & Larsson, 2019). Moreover, findings suggest emotional disorders and neurodevelopmental disorders share a considerable amount of genetic risk (Power et al., 2017; Rice, Riglin, Thapar, et al., 2019; Verduijn et al., 2017). The most recent PGC paper also found that over 90% of ADHD risk variants were associated with emotional disorders (specifically, major

depression), which demonstrates significant overlap between ADHD and emotional disorders (Demontis et al., 2023).

Genome wide association studies (GWAS) have attempted to establish whether variance in mental health disorders results from differences within the genome (Pearson, 2008). GWAS assay many hundreds of thousands, or millions of common genetic variants such as single nucleotide polymorphisms (SNPs) and associate them with conditions including, but not limited to, neurodevelopmental disorders, and mental health disorders (Pearson, 2008).

Genetic meta-analyses of specific mental health disorders have identified potential genetic loci; recent large meta-analyses of GWAS on adult depression analysing data from over eight hundred thousand individuals have identified over one hundred independent variants, over two hundred genes, and fifteen different gene sets that are associated with depression (Howard et al., 2019). GWAS of anxiety have also been undertaken - while these studies are not as large (N ~200,000) as those on depression, they have nonetheless identified genetic loci for potential replication studies (Levey et al., 2020; Purves et al., 2019). Considering the overlap and comorbidity between anxiety and depression it is assumed that anxiety disorders are also highly polygenic. Similar findings have been reported in other recent studies investigating the polygenic architecture of ADHD (Taylor et al., 2019), as well as ASD (Grove et al., 2019).

Information from GWAS studies can be composited into a polygenic risk score (PRS; (Dudbridge, 2013; Wray, Goddard, & Visscher, 2007). Polygenic risk scores (PRS) are made using summary statistics from independent GWAS studies. First, risk alleles are identified in a "discovery” GWAS sample and given a weighted score

based on their effect sizes. Next, in a separate sample, individuals are given a composite risk score based on the number of risk alleles they carry and the weightings derived from the discovery GWAS (Wray et al., 2014). Evidence shows that genetic risk for one maladaptive phenotype may predict variation in other phenotypes. Demontis et al (2019) conducted a genome-wide meta-analysis of over twenty thousand individuals with ADHD and a control group of over thirty-five thousand individuals. The researchers found that much of the heritability of ADHD can be explained by common genetic variance, with a strong concordance between traits at subclinical and clinical thresholds. The researchers also found that ADHD PRS was associated with ADHD case/control status (OR: 1.56 [1.53, 1.60]), and identified a dose-dependent relationship, higher ADHD PRS was associated with a greater likelihood of being an ADHD case. PRS for ADHD have also been causally associated with other mental health problems, specifically, depression (Riglin, Leppert, et al., 2021).

Research has established that many individual genetic effects additively contribute towards the likelihood of developing common mental health disorders and these effects are more pronounced the earlier the age of onset of mental health symptoms. However, genetic effects alone are insufficient to account for individual risk in emotional, behavioural, or neurodevelopmental disorders. It is therefore necessary to consider familial and broader social environments and their protective or predictive roles in child and adolescent mental health. The extent to which these environments are associated with mental health problems will now be discussed.

1.3.2 Family environment and background

While the genetic heritability of mental health disorders is considerable, environmental factors also play a role in their aetiology and there are many

associated environmental risk factors. In this subsection, risk factors within the family are described.

There is strong evidence from adoption studies that implicates social and environmental risk transmission of mental health problems, in addition to genetic factors and gene-environment interplay (Tully, Iacono, & McGue, 2008). To investigate effects of the environment independent from gene-environment interplay it is necessary to disentangle the effects of the environment from genetic effects. Adoption studies eliminate genetic confounding because adoptees do not share genetic material with their adoptive parents, assuming that the adoptee was not adopted by a biological relative (Tully et al., 2008). Tully et al (2008) conducted clinical interviews with adopted and non-adopted adolescents and their (adoptive, if adopted) parents, and found that maternal depression influenced the risk of both adopted and non-adopted children being diagnosed with emotional (depression, anxiety), behavioural (conduct disorder) and neurodevelopmental (ADHD) disorders. In addition to adoption studies, much previous evidence for environmental transmission of mental health risk factors in children has come from studies on prenatal and perinatal environmental risk factors. Prenatal and perinatal environmental risk factors are important in the context of the present thesis because these risks precede entry into school. There are many such risk factors that are associated with increased neurodevelopmental disorder risk, including (but not limited to) parental age at time of conception (Hvolgaard Mikkelsen, Olsen, Bech, & Obel, 2017; Janecka et al., 2017), and smoking (Langley, Heron, Smith, & Thapar, 2012). However, there is evidence that, in at least some of these associations, genetic and environmental confounding explains these associations (Langley et al., 2012; Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014). Amongst the most

reliable prenatal and perinatal factors for neurodevelopmental disorders and mental health problems are preterm birth, and low birthweight. Studies of premature and low birth weight children have consistently found that these children are more likely to have difficulties with cognition and attention, as well as being physically smaller than their same-aged peers, and more predisposed to mental health conditions and neurodevelopmental disorders (Ask et al., 2018; Singh, Kenney, Ghandour, Kogan, & Lu, 2013; Spittle & Orton, 2014; Wolke, Baumann, Strauss, Johnson, & Marlow, 2015). The more preterm the child, the more likely they are to have physiological, neurodevelopmental, and mental health problems in relation to their peers (Singh et al., 2013; Wolke et al., 2015).

In addition to prenatal and perinatal risk factors, there are social environmental risk factors that are associated with mental health problem risk, given exposure in early childhood. These risk factors include low socioeconomic status (SES), including financial income, education level, occupation status and neighbourhood quality, conflicts in the family environment, hostile parenting, marital discord, early neglect, and adverse childhood experiences including physical, emotional, and sexual abuse, neglect, domestic violence, divorce and incarceration (Blackburn, Spencer, & Read, 2010; Collishaw, Furzer, Thapar, & Sellers, 2019; Costello, Compton, Keeler, & Angold, 2003; Farah, 2017; Hughes et al., 2017; Kreppner et al., 2001; Rutter et al., 2007; Thapar & Cooper, 2016).

Longitudinal research investigating mental health has established that there are considerable differences in mental health by financial income; children from low-income families showed considerably worse mental health difficulties. Collishaw et al (2019) found that differences in child mental health between low-income families have increased over the last two decades (Collishaw et al., 2019). This rise in social

and psychological inequality could be partially explained by public spending cuts, which have affected access to support service provision, especially in the poorest of households (Collishaw et al., 2019; Sellers et al., 2019). Evidence from natural experiments suggests a causal effect of social inequality on psychiatric symptoms to support this argument; Costello et al (2003) conducted a natural experiment on a population sample of predominantly white Americans, and Native Americans living on a reservation (Costello et al., 2003). The researchers took yearly psychiatric assessments between 1993-2000. In 1996, a casino opened on the reservation and the Native Americans on the reservation received an increase in income (regardless of any direct involvement with the casino), paid biannually. This caused some families to move out of poverty. The researchers found that, before the opening of the casino, there were higher levels of mental health disorders in those who were poor relative to those who were not poor. However, after the casino opened, those who moved out of poverty showed a reduction in behavioural disorder symptoms, to levels comparable to those who were not in poverty throughout the study. Emotional problems remained unaffected regardless of income change. This evidence indicates a causal effect of financial income and social inequalities on disorders that are characterised by externalising symptoms (Costello et al., 2003), which reinforces the need to find additional potentially modifiable causal risk factors for mental health problems.

1.3.3 Extra-familial environment- friendships and peer relationships

The present thesis focuses specifically on school environment and age in school year, and this is discussed in more detail in sections below (section 1.4). However, an important part of these environments is the role of social relationships, and this

subsection outlines from a developmental perspective why these relationships are important.

Difficulties in peer relations including loneliness, social isolation and exclusion, and bullying, are significant risk factors for mental health disorders (Arseneault et al., 2010; Powell et al., 2020; Wolke et al., 2015). In contrast, positive friendships are important in the context of child and adolescent mental health because they positively influence development by providing social and emotional security, promoting social skills, improving self-esteem and by acting as a source of social support (Newcomb & Bagwell, 1995; Powell et al., 2020). As the child develops, friendship influences on behaviour become more important, especially in adolescence (Goodwin, Mrug, Borch, & Cillessen, 2012). Absent or poor-quality friendships are suggested to influence many life outcomes in education and elsewhere, including loneliness and school engagement (Waldrip, Malcolm, & Jensen-Campbell, 2008). Friendships are suggested to protect against poor outcomes even when social networks are disrupted by events such as school transition, although this should be interpreted cautiously because children who more readily adapt to school transition may also be more socially competent (Berndt, Hawkins, & Jiao, 1999; Evans & Hurrell, 2016; Monahan & Steinberg, 2011). The study of associations between friendships and mental health disorders is difficult since all friendships are different between individuals and groups of individuals, and highly dynamic across development. Nonetheless, poor quality friendships and loneliness before compulsory education are associated with higher rates of emotional and behavioural problems in young children (Engle, McElwain, & Lasky, 2011) and throughout childhood (Qualter, Brown, Munn, & Rotenberg, 2010).

However, it cannot be determined whether poor mental health is specifically caused by, or are sequalae to, differences in friendship quality from this research (Qualter et al., 2010). Moreover, the extent to which these mental health problems are specific to friendships cannot be established since there are other confounding factors that may change an individual's abilities to make friends, including life events (e.g., moving away) and neurodevelopmental disorder traits.

Of particular concern is experience of bullying, either physical, verbal, or over electronic communication methods (cyberbullying). These are commonplace in the school setting despite anti-bullying campaigns and initiatives (Arseneault et al., 2010). There is a bidirectional relationship between many psychosocial factors that influence bullying victimisation and mental health disorders; young people with internalizing and externalizing problems, peer rejection, poor quality friendships and poor social skills have been found to be at higher risk of bullying and victimisation (Cook, Williams, Guerra, Kim, & Sadek, 2010; Qualter et al., 2010). Victims are a heterogenous group, but there are some characteristics commonly attributed to victims such as being physically weak, submissive, unconfident, unaggressive, and having poor social skills, as well as looking and acting differently to, or being perceived as less popular than, their peers (Carney, Hazier, & Higgins, 2009; Rodkin & Berger, 2008; Stassen Berger, 2007; Wolke et al., 2015).

Victims and perpetrators of bullying, but especially those who are involved in both (bully-victims) are at considerably greater risk of having mental health problems; Klomek, Sourander and Elonheimo (2015) found that victims of bullying were more likely to have emotional problems as well as suicidal thoughts and tendencies, whereas perpetrators of bullying were more likely to have behavioural problems, including criminal behaviour (Klomek, Sourander, & Elonheimo, 2015). Bully-victims,

who perpetrate and receive bullying behaviours, are at especially high risk for both emotional and behavioural problems. The researchers also found sex differences in bullying responses, where girls were more likely to have emotional problems, and boys were more likely to have behavioural problems (Klomek et al, 2015). Finally, the researchers identified a dose-response relationship between bullying and psychopathology, where those who frequently perpetrated bullying, or were frequently victims of it, were both more likely to encounter and to be more severely affected by emotional and behavioural problems (Klomek et al, 2015). It is also important to consider factors that might mediate or moderate links between bullying behaviours and different mental health disorders. Recent research suggests that the association between neurodevelopmental disorders and bullying may also be mediated by underlying problems in emotion regulation (Fogleman, Slaughter, Rosen, Leaberry, & Walerius, 2018). Research findings have shown that poor social support and bullying behaviours are associated with depression and other mental health problems, and that good peer relationships and mutual friendships are likely protective for mental health (Collishaw et al., 2016).

Taken together, adverse family environment factors contribute towards the risk of mental health disorders independently, and in conjunction with, genetic factors. Be advised that environmental exposures do not determine whether a child develops mental health disorders, but they raise the likelihood of doing so in combination with genetic propensities for mental health disorders (Thapar et al., 2012). However, findings from observational research investigating environmental risk factors in neurodevelopmental disorders should be interpreted with caution since the exact causal mechanisms underlying this interplay between environment and phenotype are poorly understood (Thapar & Cooper, 2016). It is difficult to establish whether

these environmental and psychosocial factors cause mental health disorder risk, because of the reverse causation and confounding problems faced by observational epidemiological studies, which are explained in further detail in section 1.5 (Age within school year – opportunities for causal inference) of the thesis.

1.3.4 The school environment

Poor social support and bullying are both examples of environmental risk factors of mental health disorders that are potentially modifiable by interventions. Because of the increased risk for a range of deleterious mental health outcomes in children and adolescents on exposure to these risk factors, interventions that reduce bullying and increase social support may be two ways to prevent and mitigate onset of mental health disorders in young people, especially in subgroups at risk, on a populational scale. The school environment is ideal for such interventions to be carried in (Jamal et al., 2013). Schools are transformative environments for young people to learn fundamental concepts and skills for success in society. Schools also provide a consistent and comparatively controlled environment for children to interact with other children and groups thereof, and authority figures (teachers and other staff). Schools play central roles in children's social, emotional, and cognitive development throughout childhood and adolescence. Schools therefore influence children's mental health and thus have the potential to mitigate mental health inequalities (Jamal et al., 2013). There are many factors within the school environment that potentially protect or influence the risk of mental health problems, and children will vary in the ways in which they respond to these influences because of their genes as well as family and extra-familial environmental factors. In addition, research has illustrated that school and whole school approaches play causal roles in protecting against poor mental health and other deleterious outcomes, and modifying these

environments to increase school culture quality are important for improving poor outcomes, especially in children who are already at greater risk (Bonell et al., 2018; Shinde et al., 2018).

Bonell et al (2018) aimed to reduce bullying and aggressive behaviours and promote quality of life (psychological and physical health, and social, emotional, and academic functioning) in 12-year-olds with an intervention (Learning Together; Bonell et al., 2018) which combined whole school approaches, restorative practice, and social and emotional education classes. The researchers compared the effects of the intervention in a cluster-randomised trial where schools were randomly assigned the Learning Together intervention and other schools used standard practices. Restorative practices are increasingly being applied in schools and they involve discussions between pupils and teacher(s) or other parties in order to identify and mediate conflict, restore damaged relationships, and develop strategies in order to prevent harm (Bonell et al., 2018). The researchers found that the intervention improved psychological well-being and quality of life compared to the control group, as well as reducing bullying behaviours, as well as substance use and pupil contact with police.

Research has shown that whole school approaches can be effective in improving emotional wellbeing. Rates of suicide and poor mental health are high in environments where individuals have weaker social ties, feel socially disconnected and experience mismatch between individual (i.e., the child) and community (i.e., the school) norms and values (Young, Sweeting, & Ellaway, 2011). This mismatch may be especially marked in children with mental health disorders who are classified as having SEN. Studies indicate that some subgroups of children within school such as those with SEN, or low SES, may benefit more than their peers from whole school

interventions; Challen, Noden, West and Machin (2011) trialled a workshop-based intervention (UK Resilience Programme) aiming to improve psychological well-being and resilience in year 7 pupils (age 11-12). The researchers found that pupils, but especially boys with SEN and girls with entitlement to having free school meals (a proxy for low SES) benefitted significantly more from the programme than their peers, with a greater reduction of depression and anxiety scores observed in those groups (Challen, Noden, West, & Machin, 2011). The researchers also found that the pupils who had the highest baseline scores for anxiety and depression showed greater improvement compared to those who were not as at risk. This research suggests that while whole school interventions and approaches may be of some benefit to all students in the school, certain groups already known to be at greater risk of developing mental health disorders and other poor psychological outcomes are likely to benefit more from targeted intervention and inclusion practices, if they are implemented correctly.

1.4. School entry, age in school year and mental health

This next section will first define and outline the school year in England and Wales. The section will then outline and discuss children's age within the school year as a potentially modifiable underpinning mechanism that accounts for variation in several environmental factors associated with mental health, as well as mental health outcomes themselves. The section will also justify why age within school year may be an especially interesting causal risk factor of mental health problems. It will then outline how certain groups who are more predisposed to mental health disorders may be especially susceptible to age within school year effects. This is a novel but important issue that has not previously been addressed but could have important policy and practice implications.

1.4.1 Starting school

Entering a new school environment for the first time, whether it is entering primary or secondary school can be an especially profound and potentially stressful change for children and young people (Groeneveld et al., 2013). School entry provides a discontinuity in relation to the environments individuals are used to, with new rules, expectations, success criteria and pressures that children are exposed to, as well as many new peers and staff to interact with. Even after preparing children as best as possible on what to expect in these new environments, school transition can be a daunting and stressful prospect for many individuals, especially if they are already at higher risk for mental health problems (Thomson, Guhn, Richardson, Ark, & Shoveller, 2017). In addition, as discussed next, children vary in their maturity when they start school.

1.4.2 School entry cut-offs and age within school year in the UK education system

Variation in children's ages within their school year is the focus of the present thesis; theory and prior evidence of how age in school year predicts children's developmental outcomes are outlined in more detail in the section that follows (1.4.3). Age within school year is a unique variable to consider in that it is a variable that it is quasi-randomly assigned and thus allows for causal inference. The present thesis will be using data from England and Wales, and therefore will refer to September 1st as the school entry cut-off date unless otherwise specified.

In most cases, children in England and Wales enter school in the September before their fifth birthday into a reception year (year 0 or R; Department for Education, 2014a).

There is no statutory barrier to children being placed in a school year group outside of their chronological age, but parents do not have the right to insist that their child is admitted to that year group (Department for Education, 2014b), even in light of new regulations (Department for Education, 2014a) which suggest some flexibility on school entry date in England. Crucial to the present thesis is that these requests are only granted in exceptional circumstances; some children may be especially cognitively gifted and talented for their age, meaning that they could be placed in the year ahead of their peers of the same chronological age (Department for Education, 2014b). However, the more likely scenario would be that some children have special educational needs and/or disabilities and may be less ready compared to their peers for entering the school system, or they may have experienced ill health that has impacted on their attendance in early years education settings such as nurseries or playgroups (Department for Education, 2014b). Local education authorities are expected to review requests to delay school entry on a case-by-case basis, considering perspectives and advice from parents, clinicians or other professionals, and the head teacher at the school that received the request, in addition to evidence and concerns regarding the child's development (Department for education, 2014a, 2014b). Even after all of this has been submitted, local education authorities can still deny the request (Department for Education, 2014a, 2014b).

in the UK there is considerable variation between the devolved nations, individual local education authorities and individual schools in allowing deferred school entry (Department for Education, 2014a; Welsh Government for Education and Skills; 2013). Some local authorities in England (9% of LEAs) agree to all requests for summer-born children to defer school entry (Department for Education, 2019). However, most local education authorities ask for parents to make a case on why

deferment would be better for their child (62%), and only strong cases are accepted in others (30%; Department for Education, 2019). While English and Welsh policies regarding delaying school entry are broadly similar, there is less legislative support for those in Wales compared to England given that schools in Wales are not covered by the governmental Guidance for Summer Borns 2013 (Department for Education, 2014b). However, in Scotland, the youngest children in the school year (January and February-born children) are provided with a more flexible approach to school entry where they are automatically granted a delayed school year, if requested by their parents, with no missing school years or penalty to funding (Fleming et al., 2022). In Wales, holding children back for a year is extremely rare; Fleming et al. (2022) reported that 2,401 out of 305,991 children living in Wales were held back a year (0.78%; Fleming et al., 2022), compared with 57.979 out of 757,304 children living in Scotland (7.66%; Fleming et al., 2022). In Northern Ireland, the School Age (Northern Ireland) Act 2022 has recently been passed to allow for relatively young (children born in April-July 1st (cut-off: July 2nd)) children to have a deferred school entry. School entry cut-off dates also vary significantly between national governments; for example, the school entry cut-off date in Scotland is March 1st, therefore the oldest children in the Scottish school year will be born in March and those born in February will be the youngest (Goodman, Gledhill, & Ford, 2003). It is also important to note that these more flexible policies have only been recently introduced (except in the case for Scotland). The children included in the studies in this thesis would have entered school prior to the adoption of such policies.

Most children in the English and Welsh academic systems are not subject to education practices such as redshirting or grade retention, which are commonplace in many countries, including the United States (Dhuey, Figlio, Karbownik, & Roth,

2019). Redshirting is a practice whereby parents can choose to defer their children's entry into school by an extra year, and grade retention is where individuals are required to repeat a grade due to failing to make requirements for advancement into the next academic year. In England and Wales, children born in September are nearly always the relatively oldest children compared to their peers in the same academic year, and children born in August are nearly always the youngest throughout their years of compulsory schooling. If a child is born on August 31st, then they are in one school year, and a child born the day after (September 1st) will be in the school year below them (Goodman et al., 2003). If children are born in September, then they are either approaching or have reached their fifth birthday when they start school, and children born in August in the following chronological year will have only just reached their fourth birthday when the school year starts.

Differences in age within school year are expected to be especially marked when children start compulsory education; on the first day of school, the oldest children are approximately 20% more psychologically and physiologically mature, and additionally have gained more life experience (e.g. education at home) than a child born in the August of the following year, assuming similar development and life experience rates (Holland & Sayal, 2019). However, all children in the same academic year will be expected to learn from the same curriculum materials and instruction and will be expected to perform to the same standards, unless otherwise indicated, (e.g., SEN status). Age within school year is a potentially modifiable causal risk factor because school cut-off dates are arbitrarily assigned; by measuring the discontinuities at either side of the September 1st cut-off the causal impact of age within school year on mental health outcomes can be estimated.

1.4.3 Impact of age within school year and children's outcomes: summary of evidence

1.4.3.1 Educational and social outcomes

Research investigating the influence of relative age effects has shown that age within the school year has wide-ranging impacts on child development, and that these effects can persist across development into adulthood. These relative age effects have been observed in many educational and non-educational outcomes.

Relative age in the school year has been shown to influence the likelihood of being selected for sports competitions and leadership roles (Cobley, Baker, Wattie, & McKenna, 2009; Dhuey & Lipscomb, 2008; Smith et al., 2022). Research has shown that relative age effects influence the likelihood of securing desirable socioeconomic and educational outcomes post compulsory education, such as attending higher education, and obtaining a secure financial status (Bedard & Dhuey, 2006; Kawaguchi, 2011). Research has also shown that age within school year, perhaps as a result of being allowed more time to develop and interact with the world prior to school entry, influences cognitive and social skills, with older children in the school year having better quality social networks than younger children (Ballatore, Paccagnella, & Tonello, 2020; Fumarco & Baert, 2019; van Aalst & van Tubergen, 2021). Research has also found evidence to suggest that young relative age is associated with poor self-esteem (Thompson, Barnsley, & Battle, 2004), as well as lower estimations of well-being and life satisfaction (Ando et al., 2019; Fumarco, Baert, & Sarracino, 2020).

The most widely reported effects of age within school year are on education attainment. Children born in August in England were approximately 6% less likely to achieve five or more GCSE grades compared to their peers born in September

(Crawford, Dearden, & Greaves, 2013). Differences by age within school year were not limited to those born at the earliest and latest months of the school year; Crawford et al. also reported that children born in January (in the middle of the school year) were at a disadvantage compared to children born in September in GCSE grade attainment (2.6%), and children born in May were disadvantaged by 4.4% (Crawford et al., 2013). This suggests a linear relationship between relative age and education attainment.

These findings are important to consider because the attainment of five or more GCSE grades including the subjects of English and Mathematics are the headline national standards for pupil achievement in England and Wales (Crawford et al., 2013). The attainment of these grades has further ramifications for individual entry into further education (i.e., colleges and sixth-form), higher education (university-level courses) and for future employment. As discussed above, sixteen-year-old adolescents in England and Wales must make life-changing decisions to determine their future pathways into education, training, and/or employment. GCSE exam performance will influence these decisions (Crawford et al., 2013). Given that August-born children are less likely to attain the standard number of GCSE grades, one would expect to find that people born in August are less likely to enter higher education and employment. This is supported by studies showing that people born in August are approximately 2% less likely to go to universities at eighteen years (Crawford et al., 2013).

This attainment gap was investigated further by testing the role of cognitive ability in the relationship between relative age and education attainment at seven years. Crawford et al (2014) used a regression discontinuity design (this design is described in section 1.5.3) to assess differences in ability in the Millennium Child

Study (MCS) cohort. Ability in this investigation was measured by the Wechsler Intelligence Scale for Children (Wechsler & Corporation, 1991) and by key stage one (KS1) reading, writing and mathematics assessments. After controlling for background characteristics including SES, the researchers found little difference in the cognitive test scores between relatively old and relatively young children when they were assessed at the same age at either side of the discontinuity (Crawford, Dearden, & Greaves, 2014). This contrasted with the KS1 test results where the oldest children in the school year scored approximately 0.8 standard deviations higher than the youngest. Crucial to this study was timing of administration of these assessments; the WISC assessments were conducted around the time of each child's eighth birthday, whereas the KS1 assessments were sat on a fixed day in the school summer term. Therefore, all children were roughly the same age when taking the cognitive assessments, but age variation was substantial for the academic assessments. This was interpreted by the researchers as evidence that differences in cognitive maturity because of variation in the age at which a child sits their assessment accounts for most of the variation in test scores, rather than cognitive ability as measured by IQ (Crawford et al., 2014).

Differences in education attainment because of relative age differences are significantly greater the earlier in compulsory education the child is assessed (Department for Education, 2010; Crawford et al., 2013). This reflects the fact that the relative age gap between the oldest and youngest in the school year decreases proportionately to child age; at the start of school in September, the age difference between the extreme oldest and youngest in the school year is approximately 20% (60 months vs 48 months), falling to 6.25% at the start of year 11, the school year where GCSES take place (192 months vs 180 months; (Crawford et al., 2013).

Therefore, differences in education attainment because of relative age are considerable in the earliest years of compulsory schooling, but they appear to diminish over the course of child development. Department for Education data also reported that, of the lowest 20% of achievers at the foundation stage at age five by term of birth, almost half (49%) were born in the summer term months (May-August; Department for Education, 2010).

Deleterious relative age effects on education outcomes are not limited to the United Kingdom; Bedard and Dhuey (2006) compared relative age effects in US fourth grade (9-10 years) and US eighth grade (13-14 years) equivalent mathematics and science assessments across several OECD countries with different education systems and school starting ages. Some countries, such as the US or France, have a grade retention system in place where children can fail a year and must repeat it, which is not the case for other countries such as England and Japan (Bedard & Dhuey, 2006). The researchers found that the countries that did not have a grade retention system (England, Japan, Norway, and Iceland) all had large relative age effects, with an estimated difference of 11-12% in fourth grade-equivalent test scores by age within school year (Bedard & Dhuey, 2006). In countries with grade retention or acceleration systems, children who were in the school year below that expected given their chronological age were more likely to be relatively young for the expected school year, and those who were ahead of their expected school year were more likely to be relatively old (Bedard & Dhuey, 2006). Because of this fluidity in school year assignment, relative age effects have been shown to be relatively small in countries with high grade retention with between 4-10% differences in test scores by age within school year. Furthermore, the researchers found that, at eighth grade equivalent levels, relative age effects on test scores stayed significant for most of the

countries tested, with the oldest students scoring between 2-9 percentiles higher than the youngest students; however, in Denmark and Finland they became statistically non-significant (Bedard & Dhuey, 2006). This change in effect significance was attributed to a comparatively later school entry age of seven years for both countries, as well as education cultures where ability grouping is discouraged (Bedard & Dhuey, 2006), thus reducing the differences between initial and final relative age effect comparisons.

1.4.3.2 Effects of age within school year on mental health

Given its association with education attainment, social skills, and well-being age in school year may be an important and potentially modifiable environmental factor that also affects child and adolescent mental health. This subsection will describe the previous research undertaken to investigate the relationships between relative age in the school year and mental health (emotional, behavioural, and neurodevelopmental problems).

1.4.3.2.1 Age within school year and general mental health: summary of evidence

Relative age effects on mental health problems are relatively unexplored from an epidemiological perspective. Three UK-based studies suggest that the youngest children in the school year have higher parent, teacher, and self-rated mental health symptom scores (Crawford et al., 2013; Patalay et al., 2015). In all three studies, mental health problems were measured using the Strengths and Difficulties Questionnaire (SDQ), a frequently used behavioural screening tool that measures conduct problems, emotional problems, hyperactivity problems, and problems with peers (Goodman, 1997). The SDQ has been used to measure risk towards emotional, behavioural, and neurodevelopmental disorders (Goodman & Goodman,

2009; Goodman, 1997), and is described in more detail in chapter 2 (section 2.2) of the thesis. Crawford et al (2013) compared teacher and parent-rated versions of the SDQ in seven- to thirteen-year-old children in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. Children born in August had greater total SDQ scores relative to their September-born peers at age seven, indicating poorer mental health. The researchers also found that relative age effects on mental health attenuate to the null as the gap between oldest and youngest children becomes proportionally smaller as chronological age increases (Crawford et al., 2013). Patalay et al (2015) investigated self-rated SDQ scores in eleven- to thirteen-year-old children in England, grouped into thirds by relative age. The youngest third of children had higher SDQ scores, primarily driven by emotional and peer problems. Lastly, Norbury et al (2016) found that the youngest children in their first year of compulsory education were at higher risk of mental health problems as evidenced by higher SDQ scores, as well as poorer language skills, relative to their peers (Norbury et al., 2016). In all three studies, children were of compulsory school age, which provides a limited snapshot of the developmental picture of relative age effects on mental health over development. This limitation and other limitations of previous research are covered in more detail later in this chapter (section 1.6).

Cross-national comparisons of large representative population surveys of mental health disorders have shown evidence for relative age in the school year as an independent, causal risk factor for child and adolescent psychopathology. Goodman et al. (2003) collected data from over ten thousand children aged five-to-fifteen years in the United Kingdom to investigate whether decreasing relative age was associated with increased mental health problems as measured with the SDQ, and the presence or absence of a psychiatric disorder diagnosis. Crucially, Goodman et al.'s research

utilised cross-national comparisons of large representative population surveys of psychiatric disorders, by comparing disorder rates in England, Wales, and Scotland which have different cut off dates (Goodman et al., 2003). The researchers controlled for age (in years), sex, SES measures, maternal psychopathology, IQ and specific learning difficulties, and found that younger relative age independently contributed toward psychiatric disorder diagnosis (OR: 1.14 (95%CI: [1.03,1.25])), as well as self-rated, parent-rated, and teacher-rated mental health symptoms (Goodman et al., 2003). These effects were present across different age brackets, and for different 'seasonal' cut-offs; for example, Goodman et al. found that the youngest children in the Scottish school year (March Cut-off), born in January and February, were as likely to be at increased risk as the youngest children in the English and Welsh school years. Root et al (2019) investigated diagnosis rates of common mental disorders (anxiety and depression) and of neurodevelopmental disorders in children using a large (N: >1 million) population-based cohort study using electronic primary care records data, and found that children who were born in the last quarter in relation to the school year cut-off date were approximately 23% more likely to have a diagnosis of depression than those born in the first quarter, across England, Wales, Scotland and Northern Ireland (Root et al., 2019). Recent research from Brazil from three longitudinal birth cohorts and a meta-analysis support the evidence that relative age influences ADHD diagnosis, suggesting that this effect is not limited to high-income countries (Meta analysis summarised relative risk OR: 1.34 [1.26, 1.43]; Caye et al., 2020). In addition, Caye et al (2020) found that after a new educational law that changed the cut-off for school entry from December 31st to March 31st, the direction of risk for ADHD in children also shifted to reflect the change in the school calendar year (Caye et al., 2020).

Therefore, cross-country comparisons demonstrate that relative age effects are observed regardless of season, and this implies that the difference in mental health risk is due to the school cut-off and not effects of season of birth (Caye et al., 2020; Goodman et al., 2003; Karlstad, Furu, Stoltenberg, Håberg, & Bakken, 2017; Root et al., 2019). This is important for ruling out potential confounds of relative age effects on mental health or neurodevelopment in summer-born children. The finding of increased mental health symptom and psychiatric disorder rates for younger children within the school year irrespective of cut-off date strengthens arguments that age in school year exerts a causal influence on risk of mental health problems.

Age within the school year not only appears to influence the risk of diagnosed mental health disorders but also influences the risk of their consequences, irrespective of where in the year the cut-off date occurs. Thompson et al (1999) analysed deaths by suicide in individuals born in the Canadian province of Alberta (school entry cut-off: September 1) between 1979-92, and found that suicide completers under the age of twenty years were more likely to have been born in the latter half of the school year (Thompson, Barnsley, & Dyck, 1999). This argument is supported by more recent research conducted in Japan; Matsubayashi and Ueda (2015) investigated suicide rates by age within school year in Japanese adolescents and young adults born between 1974-85, by analysing death records taken between 1989-2010. The researchers found that the youngest children in the Japanese school year (cut-off: April 2) were more likely to die by suicide in adolescence and young adulthood compared to older children (estimated effect range of school entry cut-off on suicide rate: 0.02-0.03 [95% CIs: 0.00, 0.06]) (Matsubayashi & Ueda, 2015). These results support the idea of a causal relationship between age within school year and risk of mental health, considering that the increased risk is present irrespective of culture,

secular time, and school entry cut-off date. The researchers suggested that this increased risk may be related to the effects of relative age on school performance, which subsequently leads to lower self-confidence, which raises the risk of hopelessness, depression and ultimately, suicide attempts or completion.

1.4.3.2.2 Age within school year and neurodevelopmental disorders

Previous research investigating effects of age within school year has used whole population approaches that assume that children are developing at similar rates to determine whether the likelihood of being diagnosed with a mental health disorder is increased or decreased in the presence of relative age effects. Developmental rates and abilities at school entry vary considerably between children and are markedly different in children diagnosed with neurodevelopmental disorders. Children who are already vulnerable due to developmental immaturity may be particularly adversely affected by being relatively young in their school year and in practice may benefit from being held back or being given focused support. However, direct evidence for this possibility is largely lacking because moderators of the relationship between age within school year and mental health have rarely been tested. It is therefore important to answer two distinct questions: First, to answer whether younger children in the school year are more likely to receive diagnoses of neurodevelopmental disorders, and second, for children with, or at high risk of neurodevelopmental disorders, whether the relationship between age within school year and mental health outcomes is more pronounced. The first question is discussed in this subsection because previous research has started to explore it. The second question is discussed later in this chapter, in section 1.6.2, as it is a question largely unexplored by previous research and one that this thesis aimed to address.

The most studied relationship between relative age effects and specific neurodevelopmental disorders has been the relationship between age within school year and ADHD. Root et al (2019) found that the youngest children were 26% more likely to be diagnosed with ADHD. In addition, Holland and Sayal (2019) conducted a systematic review on age within school year and ADHD symptoms, diagnoses, and medication prescription rates, from North American, European, and Australian studies, and found that the total risk ratio for the youngest children in the school year to be prescribed medications for ADHD was 1.27 [1.19, 1.35] relative to the oldest children. There is reportedly only one prior, but large (N: >9 million) study of relative age of ASD diagnosis; Chen et al (2022) identified that the youngest children in the school year in Taiwan are more likely to be diagnosed with ASD compared with older peers (OR=1.23 [1.16, 1.33]) (Chen et al., 2022). This suggests that relative age influences disorder risk for ASD as well as ADHD, however, further research is needed as the Chen et al study is the first to investigate this question in ASD and it will be important to establish, for example, whether these findings can be generalised to UK-based populations. Recent research shows that, in Wales, where the cut-off for school year is comparatively strict, the prevalence of being treated for ADHD increased with decreasing age within school year, but did not differ by decreasing age in Scotland, where children were more likely to be held back for one year, and 81% of held-back children would have been in the youngest quartile of their school year (Fleming et al., 2022). The authors indicated that immaturity may influence diagnosis, and that being held back may attenuate the relative age effect.

1.5 Age within school year – opportunities for causal inference

1.5.1 Defining causal inference

Evidence from cross-national comparison studies suggest the existence of a relationship between relative age in the school year and mental health outcomes, including neurodevelopmental disorder diagnosis (Goodman et al., 2003; Holland & Sayal, 2019; Root et al., 2019). In order for policy and practice interventions to effectively target potentially modifiable risk and protective factors of mental health, it is essential that it is established beforehand that these factors causally influence mental health (Thapar & Rutter, 2019).

Causal inference can be defined, using the potential outcomes framework (Rubin, 1974). A binary exposure, X, causes outcome Y for person i, the potential outcome is different if their exposure X was forced to be set at zero (Y_i^0) to if their exposure was forced to be set at one (Y_i^1). There are two separate potential outcomes for person i at the same time, but only one actual outcome is observed. In the context of a binary exposure scenario, outcome Yi^0 may be the control outcome (i.e., where the exposure did not occur), and outcome Y_i^1 the outcome where the exposure did occur. When X=0, Y_i^1 is not observed and is the counterfactual, and when X=1, Y_i^0 is not observed and is the counterfactual. For each person, the causal effect of X for individual i (Zi), is the difference between the potential outcome if the person experienced the exposure X=1 and the potential outcome if they were to experience the exposure X=0.

So:

$$Z_i = Y_i^1 - Y_i^0$$

$$Y_i = (1 - X_i)Y_i^0 + X_i Y_i^1 = Y_i^0 + X_i Z_i$$

Where Xi = 1 if person i experienced the exposure and 0 if they did not.

Z may be different for different people, and it is usually not possible to measure Z for each person, so the average causal effect of X, (E[Zi]) is estimated.

So:

E[Zi]

$=E[Y_i^1-Y_i^0]$

$=E[Y_i^1]-E[Y_i^0]$

When X is continuous, a similar definition can be provided, but note that the potential outcomes are infinite, but indexed by dose (a). Here, X has a causal effect if E[Ya] is not equal to E[Ya'] for some a, a;' values of X (Hernan et al., 2004). There is not one causal effect of X on Y under this definition, but the causal effect depends on the two doses compared.

In the context of estimating the causal effect of age within school year, one comparison could be between month of birth being August and month of birth being September. A different contrast could be between month a and month a+1 if it is assumed that the outcome changes linearly with relative age. The average treatment effect of relative age is either: (a) the difference in outcome between children born in August vs children born in September or: (b) the difference in outcome per 1 month born later in the school year, assuming linearity of effects.

E[Zi] cannot be observed, but it can be estimated if some assumptions are made. These assumptions vary depending on which analysis method is being used. The main methods used in this thesis are multivariable regression and regression discontinuity designs. For multivariable regression it is assumed that there are no

unmeasured confounders (see section 1.5.2.1 for more details on confounders). This assumption is not testable because it relies on the existence of counterfactual data. An alternative approach is to use methods that rely on finding plausibly exogenous variation in assignment of Xi, such as using regression discontinuity designs, which rely on arbitrary thresholds for assignment of Xi (Bor, Moscoe, Mutevedzi, Newell, & Bärnighausen, 2014; Thistlethwaite & Campbell, 1960). Regression discontinuity designs require some assumptions to be met for plausibly "causal" inference. Further explanation of the regression discontinuity design, and its assumptions, can be found in sections 1.5.3 and 2.4 of this thesis respectively. One of the key assumptions using the potential outcomes framework above to estimate the average causal effect, is that the average potential outcome given X=0 is the same as the average outcome for all the people who actually experienced X=0. If there are variables (known as "confounders") which affect both the exposure experienced and the outcome, then this assumption will not be satisfied unless all the confounders are conditioned on. The assumption that all confounders are known, measured, and adjusted for is known as the "no unmeasured confounders" assumption. The "gold standard" of causal inference techniques are randomised experimentation methods such as randomised controlled trials (RCTs; (Grimes & Schulz, 2002; Thapar & Rutter, 2015). This technique is defined by randomly assigning individuals to treatment or non-treatment, meaning that there is by definition no confounding (Grimes & Schulz, 2002; Imbens & Lemieux, 2008). Thus, any differences found between the groups can be attributed to the prescribed treatment (i.e. there are no confounders) and leads to unbiased estimates of the effect (Imbens & Lemieux, 2008; Rubin, 1974). RCTs, if correctly conducted, are not affected by confounding. In many circumstances, however, randomised experiments may not be possible due to

ethical or practical concerns (Thapar & Rutter, 2015). Randomised experimentation is unfeasible in the context of relative age within the school year, which is determined by the child's distance from an arbitrarily defined cut-off date for school entry. This is because one cannot assign children to be born on a prescribed date, and individuals are born only once, so it is impossible to observe the effects of treatment and non-treatment within individuals. It may also be considered unethical to cause disruption to already-established classroom groups by randomising children in their classrooms as one could potentially deleteriously change their education experiences, and parents may not want this randomisation to occur at their children's expense. In such scenarios, one can take advantage of study designs that are almost-robust to confounding "as-if" randomised (Thapar & Rutter, 2015). These include natural experiments, such as twin designs, adoption designs, maternal vs paternal exposure during pregnancy, mendelian randomisation, and regression discontinuity. In these natural experiments, associations between exposures and confounders are not manipulated by researchers (Thapar & Rutter, 2015).

The next subsection will first outline some of the difficulties in identifying which risk factors are causal in observation studies, and then describe a natural experiment design (regression discontinuity) that can be used to overcome some of these problems.

1.5.2 Difficulties in identifying causal risk factors

The extent to which environmental risk factors play causal roles in psychiatric and neurodevelopmental disorders is problematic for observational and epidemiological research (Thapar & Rutter, 2015). This is because the relationship between risk factors and disorders is assessed on a correlational basis by observing associations between exposures and outcomes (Grimes & Schulz, 2002; Thapar & Rutter, 2015).

By observing these associations, there is no direct manipulation of the risk factor or exposure taking place to cause a change in the outcome (Thapar & Rutter, 2015). Individuals taking part in epidemiological studies that aim to measure environmental risk factors may therefore be non-randomly allocated to 'treatment' and any associations may then be subject to confounding, and biases such as selection bias, and information bias (Thapar & Rutter, 2015).

1.5.2.1 Confounding and reverse causation

Confounding is when a potential risk factor and an outcome are influenced by a third variable (Thapar & Rutter, 2015). This can give rise to a spurious association between risk factor and outcome, even if there is in fact no causal effect. Confounding can also obscure true causal relationships. Attempts to adjust for confounding in observational studies, using statistical techniques such as stratification, standardisation, and multivariable analyses, may not remove all of the confounding, and residual confounding from unknown or unmeasured variables may still remain (Kahlert, Gribsholt, Gammelager, Dekkers, & Luta, 2017; Thapar & Rutter, 2015). An additional important issue is that of reverse causation, where the direction of cause and effect goes from the outcome to the exposure, rather than from exposure to outcome (Grimes & Schulz, 2002; Thapar & Rutter, 2015). One example of this is the association between socioeconomic status (in adulthood) and adult depression; low SES may be a causal risk factor for depression, but it is also likely that low SES is a consequence of depression, due to the increased likelihood of economic problems faced by those who are depressed, or by depressed individuals or even parents of individuals choosing and changing their environments (Freeman et al., 2016; Thapar et al., 2012; Thapar et al., 2017).

1.5.2.2 Selection and information bias

Selection bias can occur where individuals are non-randomly selected into the analysis sample (i.e., into the study, or into the group with complete data; Grimes & Schulz, 2002). Examples of selection bias include not accounting for participants' attrition from participation over time, as well as nonresponse to items, questionnaires, or clinic visits (Lee et al., 2021; Rubin, 1976; Sterne et al., 2009). Selection bias from missing data is covered in section 1.5.2.3 of the thesis.

Information bias (also known as measurement bias) is where the exposure and/or outcome are incorrectly determined or measured with error (Grimes & Schulz, 2002). Examples include social desirability bias (i.e., changes in participant behaviours and responses to conform to desirable (or perceived-as-desirable) social norms), recall bias (i.e., when participants do not accurately remember details or events accurately), measurement error bias (when variables are poorly recorded), and Hawthorne effects (i.e., changes in behaviours and responses because of being aware of being watched). It is important that while random measurement error in the exposure causes bias, random measurement error in a continuous outcome does not. In the present thesis, where age in school year is the exposure variable, and therefore not prone to this error, the only impact of measurement error in a continuous outcome should be to widen confidence intervals. For a binary outcome, there will be bias and should be towards the null, if there is error/misclassification in a binary variable.

1.5.2.3 Problems caused by missing data in research

Missing data is an inevitable problem in longitudinal research, especially in longitudinal cohort studies. Missing data can substantially affect the conclusions that can be inferred from analysis (Rubin, 1974, 1976; Sterne et al., 2009). Restricting to

those participants with complete data for the analysis model (complete case analysis, or list-wise deletion) can lead to selection bias due to selection on characteristics of those who have complete data, as well as a loss of statistical power (Lee et al., 2021; Sterne et al., 2009) There are three categories of missing data: Data is Missing Completely At Random (MCAR); Data is Missing At Random (MAR); Data is Missing Not At Random (MNAR) (Sterne et al., 2009). A variable is MCAR if there are no differences between the missing values and the observed values. In this scenario, missingness does not depend on anything related to the substantive research question; for example, a measurement could not be taken due to human or machine error. This scenario is rare but is nonetheless a strong assumption. Data that is MCAR will not introduce bias when taking a complete-case analysis approach. Data that is MAR means that the probability of data being missing depends on the observed data, but not the unobserved data. A variable (X) is MAR if another variable in the dataset (Y) can be used to predict missingness on X. For example, men may be less likely to respond than women on questions on mental health. Thus, gender predicts missingness on mental health. In this situation, complete-case analysis may result in bias unless gender is included as a covariate in the model. A variable (X) is MNAR if the missingness is systematically related to the unobserved data, that is, the missingness is related to events or factors which are not measured by the researcher, i.e., the probability of X being missing is related to X. For example, data missingness on smoking may be dependent on smoking status. Another example is that participants with severe depression may be less likely to complete the survey on depression (Sterne et al., 2009). In these scenarios, complete case analysis will be biased if the outcome is MNAR, but not biased if exposure is MNAR. Multiple imputation (MI) can be used to deal with the problem of

missing data if data is MCAR or MAR and is explained in chapter 2 (section 2.4.3) of the thesis.

1.5.2.4 Using complementary data to attempt to counteract biases: Longitudinal population cohort and electronic healthcare records studies

Longitudinal population birth cohort studies such as ALSPAC, which are based on recruiting and following up parents and children over developmental time, are useful for covering longitudinal associations, as well as tracking developmental change and long-term outcomes (Canova & Cantarutti, 2020; Fraser et al., 2013; Maughan & Collishaw, 2015; Thapar & Rutter, 2015). As observed within the ALSPAC cohort, a rich collection of data, including biological, clinical, and genetic information can be acquired over the length of time that individuals and their families are followed (Boyd et al., 2013; Fraser et al., 2013). However, studies using longitudinal population cohort data face some limitations. They are time consuming, expensive, and they often have problems with participant attrition over time, which consequently leads to reduced statistical power, as well as selection bias if participant attrition is not the result of data missingness at random (Casey, Schwartz, Stewart, & Adler, 2016; Farmer et al., 2018). In addition, with unselected longitudinal population cohorts it is difficult to consider rarer clinical outcomes (e.g., a diagnosis of ADHD; Powell et al., 2020) because of the low rates of these outcomes observed in these cohorts.

To overcome issues with attrition and to examine patient clinical outcomes (including rare outcomes), use of electronic health care records data via secured and anonymised data linkage systems for research purposes is becoming increasingly commonplace. Some additional advantages for electronic healthcare records data over traditional epidemiological longitudinal population cohort data are that there may be less chance of recall bias (i.e. less chance of bias in individuals recalling

exposures or other variables as a result of having received a diagnosis), as well as being less prone to Hawthorne effects, and social desirability bias (Casey et al., 2016). Similarly, electronic health care records data can be used to study conditions that tend to be stigmatised, such as substance abuse. Electronic health care records data can also be used to study rare and serious outcomes given their (usually larger) sample size and power (Casey et al., 2016). The benefits of using electronic health care records data compared to epidemiological longitudinal population cohort data to measure relative age effects are that they counteract some issues with cohort data such as representativeness, and selective attrition issues. However, these advantages come at a cost of potential sample selection bias, since most individuals do not seek help for their mental health problems, and unmeasured confounding (Farmer et al., 2018; Sauer et al., 2022). This thesis will use data from both epidemiological longitudinal population cohorts and electronic health record cohorts, from ALSPAC (epidemiological longitudinal population cohort), and the Secure Anonymised Information Linkage (SAIL) databank (electronic health record cohort), which are both covered in more detail in chapter 2. By using health record and epidemiological longitudinal cohort data which have different strengths and limitations, the studies together provide important triangulation of evidence that can improve the robustness of findings, especially if results from one study design accords with the other (Hammerton & Munafò, 2021).

1.5.3 Using natural experiments: The Regression Discontinuity Design

Causal inference in observational studies usually involves making the assumption that no unobserved factors confound the relationship between exposure and outcome variables (Bor et al., 2014). This assumption is untestable. If this assumption is violated, biased estimation of causal effects will occur. However,

regression discontinuity designs require fewer assumptions and conditions than other quasi-experimental methods to plausibly obtain estimates of causal effects (Kim & Steiner, 2016; Moscoe, Bor, & Bärnighausen, 2015). Regression discontinuity is the main statistical method used throughout this thesis, so this type of natural experiment will be explained in more detail. Regression discontinuity is a quasi-experimental design that is defined by assignment to a treatment group based on a continuous underlying variable or decision rule, such as exceeding a cut-off point on a continuum (Moscoe et al., 2015; Thistlethwaite & Campbell, 1960). This continuous underlying variable is often referred to as the forcing variable, assignment variable, or running variable. Under the conditions that there exists a continuous variable that ranks the population of interest, and that there is a clearly defined cut-off point to that variable, treatment assignment based on this running variable can be similar to treatment assignment in randomised experiments; participants whose results lie in an area close to the cut-off point (above or below) are assumed to have similar characteristics, except for whether they exceed the cut-off score (Moscoe et al., 2015). If outcomes are different between individuals close to this cut-off, it can be inferred that these differences are caused by the cut-off (Moscoe et al., 2015).

Relative age in England and Wales is assigned quasi-randomly since one cannot directly influence a child's exact delivery date (assuming natural birth), even though children's dates of birth are unevenly distributed across the school year with a higher birth rate in late September (Borja & Martin, 2017). Potential confounders of mental health outcomes would be plausibly independent of birth being either side of the school entry cut-off within a narrow timeframe around that date, with this assumption becoming less plausible as the bandwidth increases. The assumption that being born either side of the cut-off is randomly allocated cannot be tested, but its

association with observed confounders can be. Thus, observational studies of relative age allow for causal inference, using regression discontinuity methods where there is a continuous variable (day of year born) which has a cut-off (1st of September in England and Wales) at which the treatment (entry to school) is applied (Moscoe et al., 2015; Thistlethwaite & Campbell, 1960). Assumptions and a simulated example of the regression discontinuity design are explained further in chapter 2 of this thesis (section 2.4).

1.6 Limitations of previous research and knowledge gaps

There are several important knowledge gaps and limitations from prior and concurrent research to this thesis which are identified in this section.

1.6.1 An incomplete developmental picture of relative age effects

First, it is not known whether differences in mental health by relative age occur prior to starting school. Typically, before school entry children are not grouped together according to date of birth relative to the school entry cut-off; if mental health differences by relative age emerge after, but not before, school entry, it can be inferred that these differences are caused by this grouping at school entry. Second, the extent to which relative age effects mental health problems extend into adulthood is not fully known. To get a clearer picture of relative age effects, it is not only important to consider what happens when relatively young children enter compulsory education, but also when they leave.

1.6.2 Moderation of age within school year effects on mental health by neurodevelopmental disorders

Previous research has mostly used whole population approaches that assume similar rates of development. Research is needed on whether high-risk groups are more affected by relative age than those who may be less at-risk. Relatively young

children are more likely to be diagnosed with neurodevelopmental disorders, e.g., ADHD (Pottegard, Hallas, Hernandez, & Zoega, 2014; Root et al., 2019), but this may be due to teacher ratings of relative cognitive immaturity. As previously explained in section 1.2, children with neurodevelopmental disorders are already at an increased risk of mental health problems as well as poor education attainment and social impairments. Less is known on what happens to those children who are vulnerable to, or are already diagnosed with, neurodevelopmental disorders if they are young vs old on school entry. It is not known whether neurodevelopmental vulnerability moderates the relationship between age within school year and mental health outcomes in young people. In addition, what is not known is whether children with neurodevelopmental disorders who are young for their year have particularly poor outcomes relative to other children with neurodevelopmental disorders who are older for their year. This may be due to a variety of factors that are associated with both neurodevelopmental disorders and with mental health disorders, including poor peer relationships and bullying, academic competence, or differences in maturity, amongst others. Although some studies have examined links between age within school years and neurodevelopmental disorders (Root et al., 2019; Holland & Sayal, 2019; Chen et al., 2022), they address a different question, that of the probability of diagnosis by relative age, and not whether children with (or at high risk of) neurodevelopmental disorder who are young or old for their year are especially vulnerable to poor mental health outcomes. This question has only recently started to be explored (Kuntsi, Larsson, Deng, Lichtenstein, & Chang, 2022), (see chapter 5, section 5.2) and it is a question that warrants further investigation.

1.6.3 Variation in outcomes according to informants

Research has identified that relatively young children are at risk of poor education outcomes, low self-esteem, bullying, poor social networks, and emotional problems (Crawford et al., 2013, 2014; Fumarco & Baert, 2019; Fumarco et al., 2020; Patalay et al., 2015; Thompson et al., 2004). However, longitudinal follow-up of the same children over the school year is required to establish how age within school year leads to poor mental health, and how certain risk or protective factors moderate this relationship. In order to more accurately establish the extent to which emotional problems persist throughout childhood, and which groups may be more vulnerable, it is necessary to consider that there is a sizable variation in the relationships between risk factors and ratings of child mental health, depending on the informant, such as parents, teachers, or the children themselves (Collishaw, Goodman, Ford, Rabe-Hesketh, & Pickles, 2009). For example, Collishaw et al found that sex differences in hyperactivity and peer problems, were especially observed if these symptoms were rated by a teacher, rather than by parents or children. Contrastingly, girls were more likely to self-report higher emotional problems than when rated by teachers and parents (Collishaw, Goodman, Ford, Rabe-Hesketh, & Pickles, 2009). Previous research has shown that parent-reported and teacher-reported SDQ measurements differed considerably by relative age in the school year; teachers reported greater average differences in SDQ total difficulty measurements (Crawford et al., 2013).

Squires et al (2012) investigated whether relatively young children and adolescents were more likely to be labelled as SEN students, in over four hundred English primary and secondary schools (N: 15640). Children born in August were one and a half times more likely to be classed as SEN than those born in September. The researchers found that the month-of-birth effect was attenuated when clinician

ratings of SEN were taken into consideration (Squires, Humphrey, Barlow, & Wigelsworth, 2012). Thus, the overrepresentation of relatively young people in SEN may be due to informant effects.

Some recent research has suggested that relative age effects in children suspected of having ADHD may be due to teachers' judgement of the child's perceived immature behaviour compared to their older peers, however, mixed evidence indicates that further research into relative age effects in individuals at risk of ADHD is warranted. Research in the United States (cut-off: 1st September) did find a meaningful effect of relative age on parent-report ADHD symptoms, but this effect was negligible compared to the effect on teacher ratings of ADHD (Elder, 2010). Thus, adult perceptions of immature behaviour in relatively young children compared to their older peers may differ between raters of that behaviour.

These findings are all important because teachers usually only know individual children in the school environment and only for a few years. Teachers may compare the youngest children in their class to their more mature peers. Further, children's behaviours may be different in the school environment to those displayed elsewhere; for example, children may be more hyperactive at school, but may not display these behaviours to the same degree at home. To overcome these limitations, parent-reported, and self-reported sources of mental health problems were used in chapters 3 and 4 of the thesis.

1.6.4 Subjectivity of informant-rated risk of mental health

Given the variation in mental health risk ratings according to different informants, more plausibly objective measurements of mental health risk may be needed to elucidate the effects of relative age in the school year on mental health. Halldner et

al (2014) used data from Swedish (cut-off: 1st January) longitudinal population cohorts and registry data and found no evidence of an effect of relative age on parent or self-reported ADHD symptoms in children and adults, but found that the youngest children in the school year in Sweden (November/December births) were more likely to receive a diagnosis of ADHD (OR: 1.2–1.5) relative to their older peers born in January and February (Halldner et al., 2014). A more recent Swedish study found that a young relative age was associated with receiving an ADHD diagnosis or prescription between the ages of six and fifteen years (Kuntsi et al., 2022). Furthermore, and crucial to this thesis, a negative interaction (OR: 0.78) was observed between relative age, ADHD diagnosis, and depression (Kuntsi et al., 2022), where individuals with ADHD and who are (or were) relatively young for their school year were less likely to be depressed. The researchers concluded that relatively young children with ADHD were more likely to have less severe ADHD, suggesting that there may have been a lower threshold for diagnosis of ADHD for relatively young children (Kuntsi et al., 2022).

This is important for the following reasons: First, diagnoses of ADHD are made based on inattentive and/or hyperactive/impulsive behaviours to the degree that they are disruptive and inappropriate for the person's developmental level (APA, 2013). For a child to receive a diagnosis of ADHD, the behaviours of the child would have been compared to other children at home or at school, by parents and teachers. Such a comparison within age group is often made between children within the same school year, and given previous research findings, this is more likely to be the case for teachers than parents (Crawford et al., 2013). Second, behaviours pertinent to ADHD, such as difficulties in turn-taking, sitting still, and concentrating on tasks, are more frequent in younger children, but these behaviours will likely decrease over

time (Galéra et al., 2011); relatively young children within the same class may be perceived as immature because of the age gap between them and their peers, especially early in education, and in countries that start school at an earlier age, because 12 months difference makes up a greater proportion of their overall lifespan at that point. Last, the present thesis considers that ADHD exists as the extreme of a continuous distribution of underlying symptom traits, with certain questionnaires such as the SDQ being utilised to measure this distribution of behaviours within children (Goodman, 1997; Thapar, 2018). Under this assumption, it is plausible that relatively young children who are close to the diagnostic cut-offs are more likely to receive a diagnosis when compared to an older child, because of their (perceived) immaturity. It is therefore necessary to consider multiple sources of ADHD risk, such as information from multi-informant sources of risk of mental health problems, from different settings (research and healthcare), as well as more objective measurements of risk such as polygenic risk scores.

1.6.5 Specificity of mental health measures

Lastly, most previous studies have looked at general mental health symptom screens such as the SDQ. However, studies examining SDQ subscales highlight some specificity across different domains of mental health (Patalay et al., 2015). To better understand mental health domain-specific effects, more sensitive and specific measurements of particular mental health outcomes are needed. Depression, a particularly important youth mental health outcome is poorly assessed by the SDQ and examining dedicated measures such as the Short Mood and Feelings questionnaire (SMFQ) for depression would be helpful (Angold et al., 1995; Angold & Costello, 1987).

1.7 The present thesis: summary, aims and hypotheses

To summarise, approximately 1 in 8 children in the UK have a mental health disorder including emotional disorders (e.g., depression, anxiety), behavioural disorders, and neurodevelopmental disorders (e.g., ADHD, ASD) (Sadler et al., 2018). These disorders are caused by many genetic and environmental factors, as well as complex interactions between them. These difficulties cause distress and harm to affected individuals and their families, impact on education, and raise the risk of more serious consequences such as persistent mental health and physical illnesses later in life. Depression and anxiety are the most common forms of mental health disorders in children and adolescents, and epidemiological evidence suggests that these disorders are rising in prevalence over recent decades (Armitage et al., 2023; Collishaw, 2015; Sadler et al., 2018).

Identifying causal risk factors is a research priority to prevent these problems more effectively in these age groups. Whole school interventions have shown success in preventing and ameliorating mental health (Bonell et al., 2018), but these often do not account for different needs and abilities of different children, for example those with neurodevelopmental disorders, and there are other school-based factors that remain relatively unexplored in this context. One such potentially modifiable causal risk factor is age within the school year. Children are between four and five years old when they start compulsory education in the UK. Age within school year is a potentially modifiable causal risk factor because school cut-off dates are arbitrarily and exogenously determined. Children born at the start of an academic year (September) are approximately 20% more physically and psychologically mature at school entry than children born at the end of the academic year (August) because of this cut-off date. As explained in section 1.6, causal effects of age within school year

can be estimated using regression discontinuity designs by comparing children with birth dates close to this arbitrary cut-off who are the youngest and oldest in their academic year groups. Studies on the effects of relative age have found that relatively young children perform worse than their relatively older peers in education and are more predisposed to mental health disorders and lower self-esteem (Crawford et al., 2013; Patalay et al., 2015; Root et al., 2019). Mental health disorders are more common in the youngest children in the school year, irrespective of where in the chronological year school entry cut-off dates occur (Goodman et al., 2003). However, few studies have tracked relative age effects on mental health from early childhood, throughout schooling and post-school entry. Therefore, this thesis first investigated the effect of relative age in the school year on mental health across development, considering both before and after compulsory school age, in the same group of individuals.

The present thesis then focused on children with, or at high risk of, early neurodevelopmental problems, who are already at high risk of other common mental health problems, to investigate whether they are particularly affected by effects of relative age within the school year, in comparison to other children without these vulnerabilities. This research is important for the following reasons: theoretically it will help to understand the interplay of individual vulnerability and environment in determining pathways of risk and resilience, in this case using a robust design that permits greater confidence around causal inference. This research is also important because it will identify those children who are at highest risk of mental health problems throughout compulsory schooling, and who are therefore a priority for earlier support and preventative intervention. Results from the present thesis will also be relevant for education policymaking by providing evidence on whether

children should be rigidly assigned to school entry based on date of birth or whether there should be greater flexibility reflecting a child's developmental maturity. The present thesis will utilise causal inference methods in epidemiological research including regression discontinuity analyses, and moderation to test effects of age within school year on mental health outcomes (symptoms, diagnoses, and functional impairment), and whether and why they might differ for children with or at high risk of neurodevelopmental disorders.

This thesis used i) the ALSPAC longitudinal birth cohort for whom data is available on week of birth, neurodevelopmental vulnerability risk before and at school entry (ADHD genetic PRS score and parent rated symptoms) and child mental health and depression measures across childhood, adolescence and early adulthood; as well as ii) data from individuals aged 16-25 years who received a childhood diagnosis of ASD or ADHD and matched individuals without a diagnosis, identified via primary and secondary health records in Wales using the SAIL electronic healthcare records database for whom data is available on week of birth, diagnoses of anxiety and depression, self-harm, and substance (drug/alcohol) misuse. The next chapter (chapter 2, general methods) will explain these datasets and statistical techniques used in the present thesis in more detail.

1.7.1 – Aims and hypotheses

1.7.1.1 Aims

1. To investigate whether being relatively young for the school year exerts a causal influence on mental health and depression across development in a longitudinal population cohort (ALSPAC).

2. To investigate whether neurodevelopmental vulnerability, defined as high subjective levels of neurodevelopmental disorder traits or high objective genetic susceptibility to neurodevelopmental disorders, moderates the effects of age within school year on mental health (ALSPAC).
3. To investigate the effect of age within school year on mental health disorders and self-harm in an adult clinical population cohort (SAIL).

1.7.1.2 Hypotheses:

Aim 1:

1. There will be an effect of age within school year on mental health problems during and after, but not before, school entry; children who are relatively young will be more likely to have mental health problems at school age.
2. Differences in mental health by relative age will be strongest at school entry, attenuate but show some persistence across development.

Aim 2:

1. Children vulnerable to neurodevelopmental disorders (ADHD) are more likely to have mental health problems during and after school age.
2. Children vulnerable to neurodevelopmental disorders will be more affected by relative age effects on mental health problems than those who are not at risk of neurodevelopmental disorders.

Aim 3:

1. Young people who are relatively young for their school year will be at increased risk of mental health disorder and self-harm outcomes relative to those who are relatively old.

2. Young people with a childhood diagnosis of a neurodevelopmental disorder (ASD/ADHD) will be at increased risk for mental health disorder and self-harm outcomes relative to those without a diagnosis of a neurodevelopmental disorder.
3. Risk for adverse outcomes associated with young relative age are moderated in subgroups with a diagnosed neurodevelopmental disorder ADHD or ASD) compared to those without a neurodevelopmental disorder diagnosis.

Chapter 2: General methods

2.1 Synopsis of this chapter & data sources

This chapter will specify the methods utilised in the results chapters (chapters 3-5) of the thesis. The chapter will first describe the data sources of the thesis. The present thesis uses data from two studies based in the United Kingdom. Chapters 3 and 4 of the thesis used data from a longitudinal population-based cohort - the Avon Longitudinal Study of Parents and Children (ALSPAC), described in section 2.2 of the thesis, and chapter 5 used data gathered from electronic healthcare records – the Secure Anonymised Information Linkage (SAIL) databank, described in section 2.3. The chapter will then describe the statistical methods that are specific to the thesis, firstly illustrating a hypothetical example of a regression discontinuity design and describing assumptions of the design, then dealing with the issue of missing data using multiple imputation, and outlining sensitivity analyses using generalised estimating equation (GEE) models, used in chapters 3 and 4 (section 2.4). This next section reports some general descriptive statistics from the ALSPAC sample that are relevant to both chapters 3 and 4. Finally, in sections 2.5 and 2.6, general descriptive statistics are provided for ALSPAC data (chapters 3 & 4), and SAIL data (chapter 5) are reported, respectively. These descriptive statistics are provided in this chapter to eliminate repetition between chapters 3 and 4 (which used the same dataset), and then for chapter 5 for consistency with the other results chapters.

2.2 Avon Longitudinal Study of Parents and Children (ALSPAC)

ALSPAC is an ongoing longitudinal and transgenerational observational study of children born to pregnant women in the historical Avon administrative county in South-West England between April 1st, 1991, to December 31st, 1992 (Boyd et al., 2013). This county included the Bristol metropolitan area, as well as Bath and North

East Somerset, North Somerset, and South Gloucestershire areas (Boyd et al., 2013). This section will describe the participants (2.2.1 ALSPAC: sample) as well as the inclusion and exclusion criteria for the studies that used data from these participants. The section will then describe the ethics and data availability, as well as the measurements for age within school year and mental health used in chapters 3 and 4.

2.2.1 ALSPAC: Sample

This study collects data using questionnaires sent by post, as well as from clinical sessions attended during childhood and adolescence. Pregnant women from three District Health Authorities (DHAs) – Southmead, Frenchay, and Bristol & Weston - were recruited. Participation of pregnant women was encouraged through media, and antenatal and maternal health services within the DHAs were used to promote the study (Boyd et al., 2013). Eligible women using these services were given "expression of interest" cards which allowed them to request further information, or to actively decline participation (Boyd et al., 2013); women who did not actively decline participation were included in future data collection, as consent was indicated on an "opt-out" basis (Boyd et al., 2013). The expression of interest card, if completed by prospective participants, contained details of address and due date that allowed ALSPAC staff to determine eligibility for selection into the cohort (Boyd et al., 2013). Women who requested further information were sent a study information booklet followed by an initial questionnaire approximately one week later (Boyd et al., 2013). The eligible sample was defined retrospectively, based on ALSPAC recruitment records, and maternity, birth, and child health records. The recruitment campaign identified 20,248 eligible pregnancies. Women with unknown contact details or who had opted out were not enrolled (Boyd et al., 2013).

A total of 14,541 pregnant women were recruited as an initial sample. Of these, 195 pregnancies resulted in twins. Additionally, there were three sets of triplets and one quadruplet (13 children total) in the study, and there were 69 births with an unknown outcome. Triplets and quadruplets were excluded by default from all ALSPAC datasets, due to the risk of identification, and children with an unknown birth outcome were not included in the dataset. Therefore, in the initial sample there were 14,676 foetuses with known birth outcomes. Of these, 14,062 were live born infants. Of these live births, 13,988 infants survived to 1 year of age. The original number of 14,541 pregnancies was later increased to 15,247 as more parents and children were recruited during later recruitment phases (Boyd et al, 2013). Of these children, 14,701 were alive at one year of age (Boyd et al., 2013). When the oldest children were approximately seven years of age, the initial sample was bolstered with eligible cases who did not initially join the study, in three separate enrolment phases (Boyd et al., 2013). Therefore, from the age of seven onwards there are data available for more than the 14,541 initially enrolled pregnancies. As a result of these additional enrolment phases, 913 more children were enrolled. The total sample size for analyses using any data collected after the age of seven is therefore 15,447 pregnancies, resulting in 15,658 foetuses. Of these, 14,901 were alive at 1 year of age. (Northstone et al., 2019).

Mothers who were recruited into the ALSPAC cohort had broadly higher than average socio-economic position indicators than averages taken from mothers living in the Avon area, as well as information gathered in the 1991 National Census (Boyd et al., 2013). Information about the mothers themselves, their children, and other family members were collected from pregnant mothers from self-report questionnaires. From 7 years, children were invited to attend annual clinical

assessments (Boyd et al., 2013). These “Focus clinics” as referred to in ALSPAC, included many quantitative physiological and psychological assessments, including (but not limited to) biological samples (e.g., blood, DNA), anthropometry (e.g., height, weight), and cognitive ability (e.g., IQ). This has led to a rich collection of biological, psychological, cognitive, social, and familial and broader environmental exposures and outcomes in the recruited children and parents, from pre-natal (e.g., gestation data), to adult stages of life (Boyd et al., 2013). This includes genetic data and polygenic risk scores, the latter of which are covered in more detail in chapter 4. ALSPAC contains multi-informant measures of neurodevelopmental disorder traits, and parent- and child reported outcome measures of mental health problems using the SDQ, and depression symptoms, using the SMFQ. These questionnaires were chosen because they are both widely used, validated measures that were assessed repeatedly in ALSPAC, using the same measure over several timepoints across development. These questionnaires are described in more detail in section 2.2.4 (ALSPAC: Measures).

Children born in the ALSPAC studies were distributed across three academic years (years at school entry - 1995-96, 1996-97 and 1997-98) including children born on either side of two separate school year discontinuities around the school entry cut-off of September 1st. School admissions policies in the Avon education authority suggested that most children would have been expected to start school in the September after they turned 4 years of age, in line with most local authorities in England and Wales. Of particular interest to the present thesis are those individuals born close to the discontinuity around September 1st of each academic year.

2.2.2 ALSPAC: Inclusion and exclusion criteria for thesis

Individuals were included in chapters 3 and 4 when data were available on week, month, and year of birth, together with their school year at any given assessment age; participants were excluded if they were not alive at one year of age (N=688), were not in the expected school year given their chronological age (N=12), and if they were the younger of a twin pair (N=186). After excluding these participants, 14,643 individuals were initially included. Specific to chapter 4, participants who did not have any SDQ data were excluded (N=3527). Participants who did not have any hyperactivity data at 4 years were also excluded (N=1944). When the effects of polygenic risk scores (PRS) were investigated, participants who did not have PRS measurements were also excluded (N=4183). See Figure 2.1 and 2.2, below for further details.

Figure 2.1: Flowchart of ALSPAC sample selection, chapter 3.

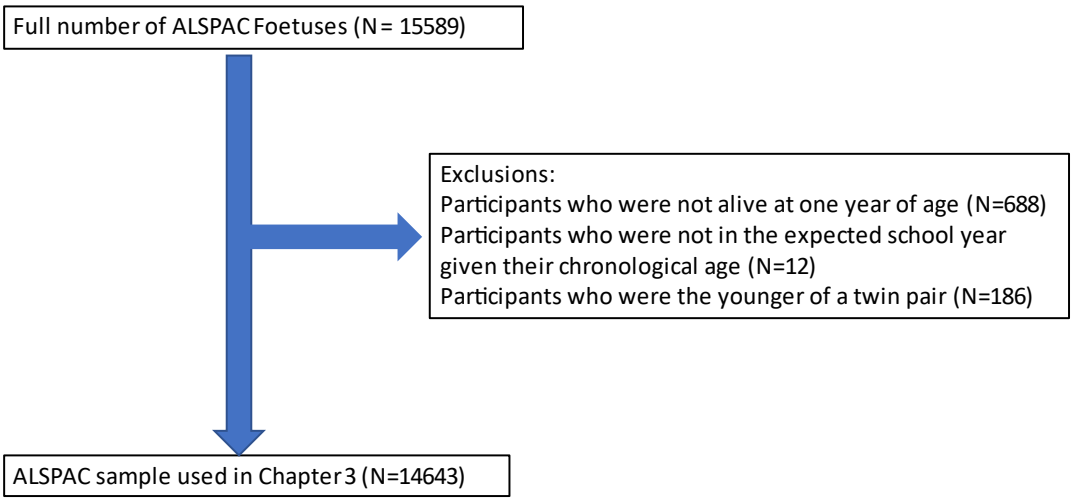
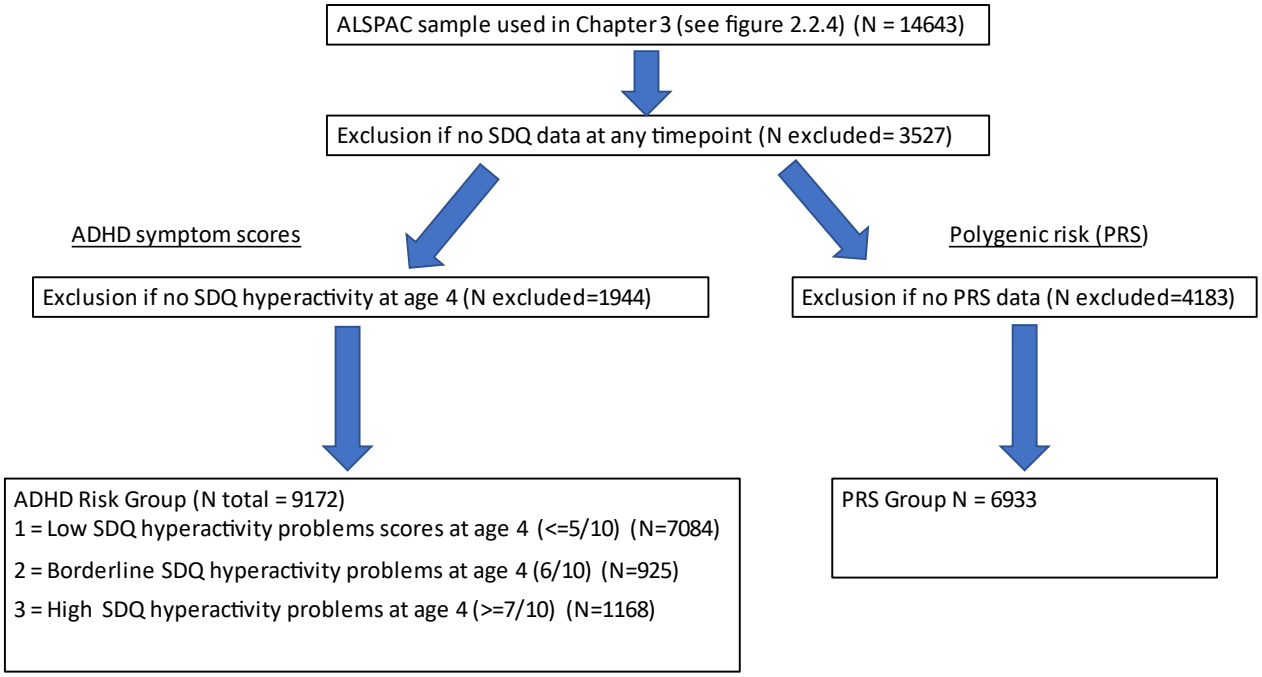


Figure 2.2: Flowchart of ALSPAC sample selection, chapter 4



2.2.3 ALSPAC: Ethics and data availability

2.2.3.1 ALSPAC: Ethical considerations

Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participating families following the recommendations of the ALSPAC Ethics and Law Committee at the time. ALSPAC data was anonymised, i.e., specific details that may be used to identify a person (e.g., names, exact dates of birth) from their records were removed, so that they are no longer considered identifiable. Because of the potential for information deanonymisation, it was not permissible to obtain precise dates of birth for a measurement of relative age in the school year.

2.2.3.2 ALSPAC: Data availability

The ALSPAC study website contains details of all data that is available to the public, which can be accessed using a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/) [last accessed 22/03/2023]. Study data gathered from participants at 22 years and onwards were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol (Harris et al., 2009; Northstone et al., 2019). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2009; Northstone et al., 2019).

The informed consent obtained from ALSPAC participants does not allow for the data to be made freely available through any third party maintained public repository. However, data used for this thesis can be made available on request to the ALSPAC

Executive. The ALSPAC data management plan describes in detail the policy regarding data sharing, which is through a system of managed open access (Northstone et al., 2019). Instructions for applying for data access can be found on this website: http://www.bristol.ac.uk/alspac/researchers/access/ [last accessed 22/03/2023], and elsewhere (Northstone et al., 2019).

2.2.4 ALSPAC: Measures

2.2.4.1 Exposure variable: Age within school year

As explained in section 2.2.3.1, children's exact dates of birth are not routinely provided due to the risk of deanonymisation, and week of birth was only granted with special permission, obtained prior to data access. The age within school year measure utilised in chapters 3 and 4 was therefore operationalised as 1 block of eight days (1-8 September) and 51 consecutive blocks of seven days ending on August 31st. Children were assigned a score reflecting week of birth relative to the academic year; the range for this relative age in school year variable was 0 (oldest in school year, born 1-8 Sept) to 51 (youngest in school year, up to 31st August). This was to ensure that if September 1st occurred in the middle of a week, there was no mixing of children born pre and post September 1st. Note that ALSPAC covered births between April 1st, 1991, and December 31st, 1992, and there are two different September 1st cut-offs (1991 & 1992) covered in the study. Children's age within school year was coded the same, regardless of birth year.

2.2.4.2 Outcome variables: Mental health 4-25 years

As explained in chapter 1 (section 1.2.4.2), the present thesis takes a continuous, trait-based approach to mental health, recognising that mental health problems in the general population exist on a continuum (Thapar et al., 2012). Higher levels of

mental health symptoms predict impairment regardless of whether they exceed specific cut points for meeting diagnostic criteria. Continuous mental health symptom scores also influence the risk of mental health problems and disorder diagnosis at a later age (Pickles et al., 2001; Thapar et al., 2012). In addition, dimensional approaches provide more information about the severity of difficulties and enhance statistical power for developmental research (van Heugten-van der Kloet & van Heugten, 2015). The present thesis used two validated and widely used measures of mental health and neurodevelopmental symptoms, the SDQ to measure emotional, behavioural, ADHD and social difficulties in chapters 3 and 4, and the SMFQ to measure depressive symptoms in chapter 3.

2.2.4.2.1 Strengths and Difficulties Questionnaire (SDQ)

The Strengths and Difficulties Questionnaire (SDQ) is a brief emotional and behavioural screening questionnaire for children and young people (Goodman, 1997). The tool can capture the perspective of children and young people, or their parents, or their teachers. The SDQ has been used by clinicians and researchers for various purposes including epidemiological research as well as clinical assessment and screening. There are 25 items in the SDQ, categorised into five subscales, each comprised of five items; Each item is rated as 0: ‘Not True’, ‘1: Somewhat True’ and 2: ‘Certainly True’, however, some items are reverse-coded (i.e., ‘Certainly True’=0 and ‘Not True’ = 2). Subscales include emotional problems, conduct problems, problems with peers, hyperactivity/inattention problems, and prosocial behaviours. The first four subscales can be summated to derive a total difficulties scale, measuring overall mental health problems. Research has identified that the SDQ possesses moderate to good internal consistency, i.e., the items within the SDQ subscales correlate with each other (Goodman, 2001; Mieloo et al., 2012; Yao et al.,

2009). The SDQ has moderate test-retest reliability, i.e., respondents to the SDQ have similar scores when assessed on repeat occasions for traits that are not expected to change over time (Yao et al., 2009). Moreover, the SDQ shows good concurrent and discriminant validity (Riglin, Agha, et al., 2021; Vugteveen, De Bildt, Theunissen, Reijneveld, & Timmerman, 2021). In the present thesis, data was used from the SDQ administered to parents of ALSPAC participants at several points during their development (see Figure 2.3 and 2.4).

2.2.4.2.2 Short Moods and Feelings Questionnaire (SMFQ)

The SMFQ is a measure of childhood and adolescent depression that was designed for the rapid evaluation of depression symptoms (Angold et al., 1995; Angold & Costello, 1987). The SMFQ has been used in many epidemiological studies, including those using ALSPAC data (Angold et al., 1995; Kwong, 2019). In ALSPAC, the SMFQ was completed by the parents, when their children were between nine and sixteen years, and by the children themselves, from the ages of ten years up to twenty-five years. The SMFQ is a 13-item questionnaire that measures depression symptoms over the previous two-week period. Each item is rated as 0: ‘not true’, 1: ‘sometimes’, 2: ’true’. There was no reverse coding in this questionnaire. The SMFQ has a range of between 0 and 26; the higher the score, the more severe the depressive symptoms (Angold et al., 1995). The SMFQ has been validated against clinical methods of assessing depression (Eyre et al., 2021; Turner, Joinson, Peters, Wiles, & Lewis, 2014). The SMFQ also shows good reliability and internal consistency (Angold et al., 1995; Turner et al., 2014). In the present thesis, self-rated SMFQ data was used on ten separate occasions, from age ten years to age twenty-five years, and parent-report SMFQ was taken on four separate occasions between

the ages of nine and sixteen years of age. The SMFQ in ALSPAC were completed in questionnaires, distributed by post or online.

Figure 2.3: Timeline of ALSPAC mental health measures, chapter 3

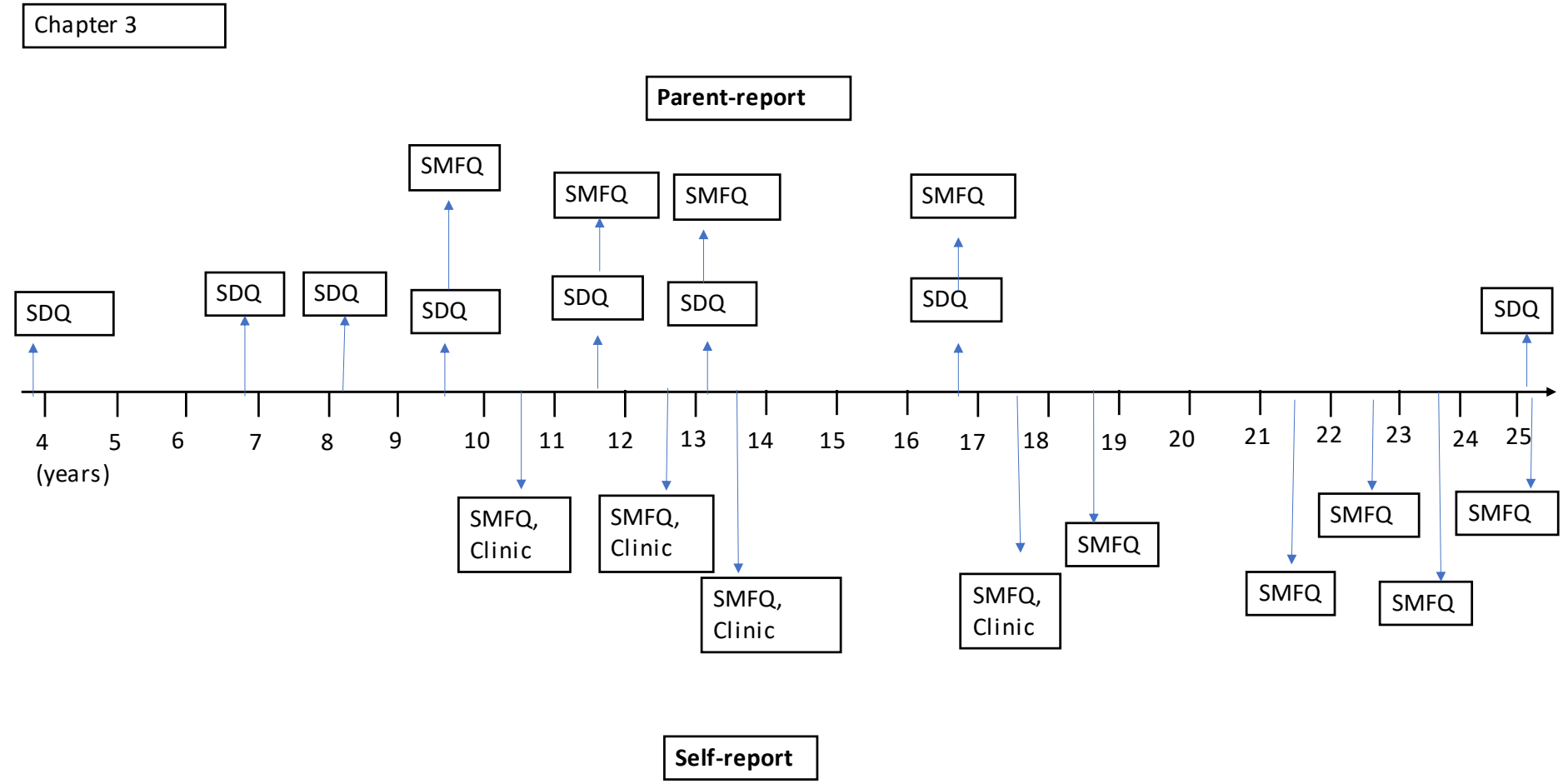
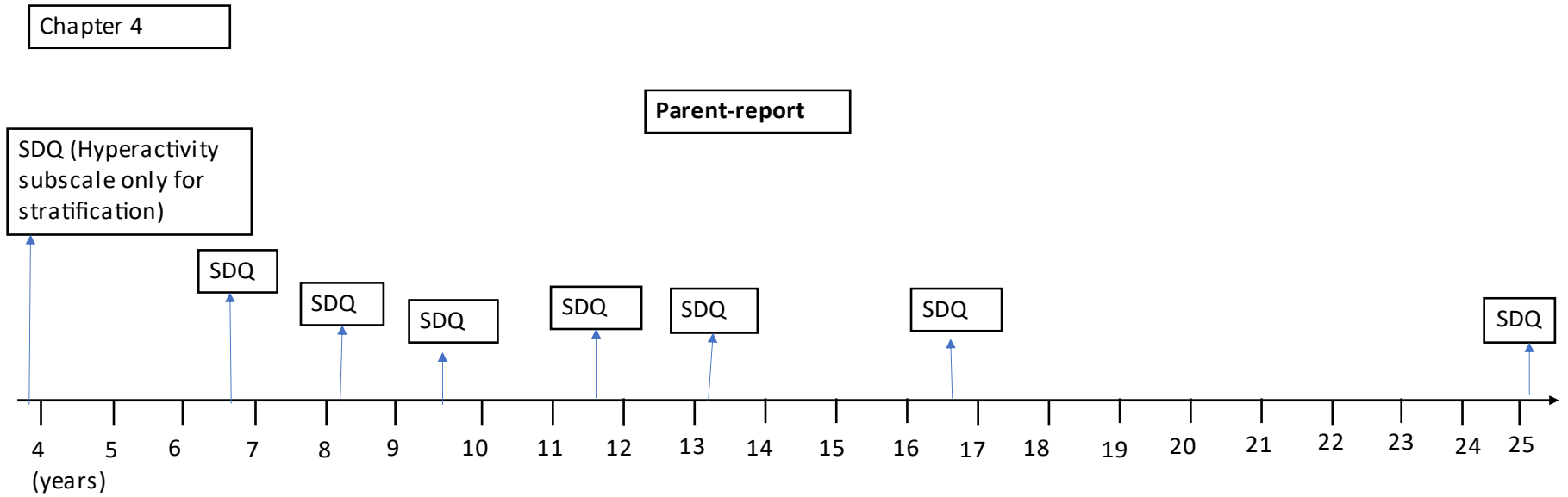


Figure 2.4: Timeline of ALSPAC mental health measures, chapter 4



2.2.4.3 Covariates

Various early pre-school entry covariates were included, including maternal background, pregnancy and birth, and child factors.

Maternal background: Age of mother at birth, mother's education (highest qualification), maternal depression at 18 weeks gestation assessed using the Edinburgh Postnatal Depression Scale; (Cox, Holden, & Sagovsky, 1987).

Pregnancy and birth: caesarean birth, birth size (i.e., single, or multiple birth), birthweight, gestational age, maternal alcohol use during last two months of pregnancy, maternal smoking during pregnancy.

Child factors: household crowding, child ethnic background, home ownership, parity, Sex. We controlled for age of child at questionnaire completion (in months, to nearest month).

2.2.4.3.2 Child age at completion of questionnaire

The child's age at completion of questionnaire was an especially important covariate to control for (Crawford et al., 2013). The questionnaires were sent out to parents to map on to specific timepoints throughout development (e.g., 47 months for first SDQ). it was important to adjust for age at completion of questionnaire to account for any variability of age at testing. The age of child at questionnaire completion (in months, to nearest month) was therefore included as a covariate. The age at which questionnaires were filled did not substantially vary in the earlier timepoints (e.g., at age 4 years), but varied more widely across participants in later measurements (e.g., at 25 years), although this was not different between August born and September born individuals (see table A2.1 in the appendices for details).

2.3 Secure Anonymised Information Linkage (SAIL) databank

As discussed earlier in the thesis (1.5.2.4 Using complementary data to attempt to counteract biases: Longitudinal population cohort and electronic healthcare records studies), many disadvantages of longitudinal population cohort data can be counteracted by using electronic healthcare records data. If analyses from electronic healthcare records cohorts corroborate those from longitudinal population birth cohorts, more robust and coherent conclusions on the nature of the relationships between relative age in the school year and mental health can be made. Therefore, in addition to using data from ALSPAC, data were analysed from the Secure Anonymised Information Linkage (SAIL) databank (www.saildatabank.com) to test for heterogeneity in relative age effects on clinical outcomes, in chapter 5 of the thesis. This next section will describe the SAIL databank and how this was utilised, and as with section 2.2 (ALSPAC), this section will describe the participants (sample) as well as the inclusion and exclusion criteria for results chapter 5, which used data from these participants. The section will then describe the ethics and data availability, as well as the measurements for age within school year and mental health used in this thesis.

SAIL is a resource of secure, anonymised, and linkable data from healthcare settings in Wales at individual level for research purposes (Lyons et al., 2009). SAIL assigns a unique, anonymised linkage field for individual patients using split file approaches which can then be linked. Five datasets contained within SAIL were used for coding the study groups and the outcomes used in the analysis: the Welsh Demographic Service; the General Practice Database; Emergency Department Data Set for NHS Wales; Patient Episode Database for Wales; Welsh Index of Multiple Deprivation.

- The Welsh Demographic Service is a register of all individuals in Wales that have had contact with NHS-based services or have registered with a GP in Wales. The register contains demographic variables and GP practice registration histories, and anonymised residential data. The register included available information on participants' week of birth.
- The General Practice Database (GPD) includes a register of attendance and clinical information records for all primary care contacts. Data of interest includes diagnoses, symptoms, prescriptions, hospital contacts and test results, which were coded in this database using NHS READ codes. An NHS READ code is a unique clinical terminology identifier for a coded clinical entry which is an entry in a NHS electronic healthcare record that has been recorded by a care professional (i.e. anyone with a professional registration, or a professional representative of, e.g. a support worker), or a patient (or an authorised representative of, e.g. a parent/guardian to a child), regarding the provision of that patient's care and treatment. This register covers over 75% (333 out of 432) of all general practices in Wales. GPs are the owners of individual-level data, and each must agree to enter their data into the SAIL databank; some GPs may have declined to contribute to SAIL. Read codes of medical diagnoses and symptoms in the GPD were entered by general practitioners (GPs).
- The Patient Episode Database for Wales (PEDW) is a register of attendance and clinical information including diagnosis (by healthcare professionals) and treatment procedures for all NHS hospital admissions in Wales. Following a patient discharge, handwritten patient notes from healthcare professionals are coded by clinical coders into clinical terminology (e.g., ICD-10). This includes

‘day cases’ where patients have been admitted for treatment or care that does not require an overnight stay in hospital, and ‘in-patients’ where patients have been admitted to hospital for at least one night. The PEDW covers the entire population of Wales, including Welsh residents treated in English trusts, during the study period.

- The Emergency Department Data Set (EDDS) is a register of administrative and clinical information for all NHS Wales Accident and Emergency Department attendances. This register covers the entire population of Wales from 2009 onwards.
- The Welsh Index of Multiple Deprivation (WIMD) is a Welsh government geographical measure of relative deprivation. WIMD categorises individuals in Wales into census-based geographical areas, Lower Super Output Areas (LSOAs). Each LSOA is comprised of a population of approximately 1500 individuals. There are over 1800 different LSOAs in Wales. The WIMD assigns all LSOAs a deprivation score, and deprivation scores of individuals are based on their address, linked to the WDS. There are eight separate domains, income, employment, education, health, access to services, housing, community safety and the physical environment. Indicators of deprivation relating to poor health include (but are not limited to) area rates of limiting long-term illnesses and GP-recorded conditions, including mental health, and premature death.

2.3.1 SAIL: Sample

The population sample from SAIL was comprised of individuals living in Wales at any point during the study period who had been born between 01/01/1991 and 31/12/2000. The study period considered in this thesis was between 01/01/2000 to

31/12/2016. The start of the follow-up period (i.e., the length of time individuals' health was monitored) for individuals was the later of two dates: individuals' sixteenth birthdays, or the beginning of the study period. The end of the follow-up period was the earlier of two dates: individuals' twenty-fifth birthdays, or the end of the study period. Therefore, individuals ranged between 16-25 years old. Fig 2.5, below, summarises which datasets were used within the SAIL databank and for which measurement, as well as participant numbers, selection into groups stratified by ADHD/ASD diagnosis status, and exclusion criteria.

The study sample was comprised of two groups. The first was a total population group where all individuals residing in Wales within the SAIL Databank born within the period of 01/01/1991-31/12/2000 and aged between 16-25 years were selected (N = 553,551). The whole-population group had data available on sex, week of birth, month of birth, ADHD/ASD diagnosis, age at end of follow-up, and follow-up length.

The second study sample provided more detailed data than the whole-population group, including information on mental health (anxiety and depression) and other related clinical outcomes. This sample was initially chosen for a case-control project that was unrelated to investigating relative age effects (Langley et al., 2023). To reduce confounding in this case/control study, participants were matched on week of birth and sex. This sample was comprised of two subgroups: i) a subgroup of individuals with and without a diagnosis of ADHD (hereafter, ADHD cases) and matched population controls (hereafter, ADHD controls), taken from the above total population group (N ADHD case = 8348, N ADHD control = 24,991), and ii) a subgroup of individuals with and without a diagnosis of ASD (ASD cases) and matched population controls (ASD controls), taken from the same total population group (N ASD case = 5678, N ASD control = 16,969). Together, this makes up the

‘Main analyses: Initial sample’ referred to in figure 2.5. Cases and controls were identified prior to this thesis by Langley et al (2023), using a list of International Classification of Diseases, 10th Revision (ICD-10) codes that were associated with ADHD or ASD from previously published literature, and NHS READ codes (Langley et al., 2023). The researchers prepared a preliminary list of READ Codes, which was then shared with mental health clinicians and general practitioners, which led to further codes being added (Langley et al., 2023). From this final list, cases were identified as having ADHD/ASD on the presence of a listed ICD-10 or READ code in their primary care records (GPD) or hospital admission (PEDW) data (Langley et al., 2023). The earliest occurrence of these codes in individual records was noted as their age at first available diagnosis (Langley et al., 2023). The ADHD codes, but not the ASD codes, were validated using a directly assessed cohort (Langley et al., 2023). The list of the codes used are presented elsewhere (Langley et al., 2023).

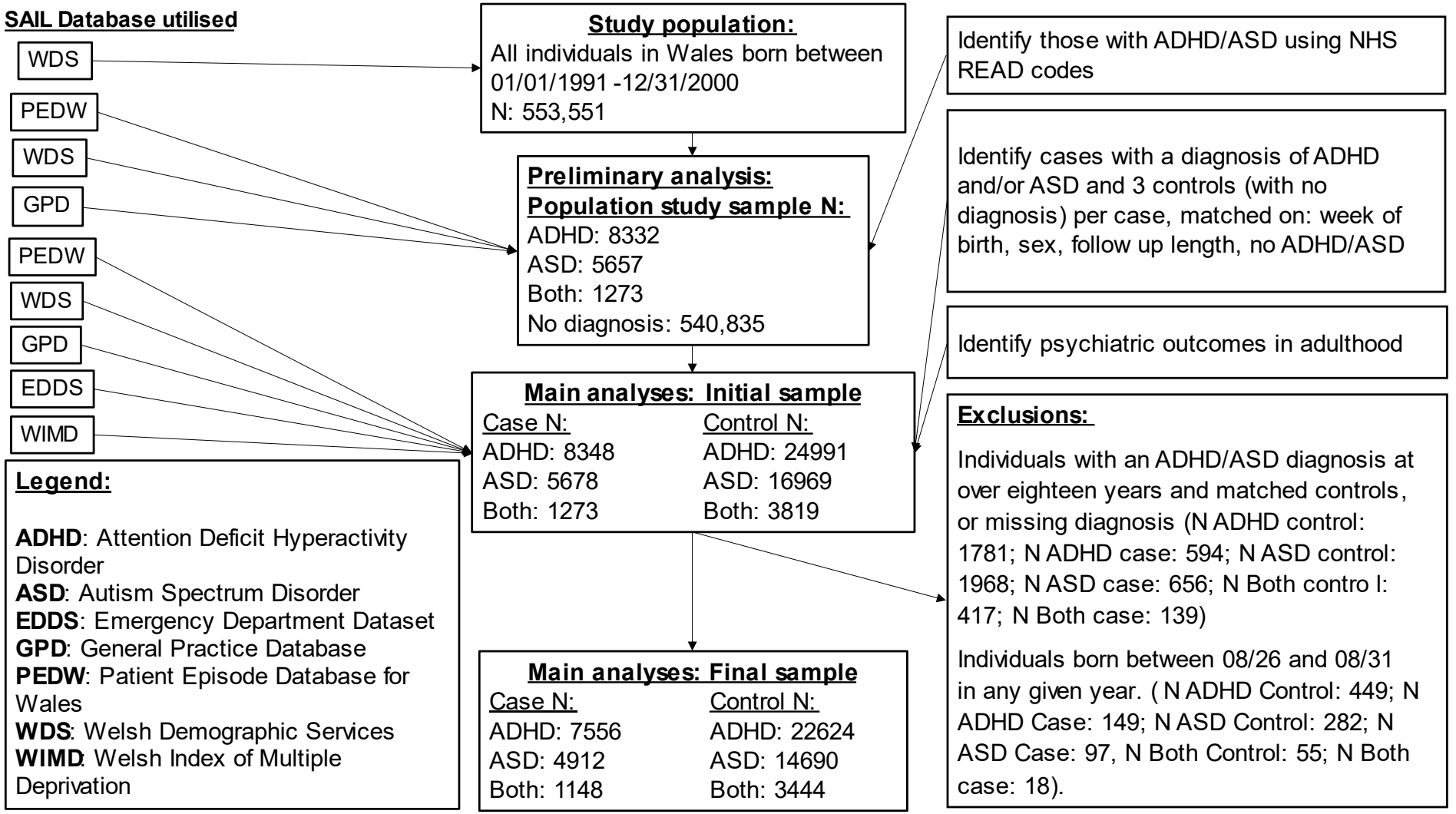
The preliminary analysis that investigated ADHD or ASD diagnosis risk in the whole population by relative age did not match participants on week of birth, otherwise it would have been impossible to detect relative age effects. In the main analyses, controls were selected from this population. Those with ADHD/ASD or insufficient coverage for a diagnosis were excluded. Three controls, matched to cases on week of birth and sex, were chosen at random from the remaining. To note, ADHD controls did not have ADHD but could have had ASD and vice versa. The cases comprised all individuals with ADHD and/or ASD in the total population, but only a selection of individuals from the population were included as controls.

2.3.2 SAIL: Inclusion and exclusion criteria for thesis

Individuals with a diagnosis of ADHD or ASD in the studies using SAIL databank data, alongside their matched controls, were excluded if they were first diagnosed

with ADHD/ASD at over eighteen years or if information on their diagnosis was missing (N excluded ADHD controls: 1781; N excluded ADHD cases: 594; N excluded ASD controls: 1968; N excluded ASD cases: 656; N excluded comorbid ADHD/ASD controls: 417; N excluded comorbid ADHD/ASD cases: 139). Individuals in both case and control groups born between August 26th and August 31st in any given year were additionally excluded (N ADHD Control: 449; N ADHD Case: 149; N ASD Control: 282; N ASD Case: 97). This was because, whilst participants' birth dates were grouped into week of birth, there was no way of telling which participants were born within the last week of August and which were born in the first week of September (i.e., the youngest or oldest in a school year). After exclusions were applied, there were 7556 cases of ADHD and 22,624 matched controls for this group, and 4912 cases of ASD and 14,690 matched controls for this group. Children who had comorbid ADHD/ASD diagnoses (and their matched controls) appeared in both sets of analyses. This is the 'Main analysis: Final sample', as seen in figure 2.5). Figure 2.5 summarises the datasets utilised within SAIL databank used in this thesis, as well as participant numbers, selection into groups for stratification by ADHD/ASD status, and exclusion criteria.

Figure 2.5: Flowchart of datasets utilised within SAIL databank used in the present thesis



2.3.3 SAIL: Ethics and data availability

2.3.3.1 SAIL: Ethical considerations

SAIL's Information Governance Review Panel granted ethical approval to conduct this research (IGRP number 0719). Under permissions granted to the SAIL Databank, individuals' informed consent was not required, and all data was anonymised.

2.3.3.2 SAIL: Data availability

This section will describe what procedures were in place for accessing the data securely and any restrictions on reporting data that might lead to individuals being de-anonymised.

Data from SAIL used in this thesis is not available to the public because of the sensitive nature of individual electronic health records data, and because the data are owned by third party organisations. All proposals to use SAIL data are subject to review by the IGRP. Before any data can be accessed, approval must be given by the IGRP. When access has been granted, it is gained through a privacy-protecting remote access system referred to as the SAIL Gateway. SAIL has established an application process, provided on this website (https://www.saildatabank.com/application-process).

Only final results (not data) can leave the SAIL databank after independent review by a SAIL Data Guardian to ensure compliance with information governance policies. The SAIL Databank is powered by the UK Secure e-Research Platform (UKSeRP). After approval is gained via safeguarding checks, access to project-specific data is granted through two-factor authentication to a secure virtual desktop. No person-level data may be transferred from this desktop. Summarised data may be

transferred for publication following review to ensure that no personally identifiable data or small cell counts (defined in SAIL as n<5) are transferred. This included a restriction on using more precisely defined age within school year data than month of birth.

2.3.4 SAIL: Measures

This section describes the exposure (age within school year), stratifying variable (neurodevelopmental disorders (ADHD/ASD)), and the outcome variables from the SAIL databank used in chapter 5 (anxiety/depression disorders, self-harm, drug misuse, alcohol misuse, and accident and emergency services (A&E) use.

2.3.4.1 Exposure: Relative age within school year

The exposure variable was relative age within the school year, determined by month of birth in relation to the school year (Sept = 1; Aug = 12). Relative age was used as a continuous variable. Analysis was repeated but limited to participants born in August and September as a sensitivity analysis.

2.3.4.2 Potential effect modifier: Neurodevelopmental disorders (ADHD/ASD)

The potential effect modifier was neurodevelopmental disorder status. In cases, this was either a diagnosis of ADHD or ASD, depending on group. Neurodevelopmental disorders were coded as binary variables (1 = has ASD/ADHD, 0 = does not have ASD/ADHD). As described above, the presence of any identified neurodevelopmental disorder code by eighteen years of age led to selection into case group (Langley et al., 2023).

2.3.4.3 Outcome variables: Mental health (anxiety and depression disorders) and related clinical outcomes

The outcome variables were the presence of adverse outcomes recorded from ages 16-25 years (or the latest that the follow up period allowed). If records of adverse outcomes were obtained from more than one of the previously described datasets (e.g., GPD and PEDW), these records were then combined to create an overall measure of the presence or absence of an outcome. These outcomes were: anxiety and depression disorders, self-harming, drug misuse, alcohol misuse, and accident and emergency services use (hereafter, A&E use). All adverse outcome variables were coded as binary variables (1 = present, 0 = absent). Adverse outcomes were identified from primary care data using validated primary care and hospital READ codes (GPD, PEDW) and the EDDS datasets, as summarised in table 2.6.

2.3.4.3.1 Anxiety and depression disorders

Presence of any anxiety and depression disorder was assessed using a previously validated measurement of mental health status, presented in more detail elsewhere (John et al., 2016). John et al (2016) designed a set of twelve algorithms to identify anxiety and depression disorders from the GPD. The researchers linked survey data containing a validated instrument (the five-item Mental Health Inventory, MHI-5 (Ware Jr & Sherbourne, 1992)) of anxiety and depression to the GP record and compared results with recorded diagnoses, symptoms, and treatment codes to assess the sensitivity, specificity of these codes and algorithms. The researchers linked data from participants aged 18-74 years (N=2799) who responded to the MHI-5, to the GPD. The researchers chose an algorithm that was based on a historical diagnosis currently treated plus current diagnosis or symptom (treated or untreated), which lead to optimal specificity, sensitivity, and positive predictive values (John et al., 2016).

2.3.4.3.2 Self-harm

Self-harming incidents (self-harm) have been previously defined as non-fatal but intentional self-harm, including self-injury, self-poisoning, and suicide attempts, but not suicidal thoughts in previous population-based e-cohort studies utilising the SAIL databank that examined contacts for self-harm across GP, hospital admissions, outpatient and emergency departments admissions (Marchant et al., 2020). Records of these incidents were gathered from the general practice database, emergency department dataset, and the patient episode database for Wales. Measures were taken from GP data using validated primary care READ codes (Carr et al., 2016; Marchant et al., 2020; Thomas et al., 2013). Hospital admissions for self-harm were identified based on the International Classification of Diseases, 10th revision (ICD-10) codes for self-harm (X60-X84) and events of undetermined intent (Y10-Y34) (Marchant et al., 2020). A standard coding system that classifies admissions to accident and emergency services departments by type and diagnosis is in practice across emergency services departments in Wales. Previous studies that have investigated rates of self-harm have determined that this system is sufficient for identifying self-harm despite not containing diagnostic information to the same extent as ICD-10 diagnostic codes (Marchant et al., 2020).

2.3.4.3.3 Drug misuse

Drug misuse has been previously defined and recorded as the harmful use, or diagnosis of dependence on, psychoactive substances except alcohol or tobacco (Quan et al., 2005; Thompson et al., 2004). Records of incidents and diagnoses were gathered from the general practice database, emergency department dataset, and the patient episode database for Wales. NHS READ Codes for GPD and ICD-10 codes for PEDW were used to identify types of contact, i.e. whether the contact was

in a primary care setting (from the GPD) or from an emergency or hospital/secondary care setting (from the EDDS, PEDW, respectively), which were validated and extended by previous research (John et al., 2020; Quan et al., 2005; Thompson et al., 2004). Any occurrence from primary and hospital care was combined to create a binary variable denoting the presence (1) or absence (0) of drug misuse.

2.3.4.3.4 Alcohol misuse

Alcohol misuse has been previously defined and recorded as the harmful use of alcohol, as well as the involvement of alcohol in an admission to hospital care, and diagnoses of alcohol dependence syndrome (McKenzie, Harrison, & McClure, 2010; Quan et al., 2005). Records of incidents and diagnoses were gathered from the general practice database, emergency department dataset, and the patient episode database for Wales. NHS READ Codes for GPD and ICD-10 codes for PEDW were used to identify types of contacts (see drug misuse), which were validated and extended by previous research (Carr et al., 2017; John et al., 2020; McKenzie et al., 2010).

2.3.4.3.5 Accident & Emergency services use

Accident and emergency (A&E) services use was defined as all recorded contacts with emergency services departments (John et al., 2020). The derived binary variable used was any recorded contact with A&E services (1=yes, 0=no). Records of incidents and diagnoses were gathered from the emergency department dataset (EDDS). This is a source of patient-level data on attendances at emergency services departments in Wales. Patient-level data are collected in the EDDS for all major accident and emergency departments in Wales. Data from the 13 emergency services departments in Wales was first received in 2009. Data for the following

years were entered into the SAIL Databank, monthly. Attendances are recorded with admission dates. There is no systematic clinical coding in the EDDS.

2.3.4.4 Covariates

Sex was controlled for as a covariate (obtained from the WDS dataset), as well as follow-up time (length of patient follow up, in years).

2.3.4.5 Summary table of SAIL data

A summary of the datasets used to derive each of the outcome and exposure variables for the present thesis is presented in Table 2.1, below. Detailed information of all specific ICD-10 and NHS READ codes used to code specific outcome measures for common mental health disorders, self-harm incidents, drug misuse, alcohol misuse, and A&E use is presented elsewhere (Langley et al. 2023).

Table 2.1: Summary of databases used within SAIL databank for chapter 5 of the thesis.

Database	Description	Coverage	Derived
Welsh Demographic Service (WDS)	An administrative register of all individuals in Wales that use NHS services, containing anonymised demographics and GP practice registration history with anonymised residential data	The entire population of Wales during the study period	Sex, Month of Birth, Neurodevelopmental disorder (ADHD/ASD)
General Practice Database (GPD)	Primary care records with diagnoses, symptoms, investigations, prescribed medication, referrals, coded hospital contacts, and test results coded using NHS READ codes.	>75% (333/432) of all general practices in Wales	Drug misuse, Alcohol misuse, Self-harm, emergency services contact, Anxiety/Depression disorders, Neurodevelopmental disorder (ADHD/ASD)
Emergency Department Data Set (EDDS)	Administrative and clinical information (general reason for attendance and attendance group to identify types of contacts) for all NHS Wales Accident and Emergency department attendances	The entire population of Wales from 2009	Drugs, Alcohol, Self-harm, emergency services contact
Patient Episode Database for Wales (PEDW)	Clinical information (specialty and diagnoses) of all NHS Wales hospital admissions (inpatient and day cases) – diagnostic information coded using ICD-10 codes	The entire population of Wales during the study period	Drugs, Alcohol, Self-harm, emergency services contact, Anxiety/Depression disorders, Neurodevelopmental disorder (ADHD/ASD)
Welsh Index of Multiple Deprivation (WIMD)	Dataset assigning a deprivation score derived from eight domains (access to services, community safety; education, employment, environment, health; housing, and income) to over 1,800 small census-based areas in Wales. Individuals are assigned a deprivation index based on their address based on WDS data.	The entire population of Wales during the study period.	Deprivation quintiles; 1= least deprived, 5= most deprived.

2.4 Statistical methods

The following section will highlight the key methods employed in the thesis. The section will first use a hypothetical example to illustrate the regression discontinuity design and describe the assumptions that need to be met in order to infer causality in the relationship between relative age in the school year and mental health problems or related adverse outcomes. The section will then describe multiple imputation as a method used to deal with the problem of missing data in longitudinal research. Lastly, the section will describe an alternative approach to multiple imputation, generalising estimating equations (GEE) models, as a sensitivity analysis to using imputed data.

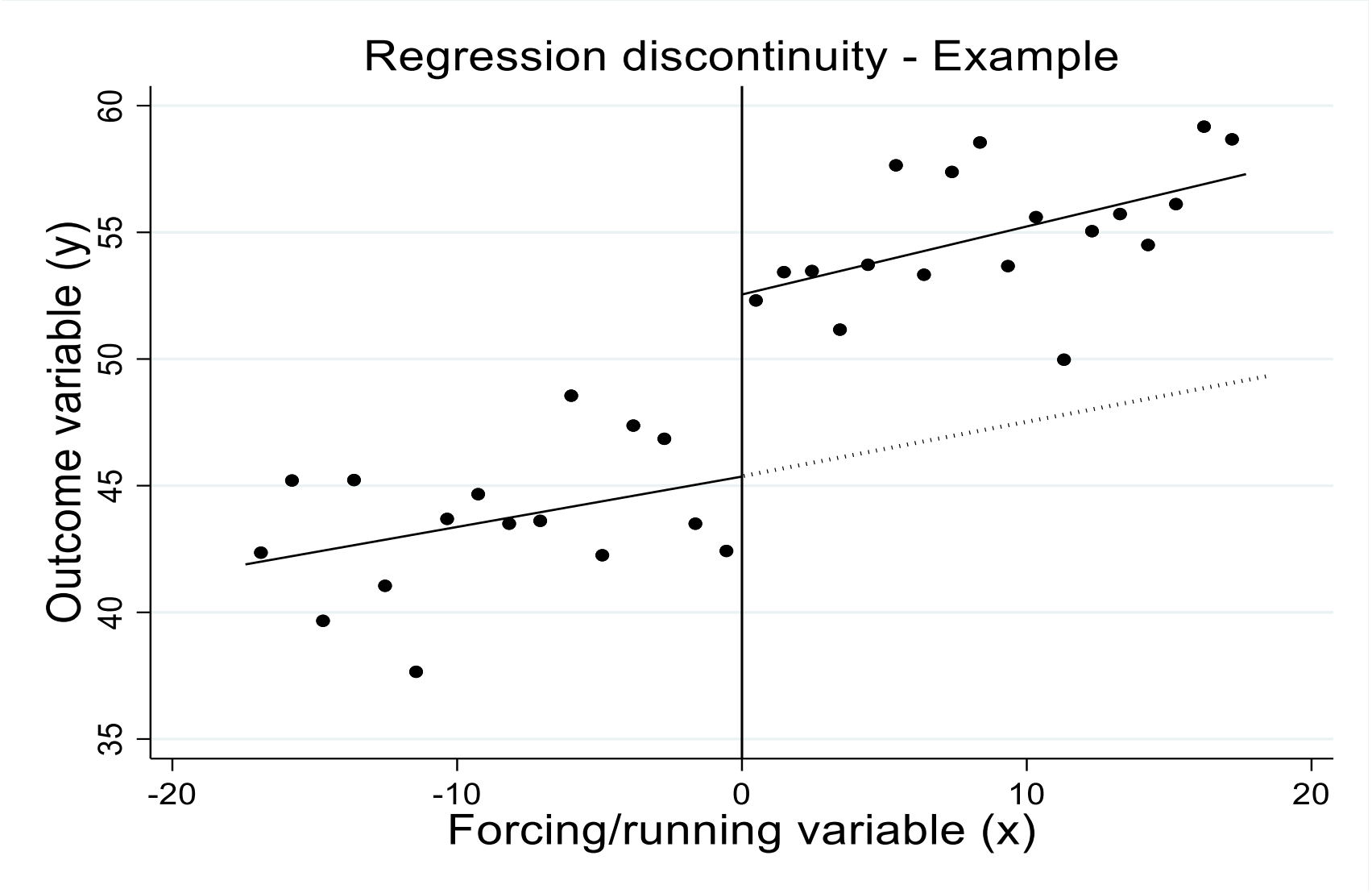
2.4.1 Regression discontinuity design: Simulated example

As noted in more detail in the previous chapter (section 1.5), one can take advantage of quasi- or non-random assignment to ”treatment” (or exposure), such as exceeding a threshold point on a continuous scale, and analysing the discontinuity change in outcome on either side of the threshold (Imbens & Lemieux, 2008). This is referred to as a regression discontinuity design, and the present thesis will use this design for estimating the average treatment effect of relative age on mental health outcomes (Imbens & Lemieux, 2008; Thistlethwaite & Campbell, 1960). Regression discontinuity is defined by the discontinuous change in probability of receiving treatment, depending on one or more underlying variables with a known and fixed threshold or cut-off score (Hahn, Todd, & Van der Klaauw, 2001).

Figure 2.6 shows the difference between the regression discontinuity design and a simple comparison of the mean value of the running variable in the groups above and below the cut-off. In this graph, the solid lines represent the observed outcomes before and after the “treatment”, or exposure value. The vertical line at x = 0

represents the cut-off, which determines which individuals receive the “treatment”. The dotted line represents the counterfactual outcome, i.e., that an individual would have experienced had they not received the “treatment”.

Figure 2.6: Hypothetical example of a regression discontinuity graph



In this hypothetical example, a treatment was assigned for those with the value of a running variable (X axis) of X > 0 arbitrary units. In context of the present thesis, this variable x could be distance in time from the September 1st cut-off, the threshold (vertical line at 0) is September 1st, and the “treatment” is being relatively old for the school year. Individuals on the left side of the cut-off (born in August) did not receive the treatment (i.e., they were relatively young in the school year, equivalent to being assigned to the “control group” in an RCT of bring old in year vs young). Those on the right side of the cut-off (born in September) did receive the “treatment” (i.e., were relatively old in the school year). The scores on the outcome variable that was selected for measurement (Y axis) were higher than what would be expected if the relationship was continuous at the threshold (dotted line).

Participants on both sides of the cut-off with running variable scores close to the cut-off are assumed to be similar with respect to measured and unmeasured confounders. Participants who lie within this window can then be statistically compared to investigate the extent to which Y differs because of assignment to treatment. If there is a “jump” in scores from one side of the threshold in X to the other, and all other assumptions for a RD are met, then it can be assumed that this jump is the result of assignment to treatment due to the threshold. The size of this average causal effect (the size of the difference across the threshold) can then be estimated. The differences between those near the cut-off are compared using various windows (bandwidths) for selection. Researchers using regression discontinuity designs need to work out the optimal bandwidth for comparisons across the cut-off; a narrower bandwidth allows for greater plausibility of the assumption of no confounding, which is crucial to the design, but this is at the expense of reduced statistical power and a less precise causal estimate than what is expected to be

provided by a wider selection window of participants. Figures 2.7 and 2.8, below, show this.

Figure 2.7: Regression discontinuity example – narrow bandwidth

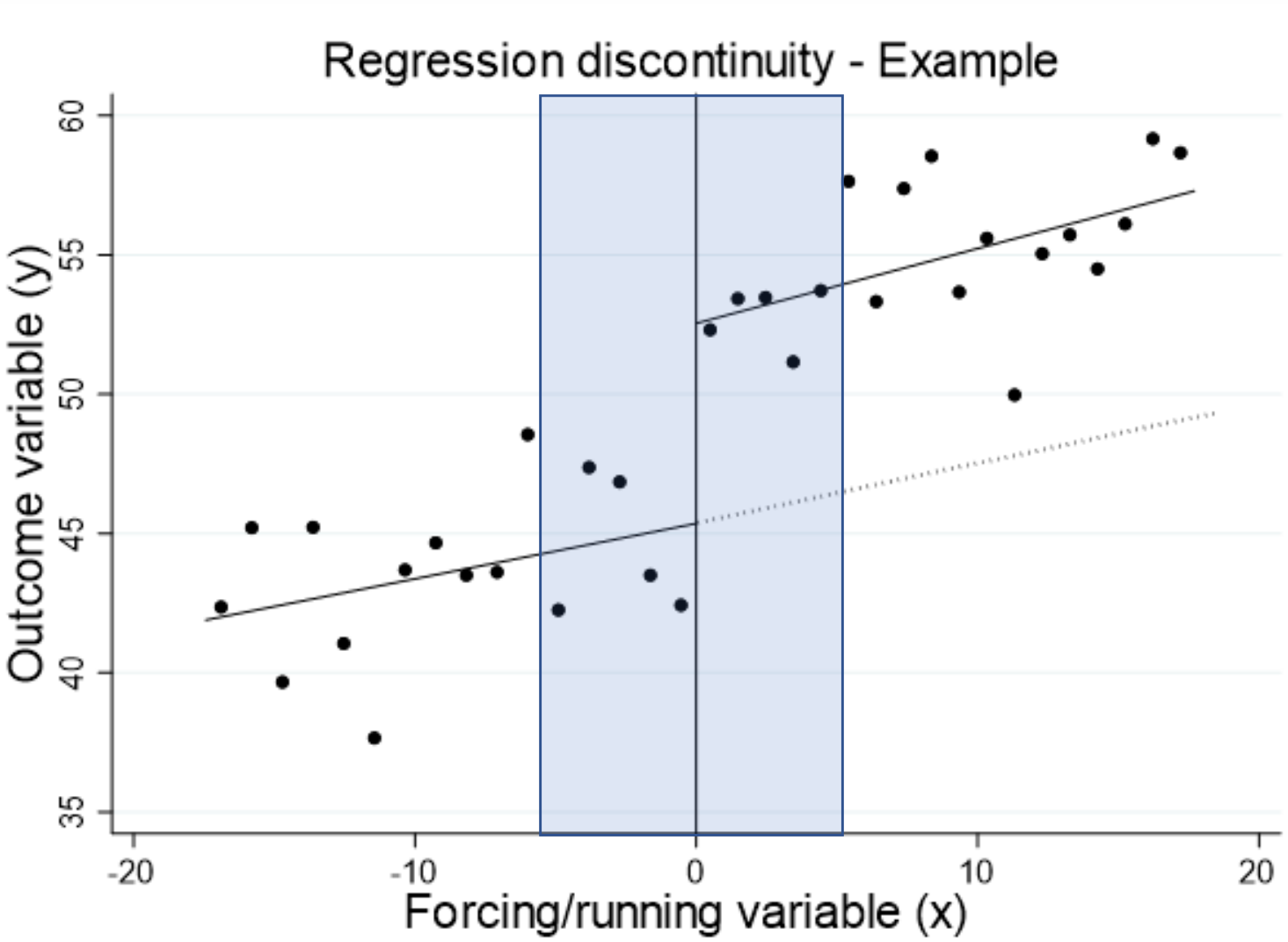
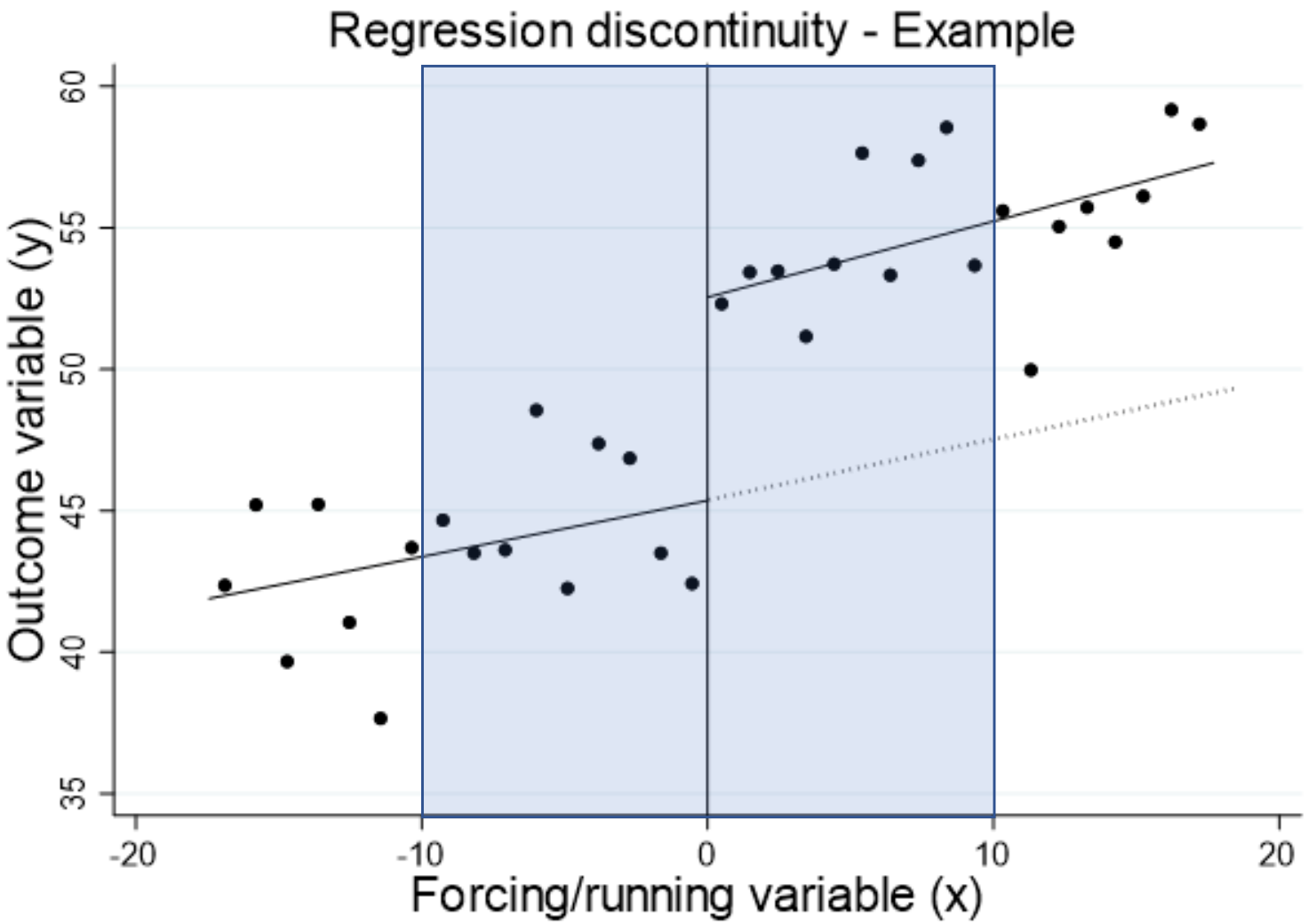


Figure 2.8: Regression discontinuity example – wider bandwidth.



In the present thesis, the forcing/running variable relates to the cut-off date for the English academic year, which is the 1st of September. The regression discontinuity designs in this thesis will be used to identify (under assumptions discussed below) the mean effects of "treatment" (i.e., being older in the school year) for population subgroups born in the regions that lie close to this discontinuity, i.e., children born in August (the relatively young) and children born in September (the relatively old). In so doing, the outcome of those above and below this threshold is compared and the difference in outcome as a 'treatment effect' is considered. In this case, age within school year is caused by the fixed cut-off date on September 1st and the likelihood of receiving the "treatment" of being relatively old for the school year is determined by one's date of birth.

2.4.2 Regression discontinuity design: Assumptions

As indicated in chapter 1 of the thesis (section 1.5), the regression discontinuity design can provide valid inference only under certain assumptions (Moscoe et al., 2015; Oldenburg, Moscoe, & Bärnighausen, 2016; Venkataramani, Bor, & Jena, 2016). The first is that the assignment to treatment rule and cut-off are known. In the present thesis, birth date (this either being week of birth in chapters 3 and 4, or month of birth in chapter 5) determines treatment assignment; children born in September year *t* are the oldest in the school year and children born in August year *t+1* are the youngest. Only in exceptional circumstances does this rule not apply; children in England and Wales very rarely deviate from their expected age for their academic year in comparison with other nations, for example, Scotland (Fleming et al., 2022). If these individuals are excluded, a simpler, "sharp" RD to estimate the average causal effect at the discontinuity can be implemented, where treatment is deterministic. This is as opposed to a "fuzzy" RD design, where treatment is

probabilistic, and which requires additional assumptions to be met such as a heterogenous treatment effect, and monotonicity (Lee & Lemieux, 2010). In all studies in the thesis, a “sharp” RD was implemented.

A second assumption is that the assignment variable must be continuous near the cut-off value (Moscoe et al., 2015).

Third, it is assumed that other variables except date of birth must be continuous at the cut-off. Therefore, no other variables known to influence mental health, such as socioeconomic status, should have a discontinuous relationship at the September 1st cut-off. This is tested using tests of covariate distribution by age within school year, and this assumption is satisfied by showing no evidence of a relationship between these covariates and age within school year.

Regression discontinuity designs are not reliant on controlling for covariates to the same extent as some other studies (Hahn et al., 2001). However, it was nonetheless important to consider the covariate distribution by birth date to check for potential assumption violations such as unbalanced distribution and potential manipulation, at least for the first main analysis of this thesis, in chapter 3.

Fourth, it is assumed that individuals do not manipulate selection into treatment groups to take advantage of potential benefits gained from assignment to treatment (Hahn et al., 2001; Moscoe et al., 2015). It is necessary to check for potential manipulation to ensure that children born close to either side of the cut-off are comparable. While children cannot manipulate their date of birth, some parents may attempt to take notional advantage of entering school and assessments at a relatively older age than their peers (Cho & Lee, 2020; Dhuey et al., 2019). Such practices are rare in the UK but it cannot be assumed that every child entering

school is in the “correct” school year given their chronological age (Fleming et al., 2022). For this reason, individuals were excluded if they were in a different school year to what was expected given their chronological age in ALSPAC (see figure 2.1).

In the present thesis, children’s birth dates:

- Are continuous.
- Are measured before treatment is assigned (i.e., before compulsory education).
- Do not change because of entering compulsory education.
- Determine age within school year at the cut-off.

2.4.3 Dealing with missing data: Multiple imputation

To overcome the limitations posed by missing data and biased complete case analysis, multiple imputation was used in chapters 3 and 4. Since there was not much missingness of data in chapter 5, multiple imputation was not used in that chapter. This section will describe multiple imputation and how this was implemented in chapters 3 and 4 of the thesis.

Multiple imputation is a popular and flexible approach to dealing with missing data (Lee et al., 2021; Sterne et al., 2009). Multiple imputation aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets, where the plausibility is based on predictive distribution of missing values given observed data, done several times, and appropriately combining results obtained from each of them (Rubin et al., 1987; Sterne et al., 2009; Lee et al. 2021). Multiple imputation can also use auxiliary variables, which are variables that predict the missing values but are not included in the analysis model, to reduce bias and improve efficiency (Lee et al., 2021).

There are two common types of multiple imputation: multivariate normal imputation (MVNI) and multiple imputation using chained equations (MICE). MVNI replaces missing values of variables using multivariate normal regressions, which are assumed to be normally distributed. Therefore, MVNI is useful if variables have a normal distribution, but less so for non-normally distributed variables such as binary or categorical variables (Lee & Carlin, 2010). MICE (also known as fully conditional specification) offers more flexibility because it does not assume normal distribution, allowing for different variable types to be imputed; linear regressions can be used to impute continuous variables, ordered logistic regressions for ordinal variables, and logistic regressions for binary variables, and these variables can all be entered together into a bespoke multiple imputation regression model (Lee & Carlin, 2010).

MICE is useful for imputing multiple types of variables and when there are many missing values, but it is nevertheless not recommended to impute variables or include variables in the imputation model with excessive missingness without auxiliary variables and model specification (Madley-Dowd, Hughes, Tilling, & Heron, 2019). It was decided that the data in chapters 3 and 4 in the present thesis was more suited to MICE than MVNI given that the exposures, outcomes, and covariates and auxiliary variables are made up of continuous, ordinal, and binary variables. Variables included in the multiple imputation model included all variables in the analysis model (exposure, outcomes, covariates) with the addition of additional auxiliary variables that are not part of the analysis model but were included in the imputation model to help predict the missing values. Interaction terms, where necessary, were also included in the imputation model because they will be tested in the analysis models.

MICE was performed using the 'mi impute chained' command in STATA v16.1. In both chapters 3 and 4, Monte Carlo errors after 200 imputations were assessed to ensure that Monte Carlo error estimates conformed to the guidelines set by White, Royston & Wood (2011) for what constitutes an acceptable amount of Monte Carlo error. White et al.'s (2011) guidelines suggest that Monte Carlo error of a coefficient should be less than or equal to 10% of the standard error. Further, Monte Carlo errors of a coefficient's T-statistic should be less than or equal to 0.1, and the Monte Carlo error of a coefficient's p-value should be less than or equal to 0.01 if the true p-value is 0.05, or 0.02 if the true P-value is 0.1. (White, Royston, & Wood, 2011). The overall estimates were obtained by averaging the results from each of these datasets using Rubin's rules (Lee et al., 2021; Rubin, 1976). Separate MICE analyses by outcome variable were conducted (parent-report SDQ in chapters 3 & 4, self-report SMFQ and parent-report SMFQ in chapter 3), and these included interaction terms in the models when testing for interactions with continuous variables (polygenic risk scores; chapter 4).

2.4.4 Sensitivity analyses: Generalising Estimating Equations (GEE) models

As a sensitivity analysis to the multiple imputation approach chosen in chapters 3 and 4, Generalized Estimating Equation (GEE) models were used (Liang & Zeger, 1986). GEE models are used to estimate the parameters of a generalized linear model, but rather than attempting to model the within-subject covariance structure, GEE models the average response. For every one-unit increase in a covariate across the population, GEE models measure how much the average response would change. The aims of GEE models are to make inferences about the population when accounting for a possible unmeasured correlation between observations from

different timepoints. The advantages of this approach are that GEE models have some robustness to attrition, but do not use imputation (i.e. only analyse available data) (Liang & Zeger, 1986).

2.5 General descriptive statistics: ALSPAC

This section displays the general descriptive statics for the next two chapters of the thesis (chapters 3 & 4), including the demographic characteristics of the ALSPAC sample, the results of assumption tests for the regression discontinuity design, and comparisons of participants with complete vs incomplete data to assess the nature of missing data in ALSPAC. Results from the main analyses of chapters 3 and 4, as well as sensitivity and secondary analyses, are presented in their respective chapters.

Regression discontinuity design assumptions were tested by comparing covariate distributions across the school year to ensure that the cut-off is not associated with any other variables besides relative age and that there was no demonstrable manipulation of age within school year by individuals. The distributions of maternal depression, maternal age, gestation, birthweight, birth size, pre-natal alcohol use, smoking, caesarean status, crowding, home ownership status, mother's education, and parity were checked for any differences across the cut-off. Furthermore, the distribution of births across the months of the school year was tested to assess for potential manipulation of age within school year. This would be evidenced by bunching in a histogram of births across the school year, and a noticeable difference in the numbers of August and September births (Moscoe et al., 2015).

2.5.1 Testing assumptions of the regression discontinuity design: Covariate pattern by month of birth

Tables 2.2 and 2.3, below, display demographic characteristics for the core sample used in the thesis. Table 2.2 shows the demographic characteristics of all participants ("Total", leftmost column), participants born in August and September (middle columns), and comparisons of participants born in August and September (rightmost column). Table 2.3 shows characteristics of participants born up to four weeks either side of the September 1st cut-off (left), and up to eight weeks either side of the cut-off (right). Examination of assumptions of the regression discontinuity design were reassuring. First, similar patterns of covariate distribution between children born August vs September were detected, showing no discernibly discontinuous relationship between 'pre-treatment' covariates and relative age. Second, a similar distribution of births in the chapter sample across the months of the year was observed (Figure 2.10), no perceptible evidence of a discontinuity in distribution of births around September 1st was found. Thus, no evidence was found to suggest that the regression discontinuity design assumptions, stated above (section 2.4.2), were violated.

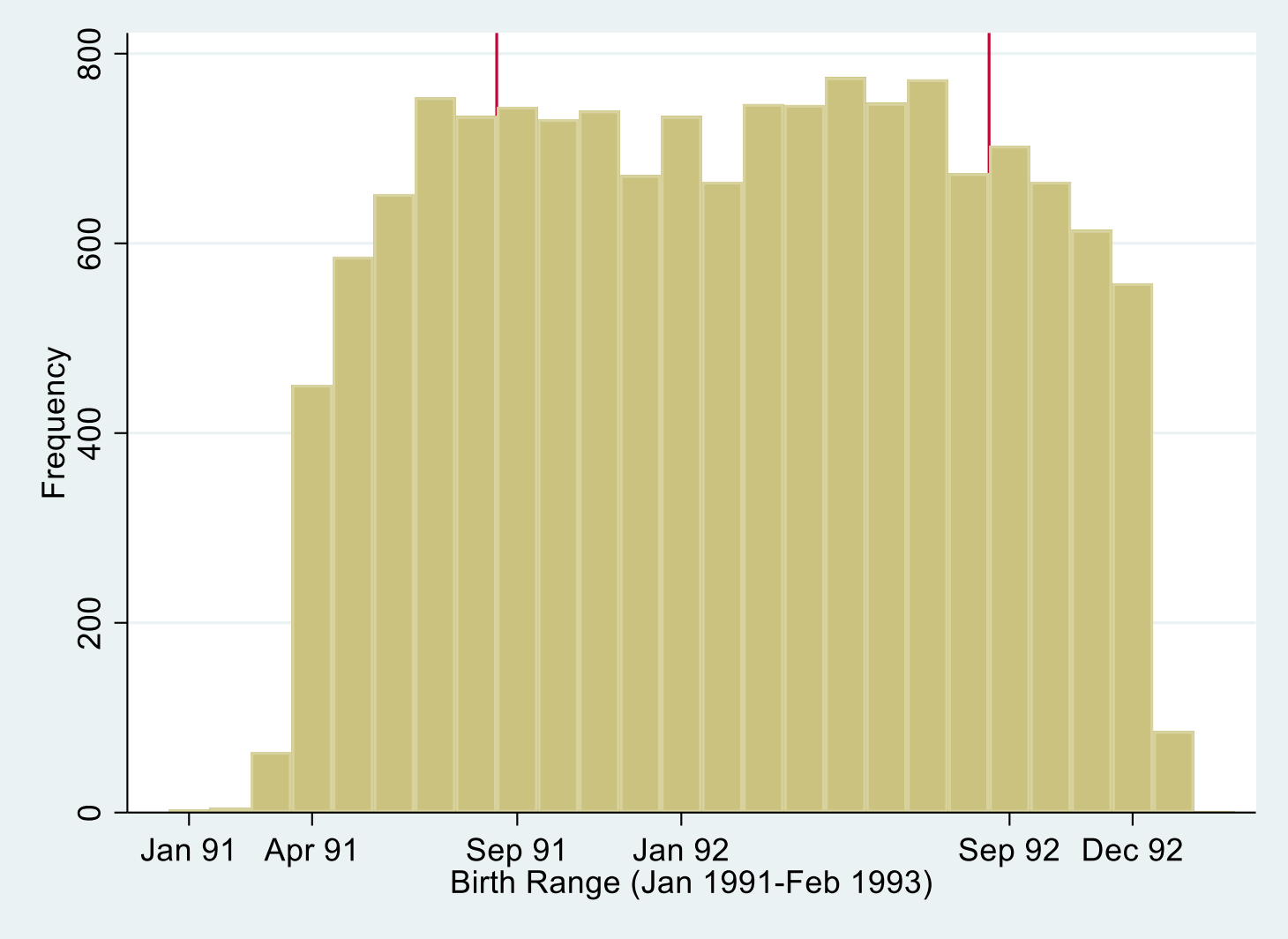
Table 2.2: Demographic Characteristics of the ALSPAC study sample

Variable	Total		August		September		Aug vs Sep
	N	Percent/Mean (SD)	N	Percent/Mean (SD)	N	Percent/Mean (SD)	Mean Diff (95%CI)
Age of mother at birth (years)	11637	28.34 (4.83)	1099	28.49 (5.11)	1162	28.13 (4.88)	.36 [-0.05, 0.77]
Alcohol during pregnancy (% yes)	11579	50.52%	1092	49.18%	1155	50.13%	-0.95 [-5.09, 3.19]
Birth size (% multiple)	14625	1.29%	1395	0.92%	1429	1.24%	-0.32 [-1.08, 0.44]
Birthweight (grams)	13577	3402.80 (549.94)	1337	3403.64 (551.78)	1358	3424.26 (527.87)	-20.62 [-61.40, 20.16]
Caesarean (% yes)	11572	10.33%	963	11.81%	1040	9.80%	2.01 [-0.56, 4.58]
Crowding (%>1)	11737	6.88%	1143	7.00%	1150	6.81%	0.19 [-1.81, 2.19]
Ethnic background (% white)	11286	94.95%	1094	94.72%	1109	94.79%	-0.07 [-1.74, .1.88]
Gestation (weeks)	13751	39.43 (1.88)	1344	39.48 (1.91)	1376	39.52 (1.78)	-0.03 [-0.17, 0.10]
Home ownership (% owned)	12824	73.32%	1256	73.09%	1262	72.90%	-0.18 [-3.28, 3.66]
Maternal depression score 18 weeks (EPDS)	11778	6.97 (4.85)	1168	6.74 (4.78)	1155	6.91 (4.94)	-0.18 [-0.57, 0.22]
Mother's education (% degree)	11463	13.72%	1112	12.77%	1123	13.00%	-0.23 [-3.01, 2.55]
Parity (% >1)	12721	55.21%	1238	52.58%	1261	55.11%	-2.53 [-6.44, 1.38]
Sex (% female)	14643	48.97%	1408	49.08%	1447	47.20%	1.88 [-1.79, 5.54]
Smoking during pregnancy (% yes)	11657	19.57%	1099	20.38%	1162	21.00%	-0.62[-3.96, 2.73]
PRS ADHD (p<0.05)	6933	-3.26E-03 (0.00)	780	-3.26E-03	790	-3.25E-03	-0.03[-0.14, 0.07]

Table 2.3: Demographic information for participants born ±4 ("4 weeks") and ±8 ("8 weeks") weeks either side of the September 1st Cut-off.

	4 Weeks		8 Weeks	
	N	**Percent/Mean (SD)**	**N**	**Percent/Mean**
Age of Mother at Birth (Years)	2141	28.30 (4.99)	4221	28.43 (4.90)
Alcohol During Pregnancy (% Yes)	2130	49.71	4204	49.19
Birth Size (% Multiple)	2698	1.04	5291	1.06
Birthweight (grams)	2546	3415.71 (540.57)	5003	3407.79 (550.86)
Caesarean (% Yes)	2126	11.10	4198	10.83
Crowding (%>1)	2332	6.78	4583	6.98
Ethnic Background (% White)	2201	94.60	4345	94.60
Gestation	2568	39.50	5046	39.46 (1.90)
Home Ownership (% Owned)	2378	73.25 (1.85)	4673	73.65
Maternal Depression 18 weeks (EPDS)	2197	6.80 (4.87)	4300	6.87 (4.82)
Mother's Education (% Degree)	2112	13.07	4186	12.82
Parity (% >1)	2357	53.54	4632	55.29
Sex (% Female)	2703	47.80	5297	48.67
Smoking During Pregnancy (% Yes)	2141	20.22	4228	20.57

Figure 2.9: Histogram of birthdates by month.



Red lines denote a period of one complete school year (Sep 1991-Aug1992).

2.5.2 Comparison of participants with complete vs incomplete data in ALSPAC

Participants with complete records at all ages and assessments were more likely to be female, first-born, white, with parents who are older, non-smokers, higher educated and less depressed than those with incomplete data (Table 2.4, below). This was similar when assessing participants with available PRS data (Table 2.5, below). This suggests that a complete-case analysis approach would be biased unless all these variables were included as covariates (Lee et al., 2021). In addition, participants with complete records had lower mean SDQ total difficulties scores at 4 years (Mean: 8.24 (SD: 4.31)) compared with those with incomplete records (Mean: 9.17 (SD: 4.66); Mean difference: 0.93 (95%CI: [0.72, 1.14])), suggesting that there is data missing not at random, explained in more detail in chapter 1 (section 1.5.2.3). It was therefore necessary to report differences between complete-case and imputed data and conduct sensitivity analyses, as recommended elsewhere (Hughes, Heron, Sterne, & Tilling, 2019; Lee et al., 2021; Sterne et al., 2009). Similar patterns of missing data were observed between August and September-born individuals, and those born 4 or 8 weeks either side of the September 1st cut-off.

Table 2.4: Logistic regressions of covariates on being a complete case in chapter 3

	SDQ (N = 2190)			Self-rated SMFQ (N = 743)*			Parent-rated SMFQ (N = 3444)*		
Variable	**Coef.**	**[95% CI]**	**p**	**Coef.**	**[95% CI]**	**p**	**Coef.**	**[95% CI]**	**p**
Age within school year	0.01	[-0.13, 0.16]	0.86	-0.06	[-0.29, 0.18]	0.65	0.04	[-0.08, 0.16]	0.52
ADHD polygenic score (p<0.05)**	-0.1	[-0.16, -0.05]	<0.01	N/A			N/A		
Age of mother at birth	0.09	[0.08, 0.10]	<0.01	0.1	[0.08, 0.11]	<0.01	0.09	[0.08, 0.10]	<0.01
Alcohol During Pregnancy (No/Yes)	0.42	[0.33, 0.52]	<0.01	0.29	[0.14, 0.44]	<0.01	0.39	[0.31, 0.47]	<0.01
Birth Size (Single/Multiple)	-0.88	[-1.44, -0.31]	<0.01	-0.33	[-1.09, 0.42]	0.39	-0.71	[-1.13, -0.29]	<0.01
Birthweight (per kg)	0.17	[0.09, 0.263]	<0.01	0.02	[-0.11, 0.15]	0.82	0.23	[0.15, 0.29]	<0.01
Caesarean (No/Yes)	-0.09	[-0.24, 0.07]	0.27	0.08	[-0.16, 0.32]	0.51	-0.05	[-0.18, 0.08]	0.44
Crowding Index (<1/1)	-1.59	[-1.92, -1.26]	<0.01	-1.26	[-1.76, -0.76]	<0.01	-1.46	[-1.70, -1.22]	<0.01
Ethnicity (white/non-white)	-0.73	[-1.00, -0.46]	<0.01	-0.53	[-0.95, -0.11]	0.01	-0.81	[-1.03, -0.58]	<0.01
Gestation (weeks)	0.04	[0.01, 0.06]	<0.01	0.04	[0.00, 0.08]	0.06	0.04	[0.02, 0.06]	<0.01
Home Ownership (Not Owned/Owned)	1.34	[1.20, 1.49]	<0.01	1.52	[1.25, 1.79]	<0.01	1.37	[1.25, 1.49]	<0.01
Maternal Depression Score (EPDS)	-0.06	[-0.07, -0.05]	<0.01	-0.06	[-0.08, -0.04]	<0.01	-0.06	[-0.07, -0.05]	<0.01
Month of Birth	0.00	[-0.01, 0.01]	1	0.00	[-0.02, 0.02]	0.93	0.00	[-0.01, 0.01]	0.94
Mother's Education (No Degree/Degree)	0.95	[0.83, 1.07]	<0.01	0.93	[0.76, 1.10]	<0.01	0.88	[0.77, 0.99]	<0.01
Parity (First/Not First-born)	-0.17	[-0.26, -0.08]	<0.01	-0.27	[-0.42, -0.12]	<0.01	-0.22	[-0.30, -0.14]	<0.01
Sex (1=F)	0.16	[0.07, 0.25]	<0.01	0.85	[0.69, 1.01]	<0.01	0.11	[0.04, 0.19]	<0.01
Smoking in Pregnancy (No/Yes)	-1.12	[-1.28, -0.96]	<0.01	-1.09	[-1.36, -0.82]	<0.01	-1.05	[-1.18, -0.93]	<0.01

Complete case: having all data at all mental health timepoints. Ns listed are based on participants with complete records at all timepoints in these outcomes.

**= chapter 3 only*

***= chapter 4 only*

Table 2.5: Logistic regressions of likelihood of being a complete case in chapter 4

SDQ + PRS (N=1669)	Coef.	[95% Conf.	Interval]	p
Age of mother at birth	0.08	0.07	0.09	<0.01
Age within school year	-0.03	-0.20	0.13	0.69
Alcohol During Pregnancy (No/Yes)	0.29	0.18	0.40	<0.01
Birth Size (Single/Multiple)	-0.42	-1.03	0.19	0.18
Birthweight (g)	0.01	-0.11	0.09	0.85
Caesarean (No/Yes)	-0.03	-0.21	0.15	0.76
Crowding Index (<1/1)	-0.98	-1.33	-0.63	<0.01
Ethnicity (white/non-white)	-0.16	-1.31	0.98	0.78
Gestation (weeks)	<0.01	-0.03	0.03	0.98
Home Ownership (Not Owned/Owned)	0.83	0.67	0.99	<0.01
Maternal Depression	-0.05	-0.06	-0.03	<0.01
Month of Birth	0.01	-0.01	0.02	0.52
Mother's Education (No Degree/Degree)	0.84	0.70	0.97	<0.01
Parity (First/Not First-born)	-0.10	-0.21	<0.01	0.06
Sex (1=F)	0.20	0.10	0.31	<0.01
Smoking in Pregnancy (No/Yes)	-0.89	-1.07	-0.72	<0.01

Complete case: having all data at all SDQ timepoints and available PRS scores. N is based on participants with complete records at all timepoints in these outcomes.

2.6 General descriptive statistics: SAIL databank

This section displays the general descriptive statistics for chapter 5, including demographic characteristics of the SAIL databank group. Sex, relative deprivation (measured by Welsh Index of Multiple Deprivation), follow-up time, and the rates of each adverse psychiatric outcome are presented by month of birth for each ADHD or ASD case/control group, in table 2.6, below.

Table 2.6: Descriptive Statistics, chapter 5

Month of Birth	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Total
ADHD controls													
N	1781	1807	1756	1752	1964	1799	1912	1853	1951	1948	2122	1979	22624
Sex (%Female)	19.4	21.3	20.1	17.6	18.5	19.2	18.4	18.5	18.6	22.5	20.3	20.8	19.6
Age in years at end of follow up, mean (SD)	20.4 (2.7)	20.3 (2.8)	20.3 (2.9)	20.4 (2.7)	20.1 (2.7)	20.2 (2.8)	20.3 (2.8)	20.2 (2.7)	20.2 (2.8)	20.3 (2.8)	20.2 (2.8)	20.4 (2.7)	20.2 (2.8)
Anx/Dep – any %	8.9	9.8	9.2	8.3	8.9	10.8	9.2	10.5	9.6	10.0	9.0	9.4	9.5
Drug misuse – any %	1.1	1.1	1.5	1.5	1.3	2.0	1.4	1.4	1.3	1.1	1.0	1.6	1.4
Alcohol misuse – any %	1.8	1.4	1.7	1.4	1.2	2.3	2.2	2.0	2.1	1.2	1.6	1.8	1.7
Self-harm – any %	1.7	2.0	2.6	2.0	2.2	2.4	2.4	2.8	2.1	2.5	2.3	2.3	2.3
A&E – any %	52.7	53.0	49.9	51.0	55.0	55.3	54.2	54.1	54.4	54.0	51.6	52.1	53.1
A&E – mean events (SD)	1.6 (2.5)	1.6 (2.6)	1.6 (2.7)	1.6 (2.7)	1.7 (2.7)	1.7 (2.8)	1.7 (2.7)	1.7 (2.6)	1.6 (2.5)	1.6 (2.4)	1.5 (2.6)	1.6 (2.6)	1.6 (2.6)
Substance misuse – any %	2.5	2.2	2.8	2.6	2.2	3.9	3.1	3.0	3.2	2.1	2.3	3.1	2.8
WIMD (1= Least deprived, 5= Most Deprived) – mean (SD)	2.8 (1.4)	2.9 (1.5)	2.8 (1.5)	2.9 (1.4)	2.8 (1.4)	2.9 (1.5)	2.9 (1.5)	2.9 (1.4)	2.9 (1.4)	2.8 (1.4)	2.8 (1.5)	2.9 (1.4)	2.9 (1.4)
Length of follow up (year) – mean (SD)	4.3 (2.7)	4.3 (2.8)	4.3 (2.9)	4.4 (2.7)	4.1 (2.7)	4.2 (2.8)	4.3 (2.8)	4.2 (2.7)	4.2 (2.8)	4.3 (2.8)	4.2 (2.8)	4.4 (2.7)	4.3 (2.8)
ADHD cases													
N	595	603	587	583	657	599	643	619	652	650	707	661	7556
Sex (%Female)	19.3	21.2	20.1	17.5	18.4	19.2	18.5	18.4	18.7	22.5	20.2	20.7	19.6
Mean age (yrs.) at end of follow up (SD)	20.1 (2.7)	20.1 (2.8)	20.1 (2.8)	20.3 (2.7)	20.0 (2.7)	20.0 (2.8)	20.2 (2.8)	19.9 (2.7)	20.0 (2.8)	20.0 (2.7)	20.0 (2.8)	20.2 (2.7)	20.1 (2.8)
Anx/Dep – any %	16.3	17.2	16.9	15.6	18.1	16.2	19.0	18.1	17.2	16.8	15.4	19.2	17.2
Drug misuse – any %	4.5	6.3	7.0	5.1	6.7	6.5	6.4	8.2	7.5	6.2	5.9	6.7	6.4
Alcohol misuse – any %	6.2	5.5	4.4	4.8	5.8	6.5	5.9	5.8	4.9	5.7	3.4	5.0	5.3

Self-harm – any %	7.4	10.4	11.6	9.1	10.0	10.7	13.1	10.0	11.8	7.8	7.9	10.6	10.0
A&E – any %	62.5	63.5	58.9	61.2	66.2	63.4	63.1	61.1	62.4	62.2	57.4	63.1	62.1
A&E – mean events (SD)	3.0 (5.6)	2.8 (4.3)	3.2 (6.4)	2.8 (4.5)	2.9 (5.4)	3.3 (5.5)	3.8 (7.8)	2.9 (4.8)	3.3 (9.1)	3.0 (5.2)	2.6 (4.1)	3.3 (8.9)	3.1 (6.2)
Substance misuse – any%	8.6	9.6	9.4	8.6	10.2	10.5	10.1	10.8	9.8	9.7	7.5	9.8	9.5
WIMD – mean (SD)	2.6 (1.4)	2.5 (1.4)	2.6 (1.4)	2.6 (1.4)	2.5 (1.4)	2.5 (1.4)	2.6 (1.4)	2.7 (1.4)	2.6 (1.4)	2.6 (1.4)	2.5 (1.4)	2.6 (1.4)	2.6 (1.4)
Follow up age difference (years) – mean (SD)	3.9 (2.7)	3.9 (2.7)	3.9 (2.8)	4.1 (2.7)	3.8 (2.7)	3.8 (2.8)	4.0 (2.9)	3.7 (2.7)	3.8 (2.8)	3.8 (2.7)	3.8 (2.8)	4.0 (2.7)	3.9 (2.8)
ASD Controls													
N	1271	1219	1296	1236	1192	1120	1279	1176	1198	1177	1363	1163	14690
Sex (%Female)	21.8	20.1	22.2	20.1	19.4	24.9	23.3	17.4	20.3	21.9	19.4	22.2	21.1
Mean age (yrs.) at end of follow up (SD)													
Anx/Dep – any %	9.7	7.4	6.7	7.9	8.5	9.4	7.7	6.9	8.2	8.2	8.7	8.3	8.1
Drug misuse – any %	1.1	<1.0	<1.0	<1.0	1.3	<1.0	1.3	<1.0	<1.0	1.1	<1.0	1.0	<1.0
Alcohol misuse – any %	1.3	<1.0	1.1	1.2	2.0	1.4	2.0	1.7	2.2	1.8	2.2	2.0	1.6
Self-harm – any %	2.3	1.7	1.2	2.3	2.3	2.7	2.0	2.6	2.3	2.8	1.7	2.2	2.2
A&E – any%	47.9	48.1	45.3	45.6	50.3	53.8	51.4	51.2	50.8	50.8	48.9	48.3	49.3
A&E – mean Events - (SD)	1.4 (2.6)	1.4 (2.3)	1.2 (2.3)	1.4 (2.4)	1.5 (2.8)	1.7 (2.7)	1.5 (2.5)	1.5 (2.5)	1.5 (3.2)	1.4 (2.5)	1.5 (2.5)	1.5 (2.5)	1.4 (2.6)
Substance misuse – any%	1.9	1.5	1.3	2.0	2.8	2.1	3.0	2.2	2.7	2.6	2.9	2.5	2.3
WIMD – mean (SD)	2.8 (1.4)	2.9 (1.5)	2.9 (1.5)	2.9 (1.5)	2.8 (1.4)	2.8 (1.4)	2.9 (1.4)	2.9 (1.4)	2.9 (1.5)	3.0 (1.5)	2.9 (1.4)	2.8 (1.4)	2.9 (1.4)
Follow up age difference (years) mean (SD)	3.9 (2.7)	3.4 (2.6)	3.7 (2.7)	3.7 (2.6)	3.5 (2.7)	3.7 (2.7)	3.5 (2.6)	3.5 (2.5)	3.8 (2.8)	3.5 (2.5)	3.8 (2.8)	3.9 (2.6)	3.7 (2.7)
ASD Cases													
N	424	407	434	413	400	373	429	393	401	394	454	390	4912
Sex (%Female)	27.1	20.1	22.1	20.1	19.3	24.9	23.1	17.6	20.2	21.8	19.4	22.1	21.0

Mean age (yrs.) at end of follow up (SD)	19.8 (2.7)	19.4 (2.6)	19.6 (2.7)	19.6 (2.6)	19.4 (2.6)	19.5 (2.7)	19.4 (2.6)	19.4 (2.5)	19.7 (2.8)	19.4 (2.5)	19.6 (2.7)	19.7 (2.6)	19.5 (2.6)
Anx/Dep – any%	15.6	12.5	11.5	12.8	11.8	16.9	14.9	11.5	15.0	12.2	9.3	14.1	13.1
Drug misuse – any%	1.2	<1.0	1.4	1.9	<1.0	2.4	2.6	2.0	1.7	<1.0	<1.0	1.5	1.5
Alcohol misuse – any%	2.1	<1.0	1.4	2.7	2.0	<1.0	1.9	1.8	1.7	1.5	<1.0	<1.0	1.5
Self-harm – any %	5.4	4.2	4.1	4.6	2.8	7.5	6.8	4.1	6.0	4.6	3.5	4.1	4.8
A&E – any%	44.8	38.6	36.4	43.3	46.5	49.1	42.2	42.0	38.9	44.7	38.8	43.6	42.3
A&E – mean events (SD)	1.5 (3.5)	1.2 (2.5)	1.2 (3.1)	1.8 (4.9)	1.5 (3.3)	1.9 (4.6)	1.8 (4.7)	1.4 (3.6)	1.5 (4.1)	1.5 (3.4)	1.5 (5.1)	1.5 (3.6)	1.5 (4.0)
Substance misuse – any%	2.6	1.5	1.8	3.6	2.3	2.4	4.0	3.3	3.2	2.3	1.1	2.3	2.5
WIMD – mean (SD)	2.8 (1.4)	2.9 (1.4)	2.7 (1.4)	2.8 (1.4)	2.8 (1.4)	2.8 (1.4)	3.0 (1.4)	2.9 (1.4)	2.8 (1.4)	2.8 (1.4)	2.8 (1.4)	2.8 (1.5)	2.8 (1.4)
Follow up age difference (years) – mean (SD)	3.6 (2.7)	3.2 (2.5)	3.4 (2.6)	3.4 (2.5)	3.2 (2.6)	3.3 (2.7)	3.2 (2.6)	3.2 (2.5)	3.4 (2.7)	3.1 (2.4)	3.4 (2.7)	3.4 (2.6)	3.3 (2.6)

To prevent identification, percentages under 1% are not precisely displayed.

2.7 General methods: Summary

As detailed in the beginning of this chapter, results in chapters 3 and 4 are based on ALSPAC longitudinal cohort data, and the results within chapter 5 are based on electronic healthcare records data (SAIL). All three results chapters used a regression discontinuity approach, and chapters 3 and 4 used multiple imputation and GEE models to attempt to reduce the potential effects of bias caused by data missingness. More specific details pertinent to individual chapters are explained within these chapters.

Chapter 3: Relative age in the school year and risk of mental health problems in childhood, adolescence, and young adulthood

3.1 Chapter synopsis

The following chapter aimed to address the first primary objective of the present thesis, which was to investigate whether being relatively young for the school year exerts a causal influence on mental health and wellbeing in development, whether effects of relative age in the school year are already present prior to school entry, whether they vary across children's school careers and whether they extend beyond school into adulthood in a longitudinal population cohort (ALSPAC). A general description of the measures and samples used is provided in the previous chapter (chapter 2), but is summarised here, and specific study information is presented in the methods section of this chapter.

The present chapter is an adaptation of an original article, “Relative age in the school year and risk of mental health problems in childhood, adolescence and young adulthood” (https://acamh.onlinelibrary.wiley.com/doi/full/10.1111/jcpp.13684) that was published as a result of work undertaken as part of this doctoral thesis. I am the primary author of the paper; I conceived and designed the study, analysed, and interpreted the data, and drafted the manuscript. My supervisors, Dr Kate Langley, Prof. Kate Tilling, and Prof. Stephan Collishaw, each contributed to the design of the study, interpretation of the results, and reviewed the manuscript.

3.2 Abstract

Purpose: Relative age within the school year ("relative age") is associated with increased rates of symptoms and diagnoses of mental health disorders, including ADHD. The present chapter aimed to investigate how relative age influences mental health and behaviour before, during, and after school (age range: 4-25 years).

Method: A regression discontinuity design was used to examine the effect of relative age on risk of mental health problems using data from a large UK population-based cohort (Avon Longitudinal Study of Parents and Children (ALSPAC); N=14643). The risk of mental health problems by relative age was compared in individuals aged between ages 4 and 25 years using the parent-rated Strengths and Difficulties Questionnaire (SDQ), and of depression specifically using self-rated and parent-rated Short Mood and Feelings Questionnaire (SMFQ).

Results: The youngest children in the school year have greater risk of mental health problems, measured using parent-rated SDQ total difficulties scores. The present chapter found no evidence of differences before school entry (estimated standardised effect size between those born on 31st August and 1st September: 0.02 [-0.05, 0.08]).

The present chapter found that estimates of effect size for a one-year difference in relative age were greatest at eleven years (standardised effect size: 0.22 [0.15, 0.29]), but attenuated to the null at twenty-five years (standardised effect size: -0.02 [-0.11, 0.07]). No consistent evidence of differences in self-rated and parent-rated depression symptoms by relative age was found.

Conclusion: Younger relative age is associated with poorer parent-rated general mental health in the school years, but not symptoms of depression.

3.3 Introduction

Up to one in eight children in the United Kingdom meet diagnostic criteria for mental health disorders (Sadler et al., 2018). Mental health disorders have become more prevalent in children over time and are associated with immediate and long-term physical and psychological impairment (Sadler et al., 2018; Vos et al., 2017). Policy and practice interventions targeting potentially modifiable risk and protective factors will only be effective if the risk factors are truly causal (Thapar & Rutter, 2019). In observational studies, it is hard to infer causality due to the possibility of unmeasured confounding (Thapar & Rutter, 2019). To overcome this, 'natural experiments' such as using regression discontinuity methods (see chapter 1, section 1.5) which approximate the random assignment of risk or protective conditions can be used (Thapar & Rutter, 2019).

As explained in chapters 1 and 2 of the thesis, one potential risk factor that is suitable for natural experiments to infer causality is a child's age within the school year, henceforth, relative age. The youngest children in the school year are over-represented in mental health disorder statistics (Root et al., 2019), however It is unclear whether this represents a real difference in disorder risk by relative age, or whether this is due to differences in help-seeking patterns or referrals to mental health services.

Relative age effects on mental health are relatively unexplored from an epidemiological perspective; three previous UK studies suggest that the youngest children in the school year have higher parent, teacher, and self-rated mental health symptom scores, (Crawford et al., 2013; Norbury et al., 2016; Patalay et al., 2015). These studies are described in more detail in chapter 1 (section 1.4).

Cross-national comparisons of large representative population surveys of mental health disorders have shown that being born in the latest third of any academic year is associated with an increased risk of depression diagnosis, as well as increased self-rated, parent-rated, and teacher-rated risk of mental health problems (Goodman et al., 2003). Crucially, these effects of age within school year were present across nations with different school entry cut-off dates and the same paper found that relatively young children did not differ from older peers on age-standardised ability tests (Goodman et al., 2003). This evidence shows that relative age effects are independent of other birth date effects such as season of birth, and that younger children are more likely to have a greater risk of mental health problems regardless of informant (i.e., parent, child, or teacher), chronological age, and a country's school entry cut-off.

There are several important knowledge gaps. First, it is not known whether differences in mental health by relative age occur prior to starting school. Typically, before school entry children are not grouped together by the school entry cut-off; nor are they expected to undertake learning of age-standardised material; if mental health differences by relative age emerge after, but not before, school entry, it can be inferred that these differences are caused by this grouping.

Second, it is not known whether relative age effects extend into adulthood. To get a clearer picture of relative age effects and potential interventions for these effects, it is not only important to consider what happens when relatively young children enter compulsory education, but also when they leave. Third, psychometric tests, such as the SDQ show different rates of mental health problem risk, and different patterns of associations with a range of risk factors, depending on the informant used – parent,

young person or teacher (Collishaw et al., 2009). This emphasises the need for multi-informant sources of information about mental health problems. Lastly, most previous studies have looked at general mental health symptom screens such as the SDQ. However, these studies highlight some specificity across different domains of mental health (Patalay et al., 2015). To better understand mental health domain-specific effects, more sensitive and specific measurements of particular mental health outcomes are needed, such as the Short Mood and Feelings questionnaire (SMFQ; (Angold et al., 1995) for depression.

This chapter aimed to investigate how relative age influences mental health before, during, and after school, using data from a large UK population-based cohort (ALSPAC) repeatedly assessed between the ages of 4 and 25 years. It was hypothesised that the youngest children in the school year will have greater reported risk of mental health problems than their relatively older peers, that relative age differences would first emerge at school entry, and that these differences would be strongest in the early school years. This is because the difference in chronological age (and therefore physiological and psychological maturity) is greatest between oldest and youngest in those years. It was hypothesised that there would be no difference by relative age before school entry because it was assumed that pre-school children are largely taught through play, and so are not usually subject to formal assessments and classroom streaming to the same degree as children who have entered the school system.

3.4 Method

3.4.1 Sample: Avon Longitudinal Cohort of Parents and Children (ALSPAC)

This chapter used data gathered from I Avon Longitudinal Study of Parents and Children (ALSPAC); further details of the ALSPAC cohort are described in more detail in chapter 2 of the thesis (section 2.2).

3.4.2 Exposure variable: Relative age in the school year

As described in more detail in chapter 2, children's exact birth dates were not provided due to the risk of deanonymisation. Children's birth dates were grouped into one eight-day block (1st-8th September) and fifty-one consecutive 7-day blocks ending on August 31st. Children were assigned a score reflecting week of birth relative to the academic year (range 0 (Oldest; 1st September) – 51(Youngest, up to 31st August)).

3.4.3 Outcome variable: Mental health and wellbeing, and depression symptoms in childhood, adolescence, and adulthood

Two well-validated child and adolescent mental health screening questionnaires were administered at several timepoints between 4-25 years; the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) was used to measure mental health and wellbeing, and the Short Mood and Feelings Questionnaire (SMFQ; (Angold et al., 1995) was used to measure depressive symptoms. These questionnaires are described in further detail in chapter 2 (section 2.2).

SDQ and SMFQ data was used continuously for statistical (increased power) and conceptual reasons. Previous research suggests that mental health and neurodevelopmental conditions such as depression and ADHD lie at the end of a continuous distribution of underlying symptom traits, with similar aetiological and

outcome profiles (Thapar, 2018; Thapar et al., 2012). See figure 2.3 in chapter 2 for the timepoints for administration.

3.4.4 Covariates

As discussed in chapter 2, an advantage of regression discontinuity methods is that they do not rely on controlling for confounders as in usual observational studies (Oldenburg et al., 2016), however, it is still important to test assumption violations such as unbalanced covariate distribution; in a regression discontinuity design, it is important that individuals lying close to either side of the cut-off are comparable with respect to their covariates, i.e. other observed factors besides relative age are not discontinuous at the cut-off (Moscoe et al., 2015). Various early pre-assignment covariates were included to examine this:

Maternal background: Age of mother at birth, mother's education (highest qualification), maternal depression at 18 weeks gestation (Edinburgh Postnatal Depression Scale; (Cox et al., 1987).

Pregnancy and birth: Caesarean birth, birth size (i.e., single, or multiple birth), birthweight, gestational age, maternal alcohol use during last two months of pregnancy, maternal smoking during pregnancy.

Child and household factors: Sex, child ethnic background, parity, household crowding, home ownership, age of child at questionnaire completion.

3.4.5 Design

A regression discontinuity design was used to compare the relative risk of mental health problems by relative age (Hilton Boon, Craig, Thomson, Campbell, & Moore, 2021; Moscoe et al., 2015; Oldenburg et al., 2016; Venkataramani et al., 2016). The exposure is "age at starting school" and the running variable is "week of birth", with

the discontinuity on 1st September. A “sharp” RD design was chosen, given the strict cut-off date for school year selection in England and Wales; it was assumed (based on LEA rules at the time) that children started school at the same time and during the school year they turn 5 years old, and that schools and LEAs adhere to this cut-off. Regression discontinuity relies on certain assumptions, described in more detail in the previous chapter (section 2.4.2).

3.4.6 Statistical Analysis

The main analysis was conducted in three ways; first, one where the exposure is continuous throughout the school year and there is no selection window near the cut-off (henceforth, “no bandwidth”), second, restricted to those born four weeks either side of the September 1st cut-off (“4 weeks”), and lastly, restricted to those born 8 weeks either side of the cut-off (“8 weeks”). The four-week and eight-week bandwidths only compare those with birthdates within those time windows around September 1st. These bandwidths were selected because in narrower bandwidths (e.g., 4 weeks) the assumption of no confounding is more plausible (Bor et al., 2014). The estimation of effects of relative age was viewed as local randomness near the cut-off (i.e. the variation in age within school year was assumed to be randomised, as if from randomised controlled trials, or as randomised as possible), by limiting analysis to observations that lie within one bandwidth on either side of the 1st September cut-off (i.e. four weeks either side of the cut-off, in the case of a four-week bandwidth). After bandwidth selection, local linear regressions were fitted on observations within the bandwidth to estimate the effect of relative age. Previous studies have used similar bandwidths (Crawford et al., 2014). A bandwidth of 8 weeks corresponds to approximately the length of a school half-term.

3.4.7 Missing data and imputation

A problem with using longitudinal cohort data is participant attrition over time; at age 4 years there were 9312 participants, decreasing to 4076 at 25 years. Complete cases were compared with those who had incomplete data and then multiple imputation by chained equations was used (see Appendix table A3.1 for further information) to account for selective attrition. Auxiliary variables that predicted missingness were included, together with variables in the analysis model (Parent-rated SDQ total difficulties (4-25 years, self-rated SMFQ (10-25 years), parent-rated SMFQ (9-16 years). Specifically, the present chapter included maternal depression, maternal age, gestation, birthweight, birth size, alcohol use in last 2 months of pregnancy, smoking, caesarean status, crowding, home ownership status, mother's education, and parity in the imputation models. A maximum sample of those with at least one measure for each mental health measure was selected for multiple imputation analysis (N Parent SDQ = 11116; N Self SMFQ = 9468; N Parent SMFQ = 9146). Linear regressions were then used for each outcome on age at starting school, then also adjusted for all abovementioned covariates. All imputation models were checked for Monte Carlo error following guidelines (White et al., 2011), further details in the chapter 2 of the present thesis.

3.4.8 Sensitivity and secondary analyses

To test robustness to assumptions about and treatment of missing data, findings are also reported from a complete-case analysis at each outcome point. In addition, a generalized estimating equation (GEE) approach to model the outcomes (parent-rated SDQ, self-rated SMFQ, and parent-rated SMFQ) by relative age was additionally implemented as a sensitivity analysis. One advantage of this approach is

that GEE models have some robustness to attrition, but do not use imputation (i.e. only analyse available data)(Liang & Zeger, 1986).

Secondary analyses tested i). differences in SDQ subscales by relative age, and ii). potential interactions by child sex.

All analyses were conducted using Stata (v16.1 SE, StataCorp LLC, College Station, TX).

3.5 Results

The results section reports the results of the present chapter. Demographic characteristics of the sample, the results of assumption tests for the regression discontinuity design, and comparisons of participants with complete vs incomplete data are reported earlier in the thesis given their relevance to other chapters (see section 2.5). This following section will first outline the descriptive statistics of mental health outcomes analysed in this chapter (3.5.1 – descriptive statistics), then outline the results from the main analysis (3.5.2 – main analysis results) and then the sensitivity and secondary analyses (3.5.3- sensitivity analyses; 3.5.4 - secondary analyses).

3.5.1 Descriptive statistics

3.5.1. Descriptive data on mental health outcome measures

Table 3.1, below, presents descriptive, unstandardised complete-case data on mental health outcome variables (Parent-rated SDQ Total Difficulties, self-rated and parent-rated SMFQ) for the whole sample (with available data at a given time point), and for children born in August and September. Below that, Table 3.2 presents the same data for individuals included in the 4-week and 8-week bandwidths. For each measure, higher scores indicate greater reported SDQ scores, which are indicative of greater risk of mental health problems.

Table 3.1: Descriptive statistics of outcome measures in August and September born children

Measure	Total		August		September	
SDQ Total Difficulties	N	M (SD)	N	M (SD)	N	M (SD)
4 years	9,312	8.92 (4.59)	894	9.21 (4.53)	935	9.28 (4.61)
7 years	8,281	7.48 (4.77)	784	7.91 (4.97)	817	7.27 (4.69)
8 years	7,669	7.84 (5.21)	699	8.34 (5.41)	722	7.61 (5.29)
9 years	7,934	6.88 (4.96)	732	7.34 (5.24)	754	6.77 (5.03)
11 years	7,253	6.56 (4.98)	648	6.96 (5.19)	683	6.28 (4.91)
13 years	6,933	6.81 (5.00)	610	7.09 (5.22)	658	6.51 (4.89)
16 years	5,554	6.15 (4.77)	523	6.42 (4.88)	533	6.10 (4.81)
25 Years	4,076	5.65 (5.11)	365	5.04 (4.50)	399	5.18 (4.64)
Self-Rated SMFQ						
10 Years	7,245	4.03 (3.50)	630	4.06 (3.61)	715	3.99 (3.61)
13 Years	6,607	3.97 (3.85)	602	3.76 (3.46)	645	4.00 (3.91)
14 Years	5,925	4.92 (4.48)	545	5.04 (4.51)	597	4.51 (4.36)
16 Years	4,939	5.91 (5.64)	452	6.07 (5.55)	465	6.21 (5.98)
17 Years	3,299	6.81 (5.90)	296	6.55 (5.49)	320	7.02 (6.36)
18 Years	4,444	6.59 (5.24)	390	6.72 (5.17)	463	7.04 (5.59)
21 Years	3,271	5.30 (5.10)	305	5.65 (5.30)	318	5.72 (5.49)
22 Years	3,869	6.20 (5.53)	354	6.32 (5.38)	367	6.15 (5.31)
23 Years	3,972	7.03 (6.05)	347	6.99 (5.79)	390	7.17 (6.30)
25 Years	3,962	6.88 (6.41)	358	7.16 (6.48)	375	6.74 (6.34)
Parent-Rated SMFQ						
9 Years	7,966	2.59 (3.26)	737	2.74 (3.46)	756	2.58 (3.21)
11 Years	7,201	2.34 (3.23)	642	2.60 (3.39)	682	2.33 (3.41)
13 Years	6,899	2.36 (3.32)	605	2.52 (3.56)	650	2.32 (3.28)
16 Years	5,383	2.14 (3.40)	503	2.16 (3.38)	517	2.31 (3.71)

Table 3.2: Descriptive statistics of outcome measures; restricted to 4-week bandwidth and 8-week bandwidth

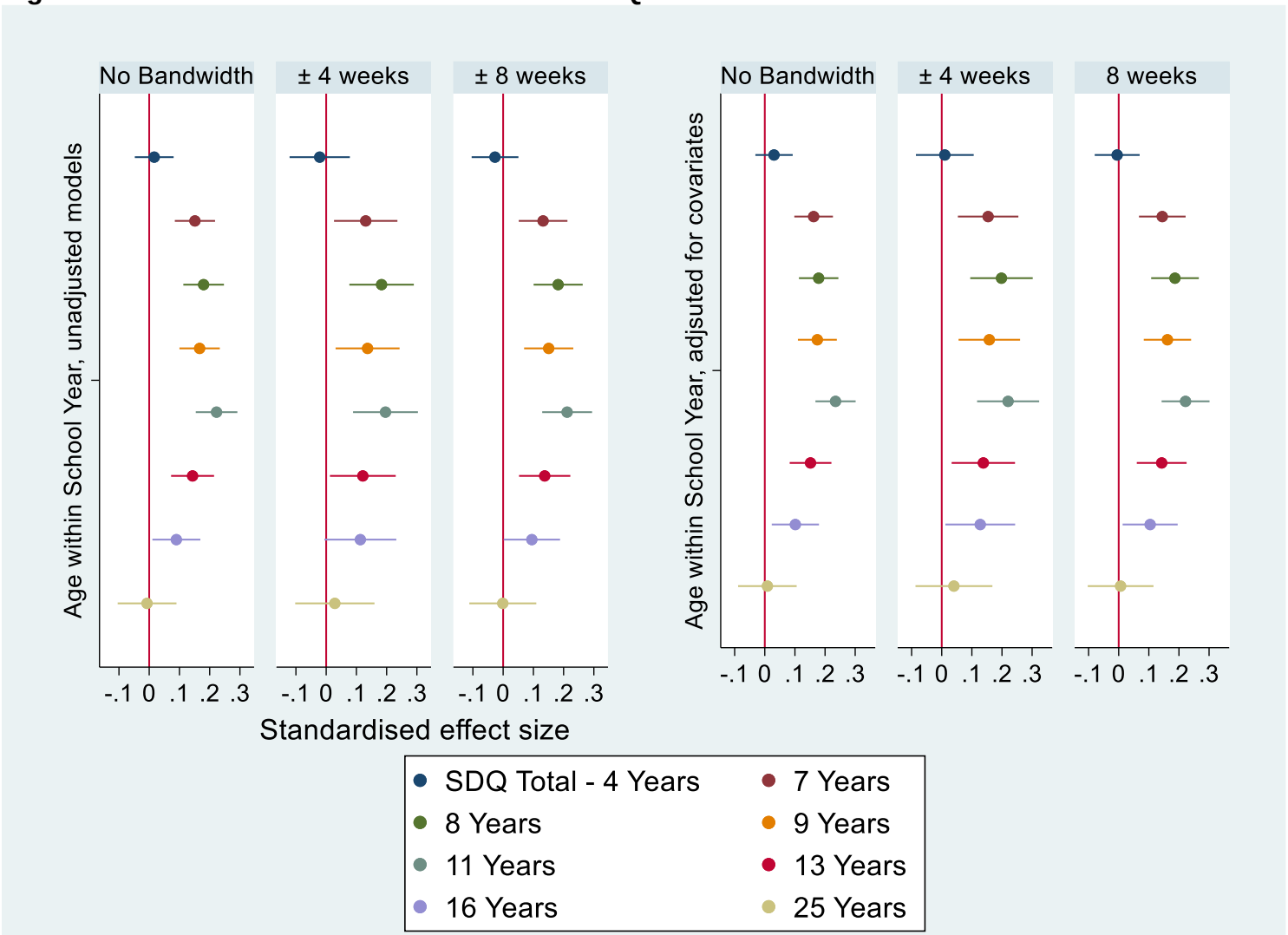
	4 weeks		8 weeks	
Variable	N	Mean (SD)	N	Mean (SD)
SDQ Total Difficulties				
4 Years	1,734	9.25 (4.56)	3,453	9.10 (4.63)
7 Years	1,527	7.57 (4.86)	3,026	7.51 (4.80)
8 Years	1,356	7.95 (5.38)	2,681	7.82 (5.22)
9 Years	1,417	7.05 (5.12)	2,867	6.85 (5.06)
11 Years	1,273	6.63 (5.06)	2,577	6.52 (4.97)
13 Years	1,210	6.79 (5.06)	2,444	6.64 (4.92)
16 Years	1,000	6.25 (4.83	2,001	6.08 (4.71)
25 Years	728	5.13 (4.55)	1,458	5.27 (4.79)
Self-rated SMFQ				
10 Years	1,282	4.05 (3.65)	2,573	4.02 (3.48)
13 Years	1,186	3.90 (3.70)	2,358	3.86 (3.68)
14 Years	1,087	4.77 (4.43)	2,139	4.77 (4.41)
16 Years	867	6.09 (5.71)	1,774	6.04 (5.77)
17 Years	585	6.83 (5.96)	1,177	6.77 (5.99)
18 Years	805	6.86 (5.34)	1,630	6.66 (5.29)
21 Years	589	5.80 (5.43)	1,181	5.40 (5.23)
22 Years	685	6.24 (5.34)	1,370	6.14 (5.46)
23 Years	694	7.09 (6.06)	1,409	7.02 (6.06)
25 Years	692	6.98 (6.40)	1,407	6.82 (6.29)
Parent-rated SMFQ				
9 Years	1,421	2.65 (3.33)	2,882	2.60 (3.32)
11 Years	1,265	2.47 (3.44)	2,554	2.40 (3.29)
13 Years	1,196	2.41 (3.44)	2,433	2.29 (3.24)
16 Years	966	2.25 (3.59)	1,928	2.17 (3.44)

3.5.2 Main results

3.5.2.1 Relative age in the school year and mental health and wellbeing at ages 4-25 years

As shown in Figure 3.1 (Parent-rated general mental health), no evidence was found for an effect of relative age on parent-rated mental health before entry into school (age 4 standardised effect size: 0.02, 95% CI: [-0.05, 0.08]). At the earliest point after school entry (7 years) a 1-year decrease in relative age in the school year was associated with a difference of approximately one-sixth of a standard deviation in SDQ total difficulties (standardised effect size: 0.15, 95% CI: [0.08, 0.22]). Being relatively young in the school year was associated with higher SDQ total difficulty scores, indicative of poorer parent-rated child mental health. These differences persisted throughout the school years, with the strongest effect at eleven years (standardised effect size: 0.22, 95% CI: [0.15, 0.29]). These differences attenuated to the null at 25 years (standardised effect size: -0.01, 95% CI: [-0.1, 0.09]). Results were materially unchanged after adjusting for covariates.

Figure 3.1: Parent-rated Mean Standardised SDQ Total Difficulties Coefficient Plots



Unadjusted Models (left), models adjusted for covariates (right), Imputed data. Standardised effect size = mean change in standardised SDQ total difficulties per 1 year difference in relative age. "No Bandwidth" = All participants included; "4 Week" = Restricted to participants born up to 4 weeks either side of September 1st Cut-off; "8 week" = Restricted to participants born 8 weeks either side of the September 1st cut-off. N=11116

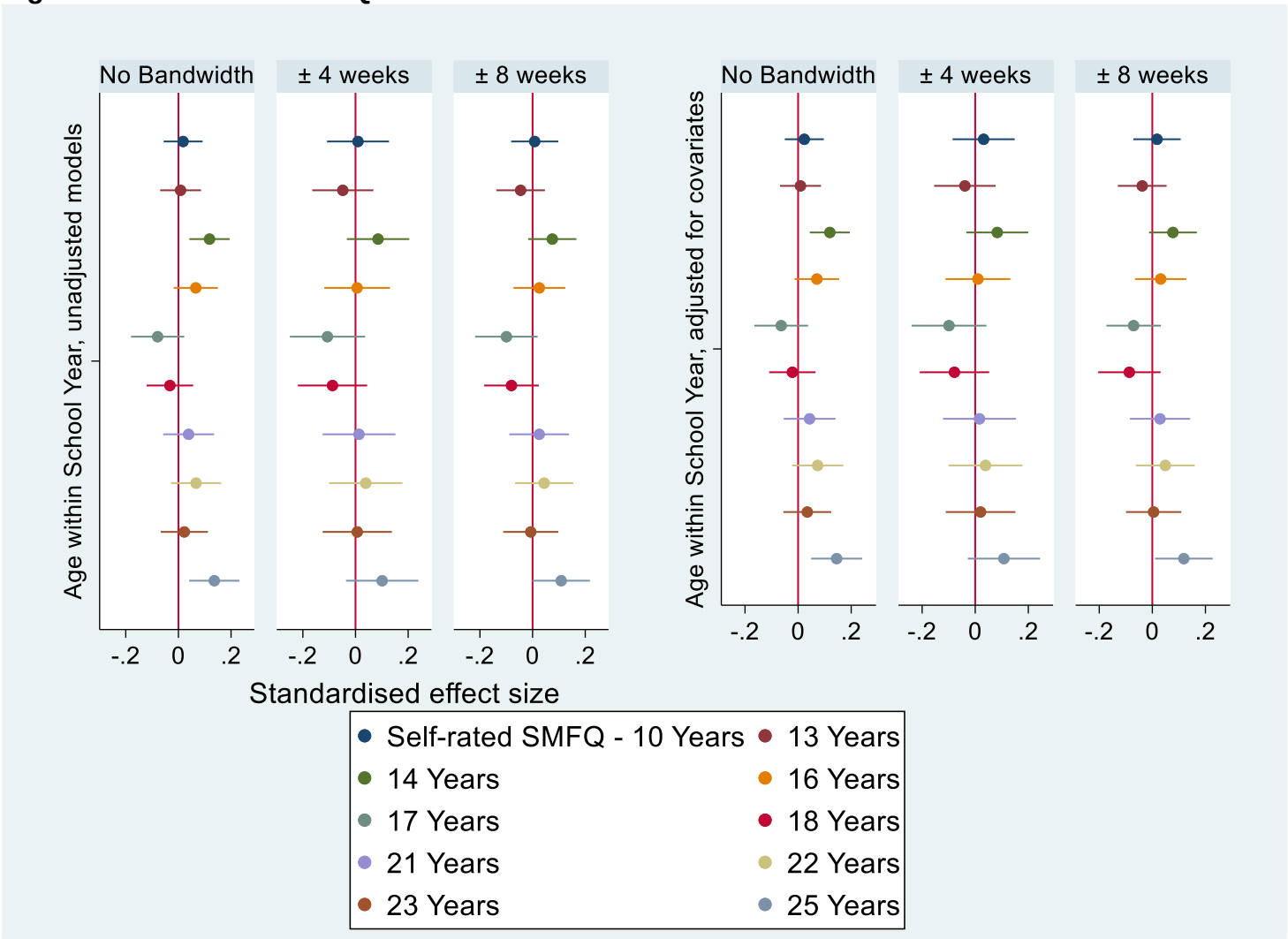
3.5.2.2 Relative age in the school year and depression at ages 4-25 years

As shown in Figure 3.2 (self-rated depression symptoms), the youngest children in the school year were more likely to report self-rated depression symptoms at fourteen years (standardised effect size: 0.12, 95% CI: [0.04, 0.20]) and at twenty-five years of age (standardised effect size: 0.14, 95% CI: [0.04, 0.23]), but there was no evidence of difference by relative age at other ages. However, there was no consistent evidence that relative age was associated with depression symptoms; most of the effects of relative age on depression symptoms crossed the null, and there was no discernible direction of effects.

Figure 3.3 (parent-rated depression) shows that relatively young children scored higher in parent-rated depression at nine years (standardised effect size: 0.12, 95% CI: [0.05, 0.19]) and eleven years (standardised effect size: 0.16, 95% CI: [0.09, 0.23]). No other evidence of differences by relative age on parent-rated SMFQ scores was found. Most effects of relative age on parent-report depression scores were positive, in other words, relative age in the school year was associated with increased (i.e., worsened) parent rated depression scores.

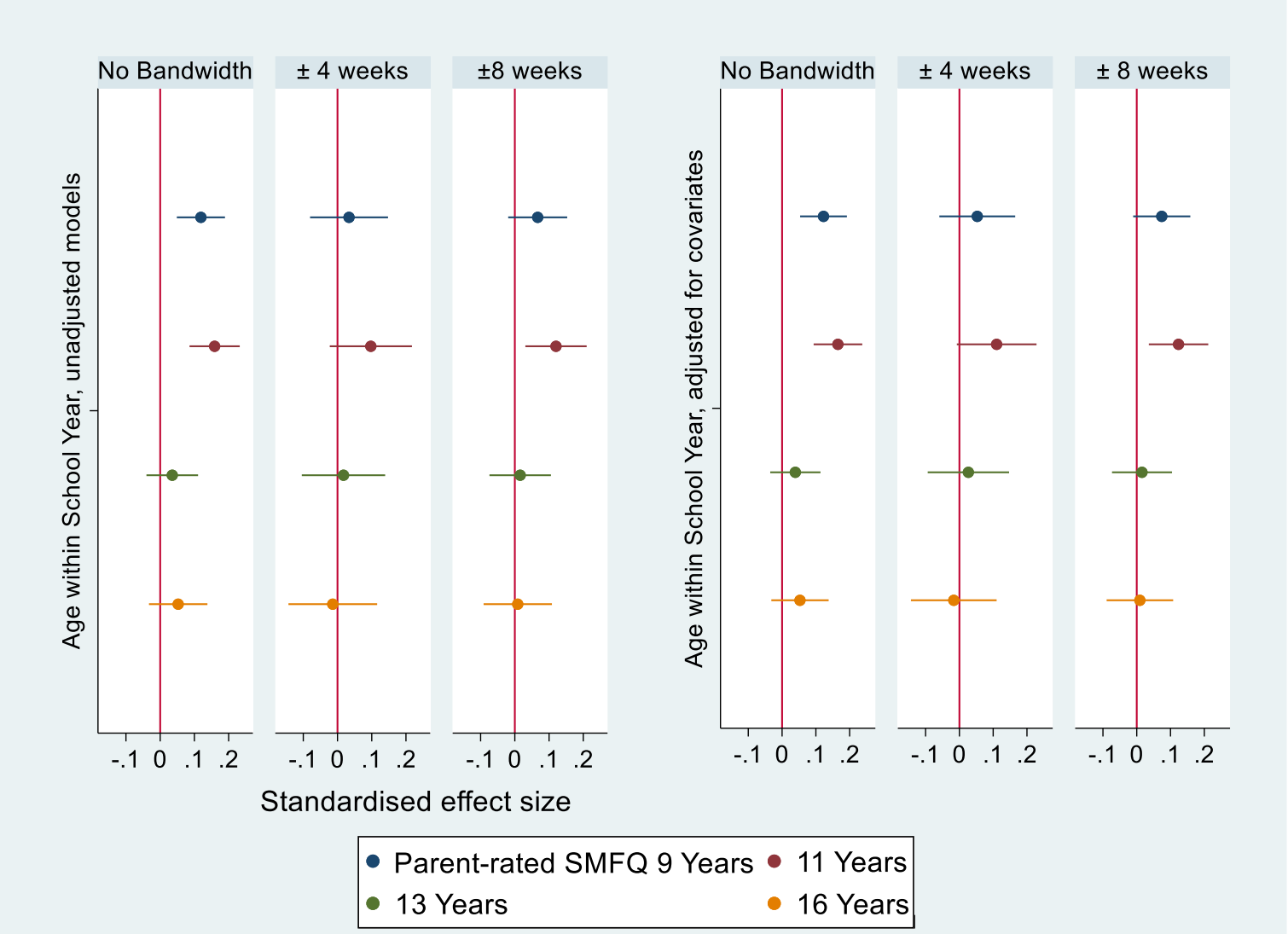
Regression tables of all key findings are also available below and in the appendices (Table 3.6; Appendix Tables A3.2-A3.9).

Figure 3.2: Self-rated SMFQ Coefficient Plots



Unadjusted Models (left), models adjusted for covariates (right). Imputed data. Standardised effect size: mean change in standardised self-rated SMFQ per 1 year difference in relative age). N=9468

Figure 3.3: Parent-rated SMFQ coefficient plots



Unadjusted Models (left), models adjusted for covariates (right). Imputed data. Standardised effect size: mean change in standardised parent-rated SMFQ per 1 year difference in relative age. N=9146

3.5.3 Sensitivity Analyses

3.5.3.1 Restricting analyses to those born ± 4 and ± 8 weeks either side of the cut-off

Most of the identified relative age effects on parent-rated SDQ scores were materially unchanged when analysis was restricted to children born up to ± 4 and ± 8 weeks either side of the cut-off, except for the association at sixteen years attenuating to the null in participants born ± 4 weeks either side of the cut-off (appendix table A3.4). For the self-rated and parent-rated SMFQ, no consistent evidence was found for relative age effects on depression symptoms in this group. Restricting the bandwidths to those born ± 4 and ± 8 weeks closest to the cut-off yielded wider 95% confidence intervals (see appendix tables A3.4-A3.9).

3.5.3.2 Complete case analysis results

The complete-case results resembled the analysis using multiple imputation, with some differences. These findings are presented in the appendix (tables A3.10-A3.12). Complete-case analysis identified effects of relative age on parent-rated SMFQ scores at 16 years (standardised effect size: 0.10 [0.01, 0.20]); these attenuated to the null in the multiple imputation analysis. The multiple imputation analysis showed an effect of relative age on self-rated SMFQ scores at 25 years (standardised effect size: 0.16 [0.06, 0.25], in contrast to complete-case analyses (standardised effect size: 0.09 [-0.02, 0.20], albeit with overlapping confidence intervals. All other findings were substantively unchanged.

3.5.3.3 Sensitivity analyses using GEE models

As an alternative approach to multiple imputation, General Estimating Equations (GEE) models of relative age effects were produced for all outcomes. The results

from GEE models agreed with the results from the models using imputed data (see Tables A3.13-A3.15 in appendices).

3.5.4 Secondary Analyses:

3.5.4.1 SDQ subscale analysis results:

SDQ subscale scores by relative age were explored. All subscale regression model information is provided in Table 3.3, below. The hyperactivity subscale followed the same pattern as the total difficulties scores, in addition to showing the largest standardised effect sizes by relative age of all subscales, up to .25 of a standard deviation at age 11 years (95% CI [.18, .32]). Parent-rated emotional problems and peer problems also showed effects by relative age in the same direction (standardised effect size emotional problems at 7 years: .13 [.06, .20]; standardised effect size peer problems at 11 years; .15 [.08; .22]. No consistent relative age differences for conduct problems were identified.

Table 3.3: Regression results for SDQ total difficulties and subscales by relative age, Imputed data

	Unadjusted			All Covariates		
SDQ Total Difficulties	Coef.	95% CI.	p	Coef.	95% CI.	p
4 Years	0.02	[-0.05, 0.08]	0.61	0.03	[-0.03, 0.09]	0.33
7 Years	0.15	[0.08, 0.22]	<0.01	0.16	[0.10, 0.23]	<0.01
8 Years	0.18	[0.11, 0.25]	<0.01	0.18	[0.11, 0.24]	<0.01
9 Years	0.17	[0.10, 0.23]	<0.01	0.17	[0.11, 0.24]	<0.01
11 Years	0.22	[0.15, 0.29]	<0.01	0.23	[0.17, 0.30]	<0.01
13 Years	0.14	[0.07, 0.21]	<0.01	0.15	[0.08, 0.22]	<0.01
16 Years	0.09	[0.01, 0.17]	0.03	0.10	[0.02, 0.18]	0.01
25 Years	-0.01	[-0.10, 0.09]	0.89	0.01	[-0.09, 0.11]	0.86
Conduct problems subscale						
4 Years	0.00	[-0.06, 0.06]	0.98	0.01	[-0.05, 0.07]	0.74
7 Years	-0.02	[-0.08, 0.05]	0.64	-0.01	[-0.07, 0.06]	0.82
8 Years	0.03	[-0.04, 0.10]	0.36	0.04	[-0.03, 0.10]	0.27
9 Years	-0.03	[-0.09, 0.04]	0.46	-0.02	[-0.09, 0.05]	0.58
11 Years	0.08	[0.01, 0.15]	0.03	0.09	[0.02, 0.16]	0.01
13 Years	0.02	[-0.05, 0.09]	0.63	0.02	[-0.05, 0.09]	0.52
16 Years	0.00	[-0.08, 0.09]	0.93	0.01	[-0.07, 0.09]	0.76
25 Years	-0.02	[-0.11, 0.07]	0.71	-0.01	[-0.10, 0.08]	0.88
SDQ Emotional problems subscale						
4 Years	0.09	[0.02, 0.15]	0.01	0.09	[0.03, 0.16]	0.01
7 Years	0.13	[0.06, 0.20]	<0.01	0.13	[0.07, 0.20]	<0.01
8 Years	0.09	[0.03, 0.16]	0.01	0.08	[0.02, 0.15]	0.01
9 Years	0.12	[0.05, 0.19]	<0.01	0.12	[0.05, 0.19]	<0.01
11 Years	0.11	[0.04, 0.18]	<0.01	0.11	[0.04, 0.18]	<0.01
13 Years	0.08	[0.01, 0.16]	0.03	0.08	[0.01, 0.16]	0.03
16 Years	0.09	[0.02, 0.17]	0.02	0.09	[0.02, 0.17]	0.02
25 Years	-0.02	[-0.11, 0.07]	0.70	-0.01	[-0.10, 0.07]	0.74
SDQ Hyperactivity problems subscale						
4 Years	0.00	[-0.07, 0.06]	0.91	0.01	[-0.05, 0.07]	0.81
7 Years	0.18	[0.11, 0.24]	<0.01	0.18	[0.12, 0.25]	<0.01
8 Years	0.22	[0.16, 0.29]	<0.01	0.23	[0.16, 0.29]	<0.01

9 Years	0.19	[0.13, 0.26]	<0.01	0.20	[0.14, 0.26]	<0.01
11 Years	0.25	[0.18, 0.32]	<0.01	0.26	[0.20, 0.33]	<0.01
13 Years	0.17	[0.10, 0.24]	<0.01	0.18	[0.11, 0.25]	<0.01
16 Years	0.07	[-0.01, 0.15]	0.08	0.08	[<0.01, 0.16]	0.04
25 Years	-0.01	[-0.10, 0.08]	0.82	0.00	[-0.09, 0.09]	0.95
SDQ Peer problems subscale						
4 Years	-0.03	[-0.09, 0.04]	0.42	-0.02	[-0.08, 0.05]	0.58
7 Years	0.08	[0.02, 0.15]	0.02	0.09	[0.02, 0.16]	0.01
8 Years	0.11	[0.04, 0.18]	<0.01	0.10	[0.03, 0.17]	0.01
9 Years	0.15	[0.08, 0.22]	<0.01	0.15	[0.09, 0.22]	<0.01
11 Years	0.15	[0.08, 0.22]	<0.01	0.16	[0.09, 0.23]	<0.01
13 Years	0.12	[0.05, 0.19]	<0.01	0.12	[0.05, 0.19]	<0.01
16 Years	0.05	[-0.03, 0.13]	0.25	0.05	[-0.03, 0.13]	0.18
25 Years	-0.01	[-0.10, 0.09]	0.87	0.01	[-0.09, 0.10]	0.91

N=11116. The numbers contained in the "SDQ Total Difficulties" column of this table correspond to figure 2 (leftmost column). Coefficient represents difference in standardised parent-report SDQ score between children born between 1st September-31st August. "Unadjusted Model" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates.

3.5.4.2 Interactions by sex:

No consistent evidence of relative age effects was found between males and females, for the SDQ and both versions of the SMFQ. These findings are displayed in the appendices (Table A3.16).

3.6 Discussion

This section will summarise and interpret the above findings, discuss the strengths and limitations of the analysis, and highlight potential implications and areas for further research.

3.6.1 Summary and interpretation of findings

The present chapter aimed to investigate the effect of relative age in the school year on risk of mental health problems in a general population longitudinal cohort studied across childhood, adolescence and into young adulthood. Using the fact that studying the effects of relative age allows use of a regression discontinuity design, it was found that the youngest children in the academic year have greater parent-rated mental health problems, and that these findings were materially unchanged after adjusting for covariates. The hyperactivity subscale accounted for the largest differences by relative age, with emotional problems and peer problems also contributing. There was no difference in risk of child behavioural problems by relative age. Further, the findings of this chapter supported the prior hypothesis that relative age differences are only present after school entry.

Moreover, relative age effects persist into secondary education, but wane after young people leave school. The largest differences by relative age were at eleven years. This differs from prior hypotheses that relative age differences would be strongest at the earliest measurement after school entry, and then subsequently

weaken as children develop, on the basis that the difference of up to one year between children becomes increasingly less noticeable by chronological age. It was expected that relative age effects on specific measures of depression would be found (Goodman et al, 2003; Root et al., 2019). However, while there was some evidence of differences between the oldest and youngest children at some time points, overall, there was no consistent pattern of effects of relative age across development; the majority of the self-rated and parent-rated SMFQ measurements showed no evidence of a relationship between relative age and depression symptoms.

The transition to secondary school appears to be a particular period of vulnerability for relatively young children, since the largest differences between the oldest and youngest in the school year in parent-rated mental health and wellbeing were observed at 11 years. This accords with previous studies identifying this transition as a high-risk period (Evans, Borriello, & Field, 2018; Rice, Frederickson, & Seymour, 2011).

The findings of this chapter support Patalay et al.'s (2015) findings that relative age influences emotional problems in children, and Crawford et al.'s findings that relatively young children show poorer social and emotional development as reflected by poorer outcomes on the SDQ. However, Crawford et al. (2013) found that parent-rated differences in SDQ scores by relative age are not present beyond the age of nine years in the ALSPAC cohort, whereas in the same cohort we find that relative age effects persist up to the age of sixteen years. However, in both studies, estimates were in the same direction. In contrast to Crawford et al, the present chapter used various approaches to account for participant attrition (which became more pronounced as children grew older) and a more precise measure of relative

age (measured in weeks not months). The two studies also differed in the covariates included.

3.6.2 Strengths

The present chapter adds to previous findings by investigating the relationship between relative age and mental health in the ALSPAC cohort both prior to and during school age, as well as extending to after young people had left school. This chapter also adds to previous findings by testing relative age effects on a specific measure of depression symptom traits (SMFQ), and by using week of birth as a more precise measurement of age within school year. To control for biases that may arise from missing data resulting from attrition in the ALSPAC cohort, imputed data using a multiple imputation approach was used. Furthermore, to test robustness, alternative selection bandwidths were investigated in the regression discontinuity design as sensitivity analyses. Further strengths of the chapter are that rich data were used from a single longitudinal population cohort, with data collected on youth mental health throughout development, and the chapter used consistent and widely implemented multi-informant measures of mental health at each time point. For example, the same measure (the SDQ) was used across development, using the same rater (the parent). Evidence supports the reliability and validity of the SDQ as a measure of mental health in children and adolescents (Goodman, 1997; 2001) and emerging evidence supports its use in young adulthood (Riglin, Agha, et al., 2021)

Crucially, assumption violations of the regression discontinuity design were checked (in chapter 2), and there was no evidence that covariates act as confounders because there was no inequality in distribution across the school entry cut-off. Therefore, this is suggestive of a causal effect of young relative age on mental health in school age children. Therefore, the present chapter's findings highlight relative

age as a possible target for intervention and demonstrates the utility of the regression discontinuity design to test causal influences when other experimental methods such as randomised controlled trials are not feasible (Moscoe et al., 2015; Venkataramani et al., 2016).

3.6.3 Limitations

The analysis within this chapter also has limitations. First, data missingness due to participant attrition may result in bias due to differences between participants who are retained vs those who drop out. Attempts were made to account for this missingness by using a multiple imputation approach to missing data; however, if children at greater risk of mental health problems are more likely to drop out of the study, the use of multiple imputation will not remove all the bias (Lee et al., 2021). The pattern of findings using GEE models, which are a different method for dealing with attrition, accorded with the imputed data, but results from imputed data and GEE models may still be affected by data that is missing not at random (MNAR; see chapter 2). Second, there were some limitations with the measurements used; there was a long gap between some measurements, including a nine-year gap between the last two SDQ measurements, so the precise timing of when effects attenuated to the null remained unknown from this chapter, in addition, further evidence is needed assessing measurement invariance of the SDQ and its subscales across the age range covered by this chapter.

Third, participants' childcare arrangements before school entry were not considered; some children may have experienced more formal pre-school settings, and whether effects of relative age differed in those children compared to children without these childcare arrangements was not tested or controlled for. Similarly, the type of schooling children entered was not considered, nor whether classes were comprised

of single or multiple academic year groups taught together. Lastly, exactly when each child started school was not known, which would lead to a “fuzzy” regression discontinuity design, described in more detail in chapter 2 (section 2.4; Lee & Lemieux, 2010). In the UK, education authorities often offer some flexibility about when in the calendar year children start their first year of school (e.g., at the start of the autumn or spring terms) with a view to helping ensure school readiness including amongst summer born children. Nevertheless, summer born children typically remain the youngest in their school year. In addition, further research is needed to assess whether there are impacts of delayed school entry on children's mental health.

3.6.4 Implications and further research

The results from this chapter have implications for future research to consider. This section will briefly describe some of these implications and future research directions that may be inferred from these findings, but these are covered in more detail in the general discussion of this thesis (chapter 6).

3.6.4.1 Implications

The effect of relative age on risk of mental health problems is modest at an individual level but may be larger at a population level. It appears that the effects of relative age may specifically impact children of school age; therefore, any intervention should be applied either during this period, or, prior to school entry provided it aims to improve mental health during this period, for example efforts to improve school readiness in pre-school children (Dhuey et al., 2019; Marti et al., 2018). Relative age effects on mental health may attenuate to the null by adulthood, but evidence also suggests there may be enduring links with broader psychosocial outcomes, such as educational attainment and employment (Lopez-Lopez et al., 2019).

Previous authors have suggested school admissions and entry system changes, including delaying school entry (Dee & Sievertsen, 2018) or age-based assessment adjustments (Crawford et al., 2013). Changes to established school structures and admission systems may be difficult to implement in practice because of the likelihood of increased disruption for schools, teachers, and families. Evidence is mixed on the benefits of this practice to children (Dhuey et al., 2019), and more evidence is required on whether age adjustments to grades and examinations counteract relative age effects. It is important to remember that in any classroom some children will be younger than others, even when combining more than one year group together or delaying school entry. Caution should be exercised on suggesting what the effect of relative age on clinical aspects of mental health problem risk looks like in practice, given the modest size of these effects, and that clinically diagnosed mental health problems were not considered. Being young for the school year may not affect individuals equally, and it is important to further investigate relative age effects on mental health using measures that consider clinical impacts both in terms of presentation of symptoms and their impacts on functioning.

An alternative approach may involve organising the school register by age within school year to raise awareness of teachers about who is relatively young within the classroom (Norbury et al., 2016) which may facilitate differentiated instruction and assessment. It is suggested that schools become more aware of relative age effects on education achievement and mental health on their pupils.

3.6.4.2 Future research directions

Investigating potential mechanisms through which relative age affects mental health was beyond the scope of the present chapter, but previous research shows that younger children in the school year have poorer education attainment and are more

likely to be bullied (Crawford et al., 2013; Mühlenweg, 2010). Both are associated with increased risk of mental health problems in children and young people (Klomek et al., 2015). Therefore, a further question for research to consider is whether bullying influences the relationship between relative age and mental health. A second question for further research is whether pubertal changes influence this relationship (Copeland, Worthman, Shanahan, Costello, & Angold, 2019). A third suggestion is exploring whether relative age has differential effects on anxiety vs depression symptoms. Relative age effects were observed on the parent-rated SDQ emotional symptom subscale, which includes both anxiety and depression symptoms, but not on the SMFQ, which specifically measures depressive symptoms. Fourth, research shows that the youngest children in the school year are perceived to have less developed language skills relative to older peers (Norbury et al., 2016). Further research is needed on whether differences in maturity of language development mediate relative age effects on risk of mental health problems.

Lastly, an important issue is whether there is heterogeneity in relative age effects on mental health, i.e., are there subgroups of children who may be particularly vulnerable to these effects? The next chapter (Chapter 4: Testing whether the association between relative age and mental health varies according to ADHD risk: evidence from the ALSPAC cohort (ages 7-25 years)) tests the possibility of identifying relative age effects in more vulnerable groups, such as children with neurodevelopmental disorders (Addicoat et al., 2019) and exploring the extent to which neurodevelopmental disorder traits moderate the relationship between relative age and mental health. This is because there are differences in neurodevelopmental maturity even prior to school entry. Relatively young children are more likely to be diagnosed with neurodevelopmental disorders such as ADHD (Root et al., 2019), but

it is not known whether relative age effects are especially pronounced among children with neurodevelopmental disorders, and whether children with neurodevelopmental disorders who are relatively young constitute a particularly high-risk group that would warrant additional support as they start school. Chapter 4 used measures prior to school entry to disentangle this from any effects of relative age on ratings of neurodevelopmental problems.

3.7 Conclusion

The present chapter provides a long-term longitudinal follow-up examining relative age effects across development using consistent measures of mental health. The chapter examined the plausibility of assumptions of the regression discontinuity design and analyses adjusted for observed covariates. Findings thus suggest a causal relationship between relative age and mental health. The youngest children in the school year have higher parent-rated general risk of mental health problems compared to their older peers. Young relative age may be a risk factor for child and adolescent mental health problems, but there was evidence of change in risk over development and specificity with respect to mental health outcomes with no consistent effect on depressive symptoms.

Chapter 4: Testing whether the association between relative age and mental health varies according to ADHD risk: evidence from the ALSPAC cohort (ages 7-25 years)

4.1 Chapter synopsis

This chapter aimed to fulfil the second primary aim of this thesis, which was to investigate whether neurodevelopmental vulnerability, defined subjectively as high parent-rated ADHD in the pre-school years, or objectively as high genetic susceptibility to ADHD, moderates the effects of age within school year on risk of mental health problems (emotional, behavioural and social difficulties) in childhood, adolescence, and adulthood (ages 7-25 years). As with chapter 3, a general description of the measures and sample used is provided in the chapter 2 (general methods), but are summarised here, and specific study information is presented in the methods section of this chapter.

4.2 Abstract

Objective:

A younger relative age in the school year is a potentially modifiable risk factor for mental health and is also associated with ADHD (chapter 3). Much relative age research has focused on association of relative age with ADHD diagnosis (Holland & Sayal, 2019), but less is known on whether children at higher risk of ADHD are particularly susceptible to relative age effects on mental health. As explained in chapters 1 and 3, the main reason to hypothesise differential effects for children with and without neurodevelopmental problems is that there are differences in neurodevelopmental maturity even prior to school entry.

Method:

This chapter used measures prior to school entry to disentangle neurodevelopmental differences from any effects of relative age on ratings of neurodevelopmental

problems. As an extension to the work carried out in chapter 3, a moderator was added to the regression discontinuity design to investigate how pre-school ADHD risk moderates the relationship between relative age in the school year and mental health in individuals aged 7-25 years in the ALSPAC cohort. Parent-rated pre-school ADHD symptoms, assessed using the parent-rated Strengths and Difficulties Questionnaire (SDQ; see chapter 2), and individual ADHD genetic susceptibility (polygenic risk scores, PRS), were tested as potential moderators of the association between relative age in the school year and mental health assessed using the SDQ total difficulties score.

Results:
Effects of ADHD symptoms and PRS on mental health were found at all ages. However, no statistical evidence of interactions between relative age and pre-school ADHD risk (symptoms or PRS) on mental health was found.

Conclusion:
Relative age and ADHD risk contribute independent effects towards risk of mental health problems across development. The youngest children in the year and those at increased risk of ADHD are more vulnerable to mental health problems but children with ADHD risk are not particularly vulnerable to relative age effects. Further research is needed to test underpinning mechanisms to the relationship between relative age and mental health.

4.3 Introduction

Findings from several studies, including those presented in chapter 3, have indicated that younger relative age is associated with a range of poor outcomes including worse educational achievement and an increased risk of mental health problems and ADHD (Broughton, Langley, Tilling, & Collishaw, 2023; Crawford et al., 2013; Goodman et al., 2003; Root et al., 2019) with evidence that suggests a causal influence of age within school year.

It is unknown if relative age effects are moderated by individual differences; being young for the school year may not affect all children equally. It is important to investigate relative age effects on mental health in individuals who may be particularly susceptible to mental health problems, and a risk stratification approach is useful for this because it will facilitate identification of which children are most likely to be affected (Katki, 2019). Previous research has indicated that children who are young for the school year are more likely to receive a diagnosis of ADHD (Holland & Sayal, 2019; Root et al., 2019) and have higher rates of ADHD problems as shown by elevated SDQ hyperactivity traits in the youngest children in the school years (Chapter 3), but the extent to which children who are already at greater risk for ADHD prior to school are especially susceptible to the effects of being young for the school year remains unknown. Thus, children who already have an elevated risk of neurodevelopmental disorders and are additionally relatively young for their school year may constitute a particularly high-risk group that warrants additional or differentiated support in school.

Recent research indicates that ADHD traits are more strongly predictive of risk of mental health problems than other neurodevelopmental disorder traits, such as those of autism (Hargitai et al., 2023). These findings suggest that ADHD is an especially

strong predictor of poor mental health, but it is unknown whether ADHD risk exacerbates the effect of relative age in the school year on mental health problem risk. ADHD is associated with an earlier-onset manifestation of mental health problems, with worse outcomes (Biederman et al., 2012; Rice, Riglin, Thapar, et al., 2019). Identifying subgroups of children with especially pronounced risk (i.e., children at high ADHD risk who are relatively young for the school year) is potentially useful and important, because children who are at highest risk can be monitored (since not everyone with ADHD and not every child who is young for the year will develop mental health problems). If it is the case that ADHD moderates the effect of relative age, then one implication might be that the youngest children in the school year with ADHD could be prioritised for specific interventions, such as a more flexible school entry.

A recent Swedish record-linkage study, described in more detail in chapter 1, identified a negative interaction between young relative age and ADHD for depression (OR = 0.78 [0.64–0.95] (Kuntsi et al., 2022)), contrary to the hypothesis that ADHD exacerbates risk of young relative age. This was interpreted by the authors that relatively young children with ADHD were more likely to have less severe ADHD, suggesting that there may have been a lower threshold for diagnosis of ADHD for relatively young children (Kuntsi et al., 2022). However, Kuntsi et al.'s paper specifically examined ADHD diagnoses during the school years; those with a first diagnosis prior to age 6 years (i.e., the age of starting school in Sweden) were excluded. ADHD itself in Kuntsi et al.'s paper is in part a function of likelihood of being referred and being diagnosed which may vary for younger and older children in the school year. The main reason to hypothesise differential effects for children with

and without neurodevelopmental problems is that even before children enter school there are individual differences in neurodevelopmental maturity.

No study to our knowledge has tested this question by taking the approach of stratifying by measures of ADHD risk before school entry. This temporal precedence is important to maintain independence of ADHD risk group from the effects of school environment. As shown in chapter 3, most mental health problems (behavioural and social difficulties) before school entry are not influenced by relative age effects. Furthermore, within the same chapter it was demonstrated that effects of relative age within the school year (including on the hyperactivity subscale) only start after school entry in the ALSPAC cohort.

The current study uses two approaches to identify early ADHD risk. The first involves subjective parent ratings of observed early ADHD symptoms. However, it is important to consider the potential for rater bias where parents may respond to questionnaires differently under different circumstances, and in principle could still be subject to relative age effects. Genetic ADHD risk is an objective measure that overcomes this potential problem but has the disadvantage that it is only weakly related to ADHD diagnosis (Demontis et al., 2019; Wray et al., 2007). Demontis et al (2019) found that ADHD PRS was associated with ADHD case/control status, and identified a dose-dependent relationship for this, with higher ADHD PRS associated with a greater likelihood of being an ADHD case (OR: 1.56 [95% CI: 1.53, 1.60]). PRS for ADHD have also been associated with mental health problem risk in independent cohorts (Riglin, Leppert, et al., 2021). Therefore, ADHD PRS can be used as a proxy for ADHD risk that is independent of relative age effects.

In summary, ADHD and young relative age are both known risk factors for poor mental health, including anxiety and depression. However, there is considerable variation in mental health outcomes for children in these higher risk groups. Understanding whether ADHD exacerbates relative age effects can help inform more refined decisions can be made on the targeting and personalisation of interventions for children at particularly high risk. Furthermore, it is beneficial that research prioritises risk factors that are potentially modifiable and exert a causal influence on mental health symptoms such as emotional, behavioural and social difficulties. The use of a regression discontinuity design to examine the role of relative age and the use of multiple independent measures of ADHD risk advance our understanding of causal influence.

The purpose of this chapter was to investigate whether ADHD traits and/or genetic risk interact with, or provide additive effects towards, the relationship between relative age and mental health problems. The hypothesis that any association between effects of relative age within the school year and mental health problems will be stronger for children at risk for a neurodevelopmental disorder (ADHD) than for those without, was tested. To test this, the impact of relative age was measured, as well as of the role of early ADHD risk measured using parent ratings of hyperactivity before school entry or as ADHD genetic risk (PRS). Mental health problems were assessed in the school years, and in early adulthood (7-25 years).

4.4 Methods

4.4.1 Sample

This chapter utilises the same ALSPAC sample as previously described in detail in chapter 2 (section 2.2).

4.4.2 Age in school Year

As described in Chapter 2, the main exposure variable of the present study is relative age within the school year. In the main analysis, the standardised effect size of relative age, i.e., the mean change in standardised outcome score (see section 4.4.3 below) per 1 year difference in relative age, was measured, henceforth "standardised effect size".

4.4.3 Mental health outcomes

Standardised parent-rated Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) subscale scores (conduct, hyperactivity, emotional and peer problem scores) were used to measure emotional, behavioural, and social difficulties as symptoms of mental health problems. As a secondary analysis, the total difficulties score (comprised of all subscale scores added together) was used to measure general mental health problem risk. The SDQ was administered at seven timepoints between 7-25 years. Further information is presented in chapter 2 (section 2.2).

4.4.4 Definitions of ADHD risk

ADHD risk was assessed in two ways: first, by stratifying into groups by parent-rated ADHD symptoms at age 4 (SDQ-hyperactivity subscale) and second, in terms of genetic susceptibility (continuous ADHD PRS). In this study, a categorical cut-off for ADHD symptom scores was used to make comparisons between individuals, and PRS was used as a continuous measurement. This study was interested in whether

individuals who were young for their school year and already at higher risk for ADHD were especially vulnerable to mental health problems.

4.4.5 ADHD Symptoms

The parent-report SDQ hyperactivity subscale at 47 months (hence, 4 years) was chosen to define ADHD symptom groups before school entry. The SDQ hyperactivity subscale comprises 5 items, and scores range from 0 to 10. ADHD symptom risk groups were classified based on the 3-band categorisation of the SDQ (Goodman et al., 1997). This categorisation has been shown to reliably identify the top 10% of the population at high risk for ADHD using a cut-off of 7, and scores of 6 and 0-5 to identify those at borderline and low risk respectively (Green et al., 2005; Riglin, Agha, et al., 2021). In the main analysis, the standardised effect size of ADHD symptoms was measured (hence “standardised effect size”); this was defined as the mean change in standardised outcome score in the borderline or high-risk group compared to the low-risk ADHD group.

4.4.6 ADHD Polygenic Risk Scores

Polygenic risk scores (PRS) for ADHD were generated and derived by Riglin et al using the most up-to-date genome-wide association study of ADHD at the time as the discovery sample (Demontis et al., 2019; Riglin, Leppert, et al., 2021). Full details of how the PRS were derived for this chapter are presented elsewhere (Riglin, Leppert, et al., 2021). In the main analysis of this chapter, risk alleles were defined as those that were associated with case-status at $p<0.05$. Thresholds of $p<0.001$, $p<0.005$, $p<0.01$, $p<0.05$, $p<0.1$, and $p<0.5$ were additionally utilised in sensitivity analyses. PRS were standardised using Z-score transformation prior to analysis and used as a continuous measurement of ADHD genetic risk. The first five principal components of ancestry were adjusted for to control for population

stratification. Figure 2.2, in chapter 2 outlines the availability of data for subsamples used to capture early ADHD symptom and genetic risk in the present chapter. In the main analysis, the standardised effect size of PRS (hence, “standardised effect size”) was measured, this was defined as mean change in standardised outcome score per 1 standard deviation unit change in PRS.

4.4.7 Design

A regression discontinuity design was used, as described in more detail in chapter 2 (sections 2.4.1 and 2.4.2). Individuals who did not have SDQ data at any timepoint were excluded from analysis (N = 3527). Participants were excluded from analysis of ADHD symptoms scores as a moderator if they had no information on hyperactivity data at age 4 (N= 1944). When looking at PRS scores, individuals who had no data on SDQ (N=3527) and PRS (N=4183) were excluded (N excluded = 7710).

As in chapter 3, the exposure is “age at starting school” and the running variable is “week of birth”, with the discontinuity on 1st September. A “sharp” RD design was chosen given the strict cut-off date for school year selection in England and Wales. The age at which each questionnaire was completed varied across participants, but there was no difference in mean ages of completion between August born and September born children (see table A2.4, in appendices). The age of children at completion of questionnaires (in months, to nearest month) was controlled for as a covariate.

4.4.8 Statistical Analysis

A regression discontinuity design was used to compare the relative risk of mental health problems by relative age in school year and ADHD risk (early symptoms or PRS), and it tested interactions between relative age in the school year and ADHD

risk. Analyses were repeated for mental health outcomes assessed at each outcome age (7-25 years).

As a first step, general demographic information for individuals who had at least one measurement of mental health was summarised (see chapter 2 table 2.8). Demographic information and descriptive statistics are provided again for those who also had available ADHD symptom data at age 4, stratified by ADHD risk (low/borderline/high; table 4.1, below), and those who had available genetic risk data (table 4.2, below). Following this, the effects of relative age, age 4 ADHD symptom group, and the interactions between these variables on mental health outcomes (emotional, behavioural and social difficulties) between the ages of 7 and 25 years were tested. Third, the effects of relative age, ADHD genetic risk, and the interactions between these variables on mental health outcomes between the ages of 7 and 25 years were tested.

Since selective attrition is an inevitable problem in longitudinal research such as this, complete cases were compared with those who had incomplete data, and multiple imputation by chained equations (MI) was used to attempt to account for bias caused by this attrition. The main analysis for this chapter used this imputed data. Maternal depression trait scores (as measured by the Edinburgh Postnatal Depression Score (Cox et al., 1987)) sex, age of mother at birth, and age of completion of questionnaire were included in the imputation models as covariates.

Multiple imputation variables and models, and the percentage of data missing from these variables/models are presented in the appendices (Table A4.1 and A4.2). Checks were performed on whether a sufficient number of imputations was done following guidelines; as in chapter 3, 200 imputations were conducted (White et al.,

2011). As in chapter 3, complete-case analyses and generalized estimating equations models (GEE) are presented as sensitivity analyses (Liang & Zeger, 1986).

In line with how analyses were conducted in chapter 3, the analysis was carried out in three ways; first, where the exposure (age in school year) was continuous (coded 0-51) throughout the school year and there was no selection window near the cut-off. Second, analysis was restricted to those born up to four weeks either side of the September 1st cut-off ("4 weeks"), and lastly, restricted to those born up to eight weeks either side of the cut-off ("8 weeks"). The four-week and eight-week bandwidths only compare those with birthdates within those time windows around September 1st. After bandwidth selection, local linear regressions were fitted on observations within the bandwidth to estimate the effect of relative age.

4.4.8.1 Imputation for mental health risk at ages 7-25 years, relative age within the school year, ADHD symptom group, and interactions

Multiple imputation was carried out on a maximum sample of those with at least one mental health measure (N 9172 participants, of which 7084 were in the low (SDQ scores of <=5) hyperactivity risk score group, 925 were in the borderline (SDQ scores of =6) group, and 1168 were in the high (>7) risk group for ADHD). Multiple imputation was performed separately within each of the ADHD symptom group groups for the interaction between ADHD symptom group and relative age within the school year.

4.4.8.2 Imputation for mental health risk at ages 7-25 years, ADHD polygenic risk (PRS) and interaction

For the PRS analysis, multiple imputation was carried out on a maximum sample of those with at least one outcome measure, and who had genotype data (N PRS

analysis = 6933). Age of mother at birth, sex, mother's depression trait scores, and the first five principal components of ancestry were included. Since PRS was used as a continuous measurement, interactions were included within the imputation model for PRS.

4.4.8.3 Sensitivity and secondary analyses

To test robustness of findings, complete-case findings at each outcome point were analysed. In addition, generalised estimating equation (GEE) models were implemented as a sensitivity analysis. GEE models have some robustness to attrition, but do not rely on the use of imputed data (Liang & Zeger, 1986). The outcome for the GEE model was SDQ total difficulties scores, and the exposures were: ADHD symptom group*relative age in school year*age, with all two-way interactions between these variables. The GEE for the ADHD genetic risk model included PRS*relative age in school year*age, with all two-way interactions between these variables, plus principal components.

Secondary analyses tested associations with SDQ total difficulties by relative age, age 4 ADHD SDQ symptom group, and PRS.

Replication analyses used different PRS thresholds for analyses of genetic risk ($p < .001$, $p < .005$, $p < .01$, $p < .10$, $p < .50$). All analyses were conducted using Stata (v16.1 SE, StataCorp LLC, College Station, TX).

4.5 Results

4.5.1 Demographics and patterns of missing data

Section 2.5 in chapter 2 describes demographic characteristics. Table 4.1 describes demographic characteristics stratified by ADHD risk. Children with high ADHD risk were more likely to be boys and have a lower socioeconomic status (SES; measured by mother's education as a proxy variable for SES). Table 2.9 in chapter 2 shows a similar pattern of covariate distribution between children born August vs September, suggesting there was no discontinuous relationship between 'pre-treatment' covariates and relative age. PRS for ADHD did not differ between children born in August or September.

Similar patterns of missing data according to month of birth were also found. Participants with complete records at all ages and assessments were more likely to be female, first-born, white, with parents who are older, non-smokers, higher educated and less depressed than those with incomplete data. Participants who had available PRS data were also more likely to be born to older and less depressed parents and have fewer mental health problems on the SDQ (table 2.9, table 4.2, table 4.3). For each SDQ subscale measure, higher scores are indicative of greater risk of mental health problems.

Table 4.1: Descriptive statistics, stratified by ADHD risk.

	Low ADHD risk		Borderline ADHD risk		High ADHD risk	
Variable	N	Mean (SD)/ %	N	Mean (SD)/ %	N	Mean (SD)/ %
Age of mother at birth (years)	6,775	29.00 (4.60)	877	28.09 (4.55)	1,099	28.06 (4.79)
Alcohol during pregnancy (% yes)	6,751	52.81	870	53.22	1,099	51.68
Birth size (% Multiple)	7,084	1.10	925	1.51	1,168	1.20
Birthweight (g)	7,006	3438.54 (535.11)	910	3397.33 (543.20)	1,158	3393.69 (557.34)
Caesarean (% yes)	6,751	10.46	874	9.73	1,094	8.96
Ethnicity	6,725	96.24	888	96.28	1,103	95.29
Gestation (weeks)	7,084	39.51 (1.78)	925	39.42 (1.89)	1,168	39.39 (1.95)
Home Ownership (% Owned)	6,908	81.09	898	75.95	1,122	73.44
Maternal depression (EPDS score)	6,431	6.32 (4.54)	856	7.14 (4.77)	1,051	7.76 (4.90)
Mother's Education (% degree)	6,594	16.99	844	9.72	1,077	10.12
Parity (% >1)	6,871	52.95	892	54.15	1,116	57.89
Sex (% Female)	7,084	50.90	925	43.68	1,168	38.78
Smoking during pregnancy (% yes)	6,788	15.78	877	22.01	1,101	21.62

Low ADHD risk = SDQ hyperactivity scores at 4 years of age <=5; Borderline ADHD risk = SDQ hyperactivity scores at 4 years of age = 6; High ADHD risk = SDQ hyperactivity scores at 4 years of age >=7.

Table 4.2: Descriptive statistics of participants with available ADHD polygenic risk data

	Total		August		September		Aug vs Sept	
Variable	N	Mean (SD)/ %	N	Mean (SD)/ %	N	Mean (SD)/ %	Mean diff	95% CI
Age of mother at birth (years)	6,311	29.09 (4.57)	604	29.40 (4.72)	636	28.66 (4.58)	0.74	0.22, 1.25
Alcohol in pregnancy (% yes)	6,302	54.89	601	53.24	635	53.23	0.02	-5.56, 5.59
Birth size (% multiple)	6,933	0.92	659	0.46	693	1.01	-0.55	-1.47, 0.36
Birthweight (g)	6,577	3443.04 (528.56)	640	3479.27 (515.36)	666	3439.67 (501.43)	39.60	-15.60, 94.79
Caesarean (% yes)	6,287	10.05	602	10.96	633	9.32	1.64	-1.73, 5.01
Crowding index (%>1)	6,420	4.24	620	4.03	643	4.51	-0.48	-2.71, 1.76
Ethnicity (%non-white)	6,343	0.24	617	0.65	639	0.31	0.34	-0.43, 1.10
Home ownership (% yes)	6,492	81.89	627	82.78	653	80.25	2.53	-1.73, 6.79
Gestation (weeks)	6,657	39.51 (1.79)	642	39.59 (1.80)	676	39.60 (1.72)	-0.01	-0.20, 0.18
Mat. Depression score (EPDS)	6,070	6.52 (4.61)	602	6.15 (4.53)	594	6.34 (4.73)	-0.19	-0.71, 0.34
Mat. Education (% degree)	6,202	17.27	603	16.75	632	15.19	1.56	-2.53, 5.65
Parity (% 1)	6,461	54.95	622	54.82	648	53.09	1.74	-3.76, 7.23
Sex (% female)	6,933	49.13	659	48.41	693	46.75	1.65	-3.68, 6.99
Smoking in pregnancy (% yes)	6,323	15.86	604	17.05	636	17.77	-0.71	-4.95, 3.52

August = August-born children; September= September-born children. "Aug vs Sept" = Mean comparison between children born in August and children born in September.

Table 4.3: Descriptive comparisons by PRS data availability

	No available PRS data (N=4183)		PRS data available (N=6933)		Comparison by data availability		
Variable	N	Mean (SD)	N	Mean (SD)	Mean Difference	[95% conf.	interval]
Age of mother at birth (years)	3,680	27.99 (4.78)	6,311	29.09 (4.57)	-1.10	-1.29	-0.91
Alcohol in pregnancy (% yes)	3,654	47.54	6,302	54.89	-7.35	-9.38	-5.32
Birth size (% multiple)	4,182	1.75	6,933	0.92	0.82	0.40	1.25
Birthweight (g)	3,991	3391.60 (555.61)	6,577	3443.04 (528.56)	-51.44	-72.64	-30.24
Caesarean (% yes)	3,669	10.30	6,287	10.05	0.25	-0.98	1.48
Crowding index (%>1)	3,764	6.96	6,420	4.24	2.72	1.83	3.62
Ethnicity (%non-white)	3,668	10.99	6,343	0.24	10.75	9.96	11.54
Gestation (weeks)	4,036	39.42	6,657	39.51	-0.08	-0.16	-0.01
Home ownership (% yes)	3,833	72.08	6,492	81.89	-9.80	-11.44	-8.16
Mat. Education (% degree)	3,553	10.55	6,202	17.27	-6.71	-8.17	-5.25
Mat. Depression score (EPDS)	3,531	7.08 (4.90)	6,070	6.52 (4.61)	0.56	0.36	0.76
Parity (% 1)	3,811	54.29	6,461	54.95	-0.65	-2.65	1.34
Sex (% female)	4,183	48.31	6,933	49.13	-0.81	-2.73	1.11
Smoking in pregnancy (% yes)	3,685	21.00	6,323	15.86	5.14	3.59	6.69
SDQ Total 7 Years	2,789	7.75 (4.94)	5,492	7.34 (4.67)	0.41	0.19	0.63
SDQ Total 8 Years	2,407	8.17 (5.41)	5,262	7.69 (5.11)	0.48	0.23	0.73
SDQ Total 9 Years	2,434	7.30 (5.26)	5,500	6.69 (4.82)	0.61	0.37	0.84
SDQ Total 11 Years	2,140	6.82 (5.18)	5,113	6.45 (4.89)	0.38	0.13	0.63
SDQ Total 13 Years	2,022	7.06 (5.28)	4,911	6.70 (4.87)	0.36	0.10	0.61
SDQ Total 16 Years	1,510	6.32 (4.82)	4,044	6.08 (4.75)	0.24	-0.04	0.52
SDQ Total 25 Years	1,080	6.13 (5.37)	2,996	5.47 (5.00)	0.66	0.30	1.01

Restricted to those with at least one measurement of SDQ over time.

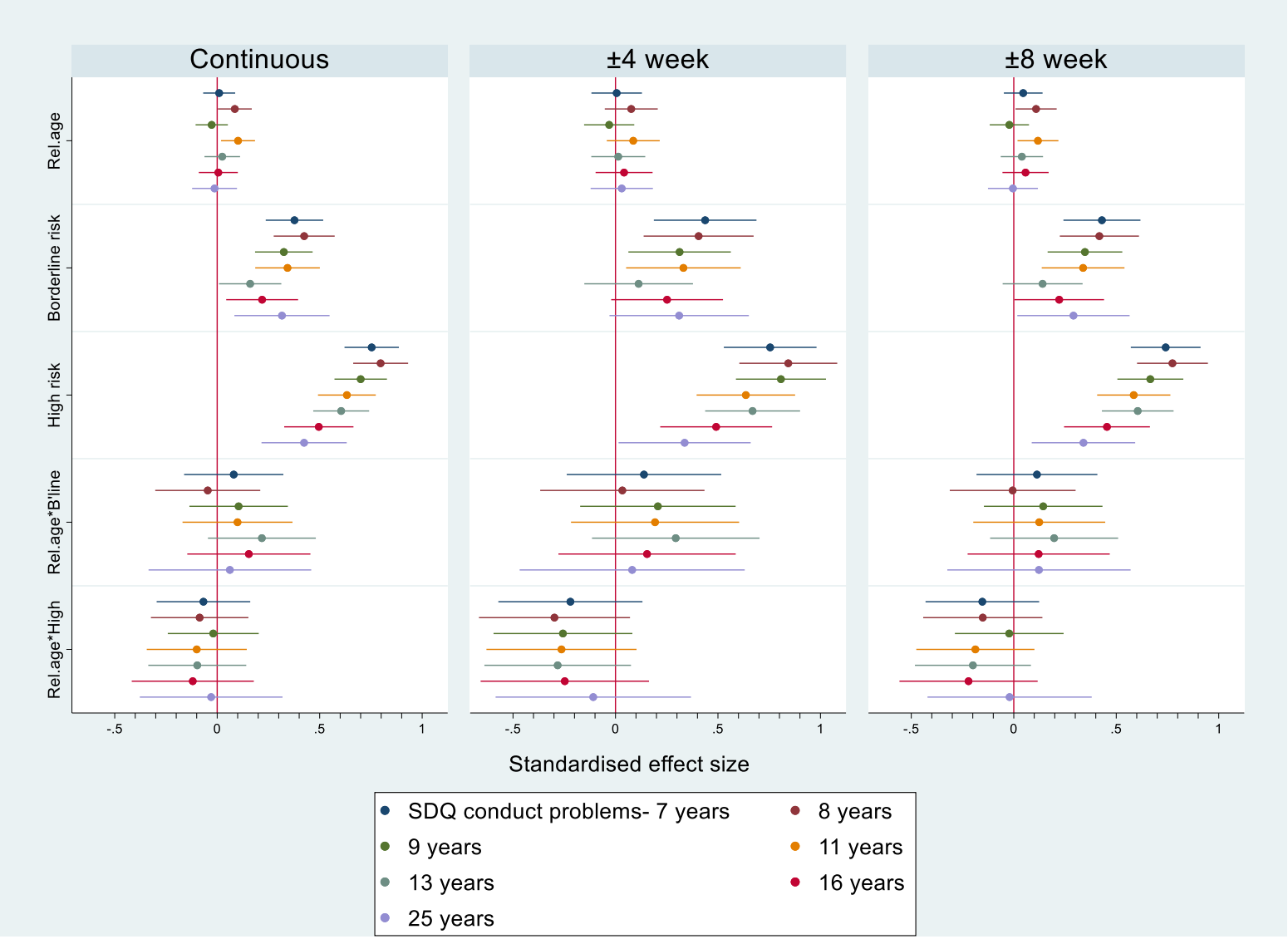
4.5.2 Primary analyses: Relative age, ADHD genetic risk and their interaction: associations with SDQ subscale scores (ages 7-25 years).

Findings for SDQ subscale scores by relative age and interactions with ADHD symptom scores and genetic risk are presented. A summary table of the continuous score analyses for the ADHD symptom group analyses is presented as table 4.4, below. A summary table of the continuous score analyses for the PRS analyses is presented as table 4.5. Further information on subscale analyses restricting participants to 4 or 8 weeks either side of the cut-off are presented in the appendices (appendix tables A4.3- A4.6).

4.5.2.1 Conduct problems

As shown in figure 4.1 and 4.2 (and table 4.4 and 4.5), no statistical evidence of effects of relative age on conduct problems was observed, in line with chapter 3 (see table 3.6). However, both ADHD symptom scores and ADHD PRS were positively associated with conduct problems at all timepoints measured, including at 25 years. There was no evidence of interactions between relative age and PRS on conduct problems at any age and for either ADHD symptom score or PRS, with all coefficients crossing the null. Interaction effects were largely positive in direction for those with borderline ADHD, but negative for those at highest risk.

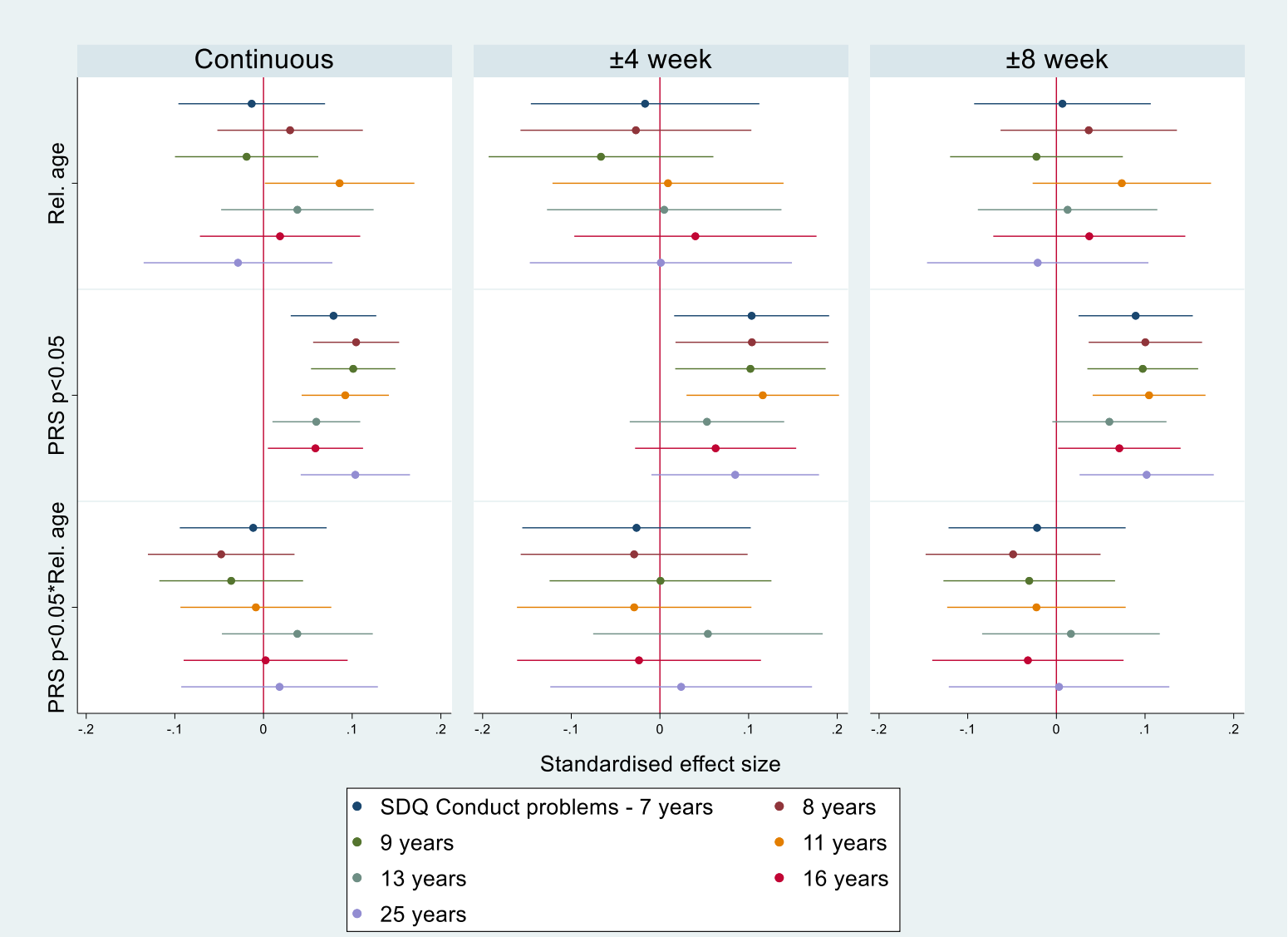
Figure 4.1: Coefficient plots of parent-rated mean standardised SDQ conduct problems, stratified by ADHD symptom group. Effects of relative age (within the school year), ADHD symptom group (SDQ hyperactivity scores at 4 years) and their interactions.



"Borderline risk"/ = Borderline risk group for ADHD symptoms by SDQ 3-band cut-off categorisation (SDQ=6); "High risk" = High risk group for ADHD symptoms (SDQ >=7). Imputed data. Unadjusted models. Standardised effect size: mean change in standardised SDQ conduct problems subscale score per

1 year difference in relative age (for Rel.Age) or mean change in standardised parent-report SDQ conduct problems subscale score compared to low-risk ADHD group (ADHD symptom group). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born ±4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born ± 8 weeks either side of the September 1st cut-off. N=9172

Figure 4.2: – Coefficient plot of parent-rated mean standardised SDQ conduct problems ages 7-25 years: associations with relative age, ADHD polygenic risk and their interaction



"Rel. Age" = Relative age within the school year; "PRS p<0.05" = ADHD polygenic risk alleles at p<0.05 threshold. Imputed data. Unadjusted models. Standardised effect size: mean change in standardised parent-report SDQ conduct problems subscale score per 1 year difference in relative age (Rel.Age), or

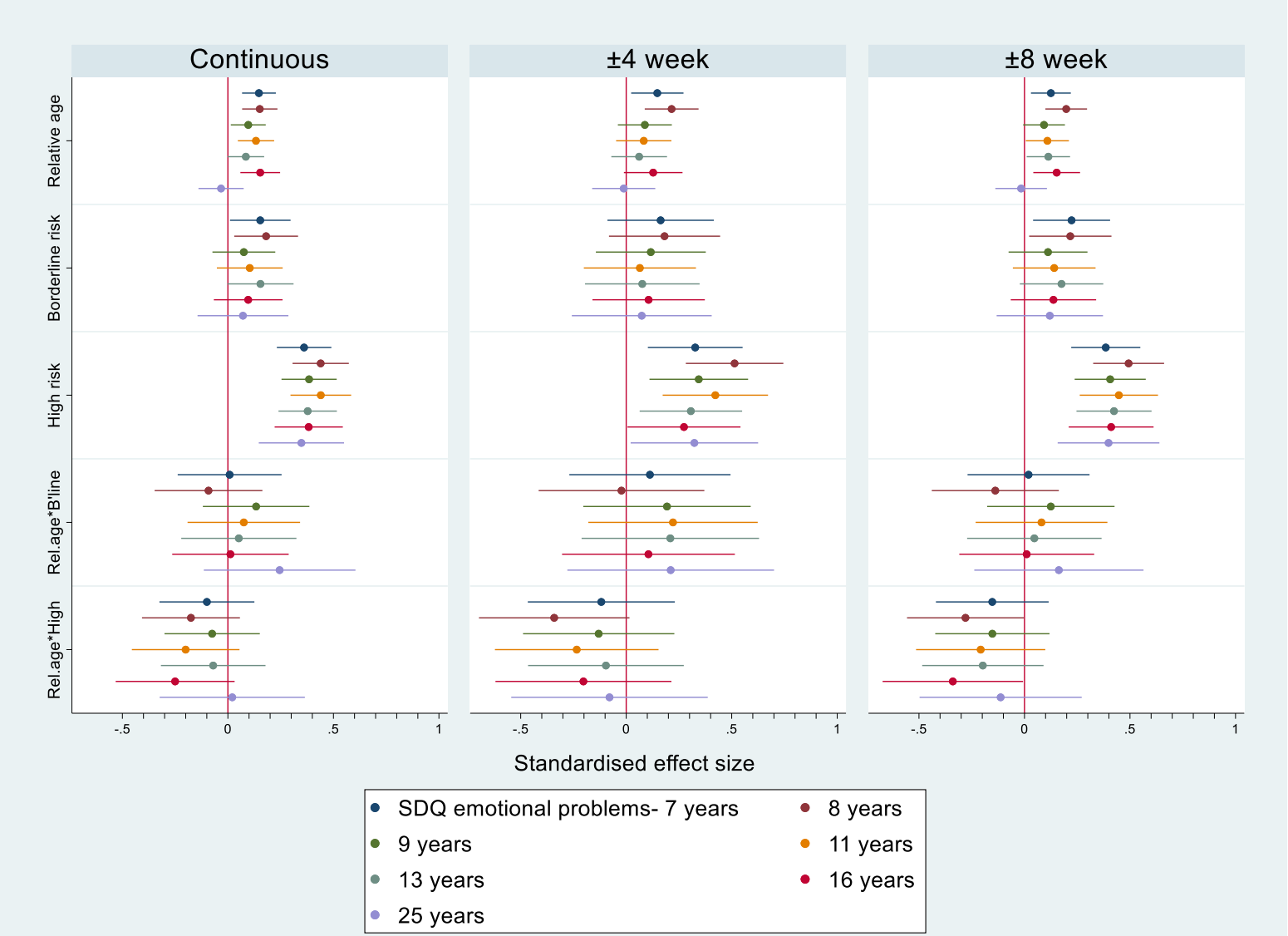
mean change in standardised parent-report SDQ conduct problems subscale score per 1 SD unit change in PRS (PRS). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born up to 4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born 8 weeks either side of the September 1st cut-off. N=6933

4.5.2.2 Emotional problems

4.5.2.2.1 ADHD risk groups

For ADHD symptom scores, relative age was associated with emotional problems up to age 16, but not at age 25, as shown on figure 4.3. Evidence of effects of early ADHD symptoms on emotional problems was not consistently observed for children with borderline ADHD; effects were all positive, but 95% CIs were wide and spanned the null. For those at high risk, there was evidence of persistent effects of ADHD on emotional problems. There was no evidence for interaction effects between relative age and ADHD for either group; effects were mostly positive for the borderline group, and negative for the high-risk group, but 95% CIs were wide and spanned the null.

Figure 4.3: Coefficient plots of parent-rated mean standardised SDQ emotional problems, stratified by ADHD symptom group. Effects of relative age (within the school year), ADHD symptom group (SDQ hyperactivity scores at 4 years) and their interactions.



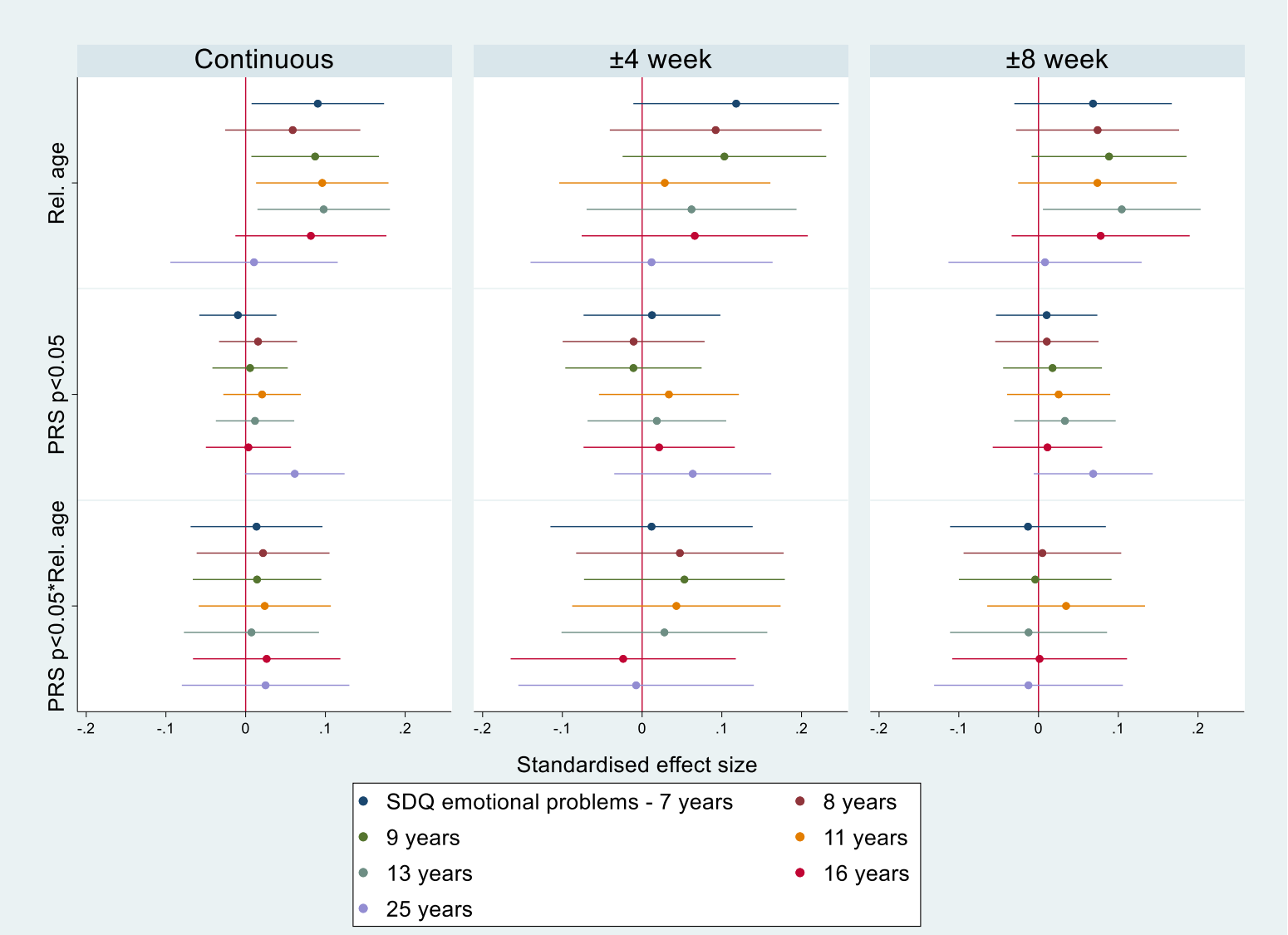
"Borderline risk"/ = Borderline risk group for ADHD symptoms by SDQ 3-band cut-off categorisation (SDQ=6); "High risk" = High risk group for ADHD symptoms (SDQ >=7). Imputed data. Unadjusted models. Standardised effect size: mean change in standardised parent-report SDQ emotional problems

subscale score per 1 year difference in relative age (for Rel.Age) or mean change in standardised parent-report SDQ emotional problems subscale score compared to low-risk ADHD group (ADHD symptom group). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born ±4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born ± 8 weeks either side of the September 1st cut-off. N=9172

4.5.2.2.2 PRS analysis

In the PRS analysis, relative age was associated with emotional problems up to age 13, except at age 8, as shown on figure 4.4. There was no evidence that relative age was associated with emotional problems after age 13. There was no evidence of effects of ADHD PRS on emotional problems at ages 7-16. There was a marginal association of ADHD PRS and emotional problems at age 25 years which was positive in direction. No evidence of interactions between relative age and PRS on emotional problems was found.

Figure 4.4: – Coefficient plot of parent-rated mean standardised SDQ emotional problems ages 7-25 years: associations with relative age, ADHD polygenic risk and their interaction



"Rel. Age" = Relative age within the school year; "PRS p<0.05" = ADHD polygenic risk alleles at p<0.05 threshold. Imputed data. Unadjusted models. Standardised effect size: mean change in standardised parent-report SDQ emotional problems subscale score per 1 year difference in relative age (Rel.Age),

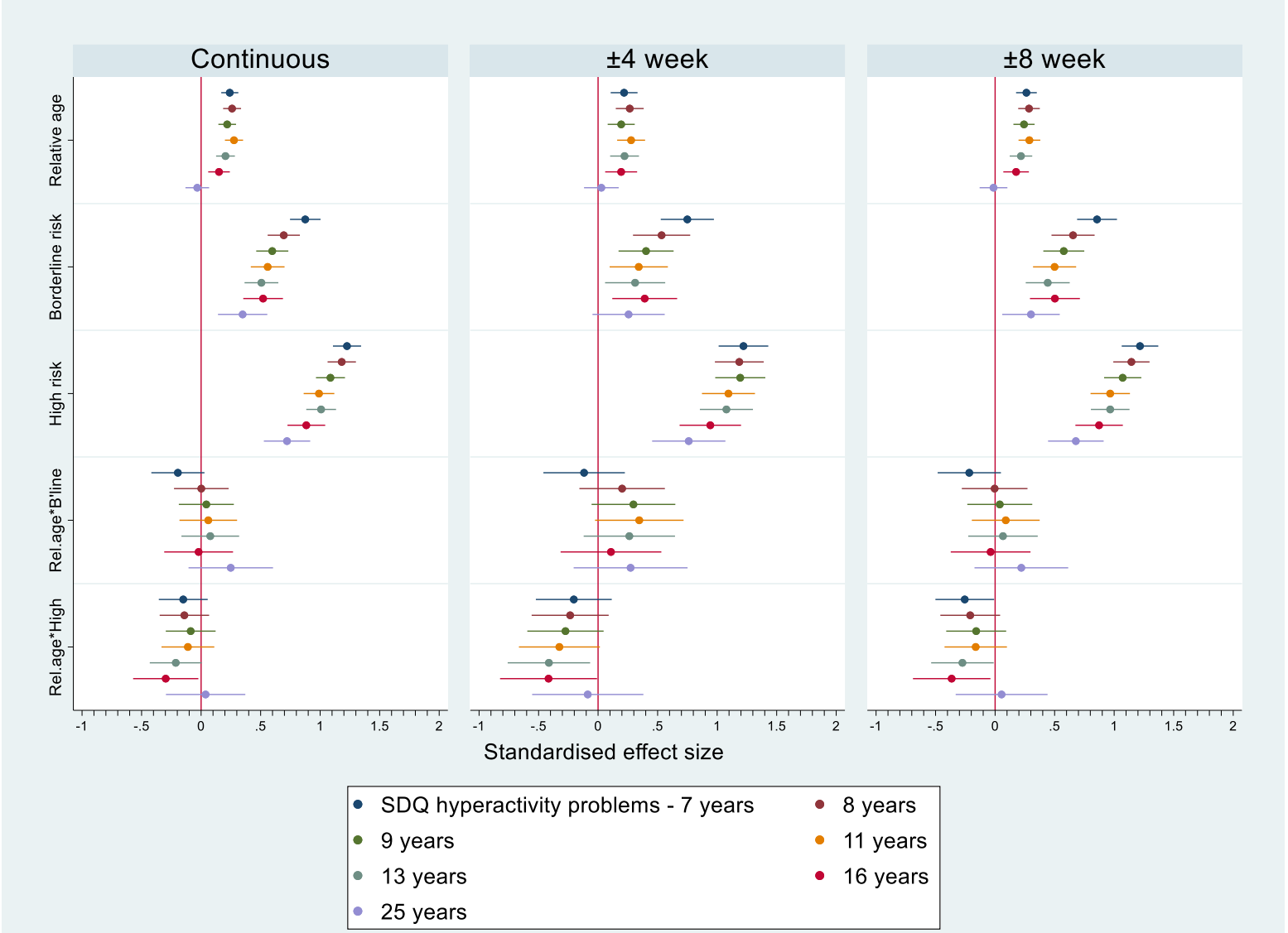
or mean change in standardised parent-report SDQ emotional problems subscale score per 1 SD unit change in PRS (PRS). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born up to 4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born 8 weeks either side of the September 1st cut-off. N=6933

4.5.2.3 Hyperactivity problems

4.5.2.3.1 ADHD risk groups

As shown on figure 4.5, relative age was more strongly associated with hyperactivity problems than other SDQ subscales. ADHD symptoms at age 4 in borderline and high ADHD risk groups predicted ADHD symptoms at all later ages. No statistical evidence of interaction effects was observed; effects were largely positive in the borderline ADHD group, and negative in the high-risk group.

Figure 4.5: Coefficient plots of parent-rated mean standardised SDQ hyperactivity problems, stratified by ADHD symptom group. Effects of relative age (within the school year), ADHD symptom group (SDQ hyperactivity scores at 4 years) and their interactions.



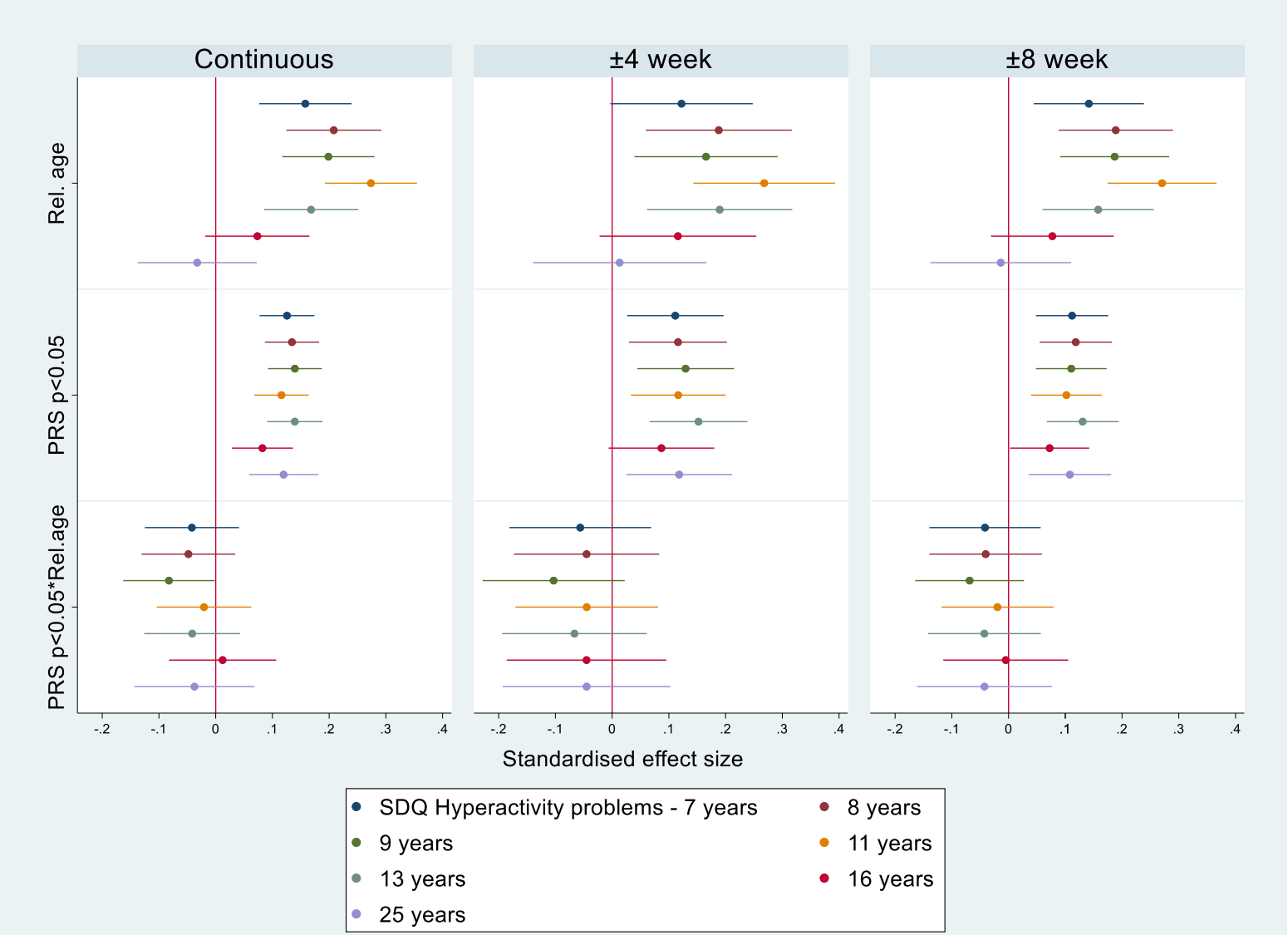
"Borderline risk"/ = Borderline risk group for ADHD symptoms by SDQ 3-band cut-off categorisation (SDQ=6); "High risk" = High risk group for ADHD symptoms (SDQ >=7). Imputed data. Unadjusted models. Standardised effect size: mean change in standardised parent-report SDQ hyperactivity problems

subscale score per 1 year difference in relative age (for Rel.Age) or mean change in standardised parent-report SDQ total difficulties score compared to low-risk ADHD group (ADHD symptom group). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born ±4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born ± 8 weeks either side of the September 1st cut-off. N=9172

4.5.2.3.2 PRS analysis

As shown on figure 4.6, relative age effects on hyperactivity were more strongly associated with hyperactivity problems than other SDQ subscales, up to age 16 years. In addition, ADHD PRS was associated with hyperactivity problems at all timepoints. No statistical evidence was found for any interactions between relative age and PRS on hyperactivity except for a marginal association at 9 years; most interaction effects were negative in direction, but with 95% CIs spanning the null.

Figure 4.6: – Coefficient plot of parent-rated mean standardised SDQ hyperactivity problems ages 7-25 years: associations with relative age, ADHD polygenic risk and their interaction



"Rel. Age" = Relative age within the school year; "PRS p<0.05" = ADHD polygenic risk alleles at p<0.05 threshold. Imputed data. Unadjusted models. Standardised effect size: mean change in standardised parent-report SDQ hyperactivity problems subscale score per 1 year difference in relative age

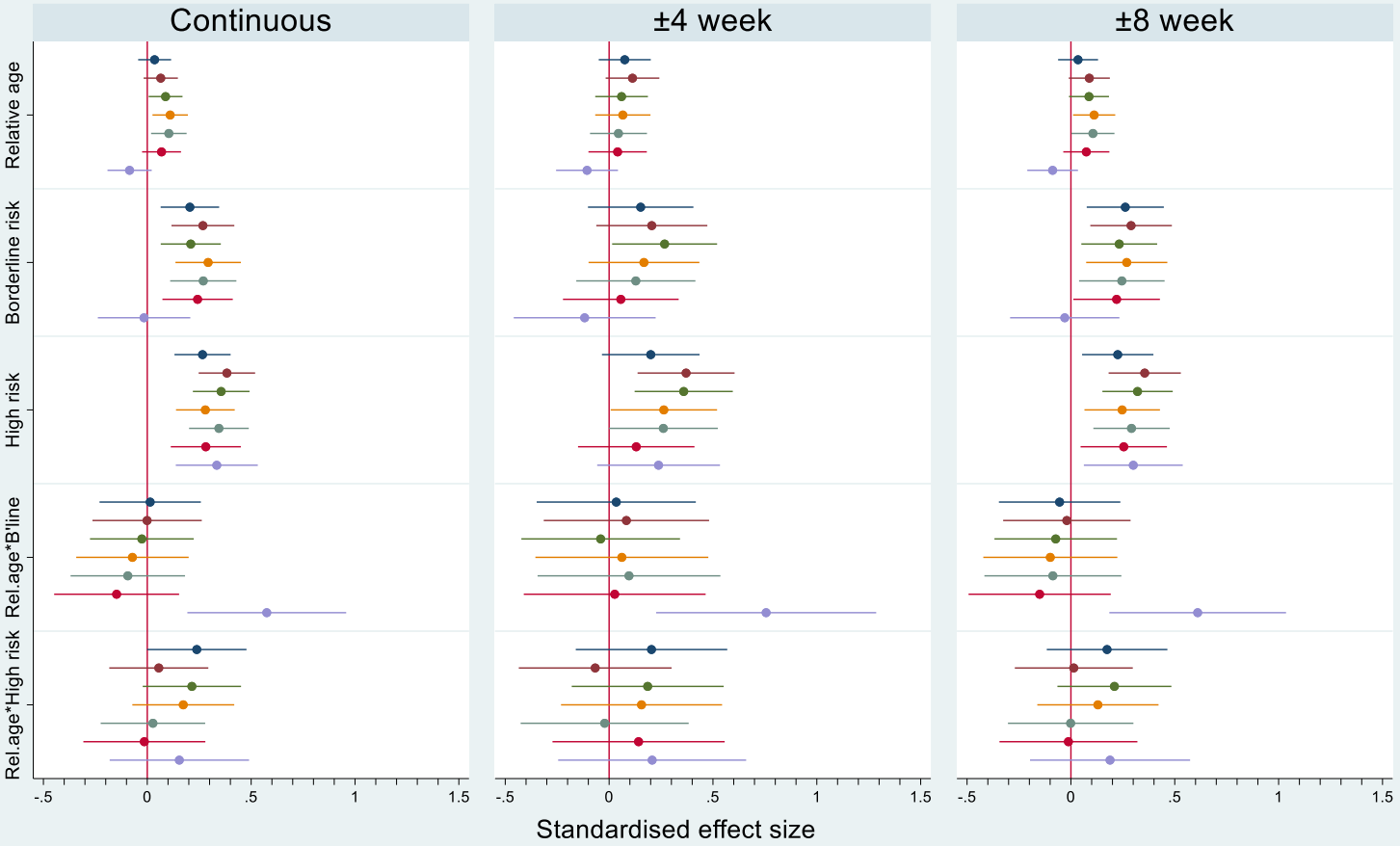
(Rel.Age), or mean change in standardised parent-report SDQ total difficulties score per 1 SD unit change in PRS (PRS). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born up to 4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born 8 weeks either side of the September 1st cut-off. N=6933

4.5.2.4 Peer problems

4.5.2.4.1 ADHD symptom groups

As shown in figure 4.7. main effects of relative age on peer problems between ages 9-13 years were observed but not at other ages; effects were still mostly positive (except at age 25). ADHD symptom group at age 4 was associated with peer problems scores throughout development, apart from borderline ADHD group and peer problems at age 25. No statistical evidence of interactions of relative age was found except for a marginal, positive interaction at age 7 in the high-risk group and a positive interaction at age 25 in the borderline risk group.

Figure 4.7: Coefficient plots of parent-rated mean standardised SDQ peer problems, stratified by ADHD symptom group. Effects of relative age (within the school year), ADHD symptom group (SDQ hyperactivity scores at 4 years) and their interactions.



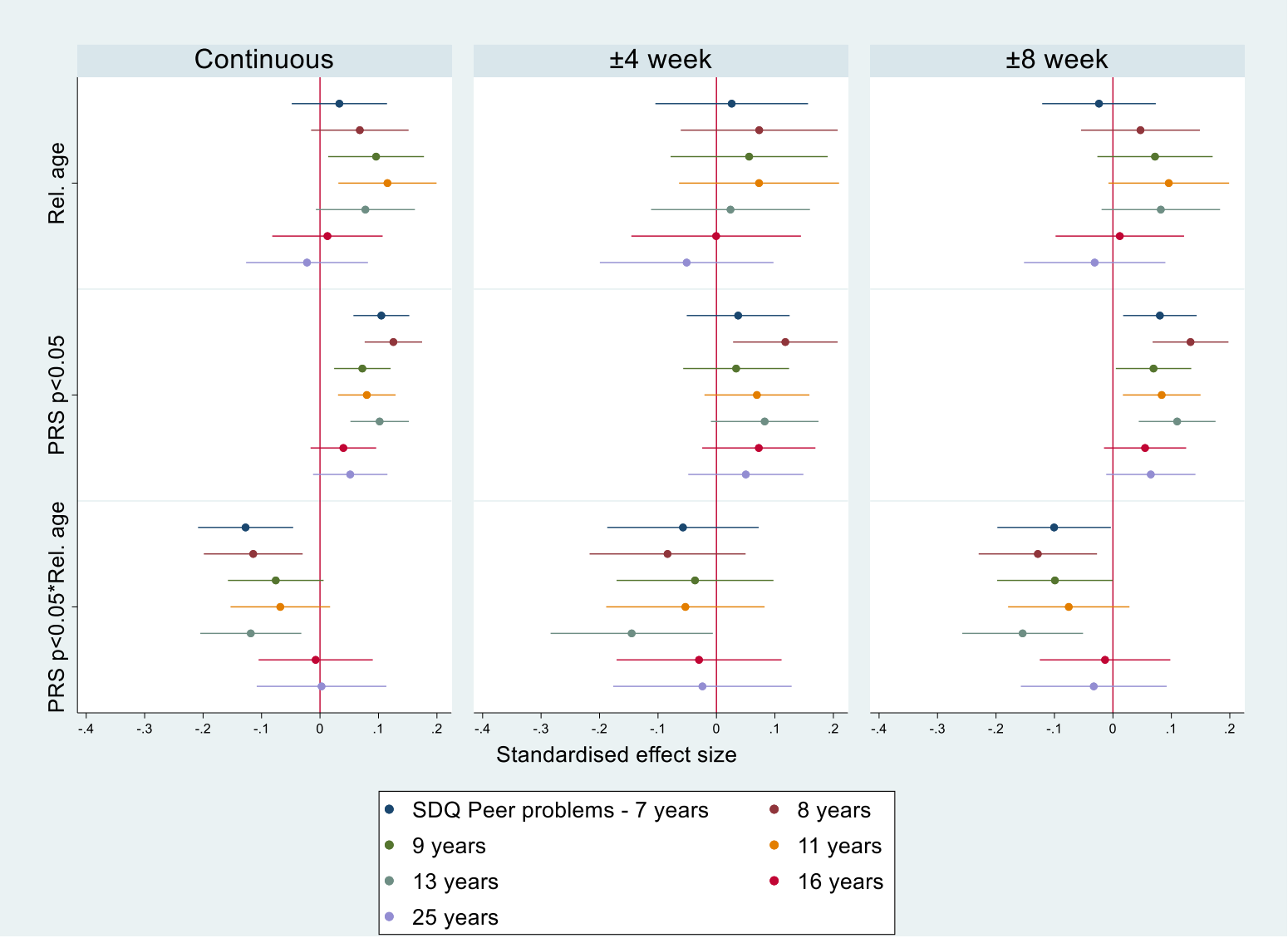
"Borderline risk"/ = Borderline risk group for ADHD symptoms by SDQ 3-band cut-off categorisation (SDQ=6); "High risk" = High risk group for ADHD symptoms (SDQ >=7). Imputed data. Unadjusted models. Standardised effect size: mean change in standardised parent-report SDQ peer problems subscale

score per 1 year difference in relative age (for Rel.Age) or mean change in standardised parent-report SDQ total difficulties score compared to low-risk ADHD group (ADHD symptom group). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born ±4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born ± 8 weeks either side of the September 1st cut-off. N=9172

4.5.2.4.2 PRS analysis

As shown on figure 4.8, main effects of relative age on peer problems at 9 years and 11 years were found. No statistical evidence was detected at other ages; most effects were positive in direction but with 95% CIs that spanned the null. Moreover, there was some evidence that PRS was associated with peer problems up to 13 years, but not at later time points. In addition, as shown in figure 4.8, (and table 4.5) statistically significant interactions between relative age and PRS on peer problems at 7, 8, and 13 years were observed. All interaction effects, conventionally significant or otherwise, were negative in direction except for at age 25 years, which attenuated to the null. This indicates that the effect of relative age in the school year is reduced for people at higher genetic risk of ADHD.

Figure 4.8: – Coefficient plot of parent-rated mean standardised SDQ peer problems ages 7-25 years: associations with relative age, ADHD polygenic risk and their interaction



"Rel. Age" = Relative age within the school year; "PRS p<0.05" = ADHD polygenic risk alleles at p<0.05 threshold. Imputed data. Unadjusted models. Standardised effect size: mean change in standardised parent-report SDQ peer problems subscale score per 1 year difference in relative age (Rel.Age), or

mean change in standardised parent-report SDQ total difficulties score per 1 SD unit change in PRS (PRS). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born up to 4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born 8 weeks either side of the September 1st cut-off. N=6933

Table 4.4: Regression results for SDQ subscales by relative age, stratified by ADHD symptoms at age 4 years. Imputed data

All	Unadjusted				Adjusted			
				Conduct problems				
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.01	-0.07	0.09	0.81	0.01	-0.07	0.09	0.78
Borderline	0.38	0.24	0.52	<0.01	0.35	0.21	0.49	<0.01
High	0.75	0.62	0.89	<0.01	0.70	0.57	0.83	<0.01
Rel.Age*Borderline	0.08	-0.16	0.32	0.51	0.07	-0.17	0.31	0.58
Rel.Age*High	-0.07	-0.30	0.16	0.56	-0.06	-0.29	0.17	0.60
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.09	<0.01	0.17	0.04	0.09	<0.01	0.17	0.04
Borderline	0.42	0.28	0.57	<0.01	0.39	0.24	0.54	<0.01
High	0.80	0.66	0.93	<0.01	0.73	0.60	0.87	<0.01
Rel.Age*Borderline	-0.05	-0.30	0.21	0.73	-0.06	-0.31	0.19	0.64
Rel.Age*High	-0.09	-0.32	0.15	0.48	-0.07	-0.31	0.16	0.54
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.03	-0.11	0.05	0.51	-0.03	-0.10	0.05	0.53
Borderline	0.33	0.18	0.47	<0.01	0.30	0.16	0.44	<0.01
High	0.70	0.57	0.83	<0.01	0.64	0.51	0.77	<0.01
Rel.Age*Borderline	0.10	-0.14	0.34	0.39	0.09	-0.15	0.33	0.47
Rel.Age*High	-0.02	-0.24	0.20	0.87	-0.01	-0.23	0.21	0.94
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.10	0.02	0.18	0.02	0.11	0.03	0.19	0.01
Borderline	0.34	0.19	0.50	<0.01	0.31	0.15	0.47	<0.01
High	0.63	0.49	0.77	<0.01	0.56	0.42	0.71	<0.01
Rel.Age*Borderline	0.10	-0.17	0.37	0.47	0.08	-0.18	0.35	0.55
Rel.Age*High	-0.10	-0.34	0.14	0.42	-0.08	-0.33	0.16	0.50
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.02	-0.06	0.11	0.58	0.03	-0.06	0.11	0.56

Borderline	0.16	0.01	0.31	0.04	0.13	-0.02	0.28	0.09
High	0.60	0.47	0.74	<0.01	0.54	0.40	0.68	<0.01
Rel.Age*Borderline	0.22	-0.05	0.48	0.10	0.20	-0.06	0.46	0.13
Rel.Age*High	-0.10	-0.34	0.14	0.43	-0.08	-0.32	0.16	0.51

16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.01	-0.09	0.10	0.91	0.01	-0.09	0.10	0.92
Borderline	0.22	0.04	0.39	0.01	0.20	0.03	0.37	0.03
High	0.50	0.33	0.66	<0.01	0.45	0.28	0.61	<0.01
Rel.Age*Borderline	0.15	-0.15	0.45	0.31	0.14	-0.16	0.43	0.37
Rel.Age*High	-0.12	-0.42	0.18	0.43	-0.11	-0.41	0.19	0.47

25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.01	-0.12	0.10	0.82	-0.01	-0.12	0.10	0.81
Borderline	0.32	0.08	0.55	0.01	0.30	0.07	0.53	0.01
High	0.42	0.22	0.63	<0.01	0.38	0.17	0.59	<0.01
Rel.Age*Borderline	0.06	-0.33	0.46	0.76	0.04	-0.35	0.44	0.83
Rel.Age*High	-0.03	-0.38	0.32	0.87	-0.02	-0.37	0.33	0.91

Emotional problems

7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.15	0.07	0.23	<0.01	0.15	0.07	0.23	<0.01
Borderline	0.15	0.01	0.30	0.04	0.14	-0.01	0.28	0.06
High	0.36	0.23	0.49	<0.01	0.32	0.19	0.45	<0.01
Rel.Age*Borderline	0.01	-0.24	0.25	0.95	-0.01	-0.25	0.23	0.93
Rel.Age*High	-0.10	-0.32	0.13	0.39	-0.09	-0.32	0.13	0.41

8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.15	0.07	0.23	<0.01	0.15	0.06	0.23	<0.01
Borderline	0.18	0.03	0.33	0.02	0.16	0.02	0.31	0.03
High	0.44	0.31	0.57	<0.01	0.39	0.26	0.52	<0.01
Rel.Age*Borderline	-0.09	-0.35	0.16	0.48	-0.11	-0.36	0.14	0.40
Rel.Age*High	-0.18	-0.41	0.06	0.14	-0.17	-0.40	0.06	0.15

9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.10	0.01	0.18	0.02	0.10	0.01	0.18	0.02
Borderline	0.08	-0.07	0.22	0.32	0.07	-0.08	0.21	0.39
High	0.38	0.25	0.52	<0.01	0.35	0.22	0.48	<0.01
Rel.Age*Borderline	0.13	-0.12	0.39	0.30	0.11	-0.14	0.36	0.37
Rel.Age*High	-0.07	-0.30	0.15	0.52	-0.07	-0.29	0.16	0.56

11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.13	0.05	0.22	<0.01	0.13	0.05	0.22	<0.01
Borderline	0.10	-0.05	0.26	0.19	0.09	-0.06	0.24	0.26
High	0.44	0.30	0.58	<0.01	0.39	0.25	0.53	<0.01
Rel.Age*Borderline	0.08	-0.19	0.34	0.58	0.05	-0.21	0.31	0.70
Rel.Age*High	-0.20	-0.46	0.05	0.12	-0.19	-0.44	0.06	0.14

13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.09	<0.01	0.17	0.06	0.08	<0.01	0.17	0.06
Borderline	0.15	<0.01	0.31	0.05	0.15	<0.01	0.31	0.05
High	0.38	0.24	0.52	<0.01	0.36	0.22	0.49	<0.01
Rel.Age*Borderline	0.05	-0.22	0.32	0.71	0.03	-0.24	0.30	0.81
Rel.Age*High	-0.07	-0.32	0.18	0.58	-0.06	-0.31	0.18	0.61

16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.15	0.06	0.25	<0.01	0.15	0.06	0.24	<0.01
Borderline	0.10	-0.07	0.26	0.25	0.11	-0.05	0.27	0.18
High	0.38	0.22	0.54	<0.01	0.38	0.22	0.54	<0.01
Rel.Age*Borderline	0.01	-0.26	0.29	0.93	-0.01	-0.28	0.26	0.95
Rel.Age*High	-0.25	-0.53	0.03	0.08	-0.25	-0.52	0.03	0.08

25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.03	-0.14	0.07	0.55	-0.04	-0.14	0.07	0.48
Borderline	0.07	-0.14	0.29	0.52	0.07	-0.14	0.28	0.52
High	0.35	0.15	0.55	<0.01	0.32	0.13	0.52	<0.01
Rel.Age*Borderline	0.25	-0.11	0.60	0.18	0.22	-0.14	0.58	0.22

Rel.Age*High	0.02	-0.32	0.36	0.91	0.03	-0.31	0.37	0.85
			Hyperactivity problems					
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.24	0.17	0.31	<0.01	0.24	0.17	0.31	<0.01
Borderline	0.88	0.75	1.00	<0.01	0.83	0.70	0.96	<0.01
High	1.23	1.11	1.34	<0.01	1.15	1.03	1.27	<0.01
Rel.Age*Borderline	-0.19	-0.42	0.03	0.09	-0.20	-0.42	0.02	0.07
Rel.Age*High	-0.15	-0.36	0.06	0.15	-0.14	-0.34	0.06	0.18
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.26	0.19	0.34	<0.01	0.26	0.18	0.33	<0.01
Borderline	0.69	0.56	0.83	<0.01	0.65	0.51	0.78	<0.01
High	1.18	1.06	1.30	<0.01	1.10	0.98	1.21	<0.01
Rel.Age*Borderline	<0.01	-0.23	0.23	0.99	<0.01	-0.23	0.22	0.99
Rel.Age*High	-0.14	-0.35	0.07	0.19	-0.13	-0.33	0.08	0.22
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.22	0.15	0.29	<0.01	0.22	0.15	0.30	<0.01
Borderline	0.60	0.46	0.73	<0.01	0.55	0.42	0.69	<0.01
High	1.09	0.96	1.21	<0.01	1.01	0.89	1.13	<0.01
Rel.Age*Borderline	0.04	-0.19	0.28	0.71	0.04	-0.19	0.26	0.76
Rel.Age*High	-0.09	-0.30	0.12	0.41	-0.08	-0.28	0.13	0.47
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.28	0.20	0.35	<0.01	0.28	0.21	0.36	<0.01
Borderline	0.56	0.42	0.70	<0.01	0.51	0.37	0.65	<0.01
High	0.99	0.86	1.12	<0.01	0.90	0.77	1.03	<0.01
Rel.Age*Borderline	0.06	-0.18	0.30	0.62	0.05	-0.18	0.29	0.65
Rel.Age*High	-0.11	-0.33	0.11	0.33	-0.10	-0.32	0.12	0.37
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.20	0.13	0.28	<0.01	0.21	0.13	0.29	<0.01
Borderline	0.51	0.37	0.65	<0.01	0.46	0.32	0.60	<0.01

High	1.01	0.88	1.13	<0.01	0.92	0.80	1.04	<0.01
Rel.Age*Borderline	0.08	-0.17	0.32	0.53	0.07	-0.17	0.31	0.56
Rel.Age*High	-0.21	-0.43	0.01	0.06	-0.20	-0.41	0.02	0.07

16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.15	0.06	0.24	<0.01	0.16	0.07	0.25	<0.01
Borderline	0.52	0.35	0.69	<0.01	0.48	0.31	0.65	<0.01
High	0.88	0.73	1.04	<0.01	0.80	0.65	0.96	<0.01
Rel.Age*Borderline	-0.02	-0.31	0.27	0.89	-0.03	-0.32	0.26	0.83
Rel.Age*High	-0.30	-0.57	-0.02	0.03	-0.28	-0.56	-0.01	0.04

25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.03	-0.13	0.07	0.53	-0.03	-0.13	0.07	0.57
Borderline	0.35	0.14	0.56	<0.01	0.31	0.10	0.52	<0.01
High	0.72	0.53	0.92	<0.01	0.64	0.45	0.84	<0.01
Rel.Age*Borderline	0.25	-0.11	0.60	0.17	0.24	-0.12	0.59	0.19
Rel.Age*High	0.04	-0.30	0.37	0.82	0.05	-0.28	0.38	0.76

Peer problems

7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.04	-0.04	0.11	0.38	0.04	-0.04	0.12	0.34
Borderline	0.21	0.06	0.35	<0.01	0.18	0.04	0.32	0.01
High	0.27	0.13	0.40	<0.01	0.20	0.07	0.34	<0.01
Rel.Age*Borderline	0.01	-0.23	0.26	0.91	<0.01	-0.24	0.24	0.99
Rel.Age*High	0.24	<0.01	0.48	0.05	0.25	0.01	0.49	0.04

8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.06	-0.02	0.15	0.12	0.06	-0.03	0.14	0.18
Borderline	0.27	0.12	0.42	<0.01	0.24	0.09	0.39	<0.01
High	0.38	0.25	0.52	<0.01	0.33	0.19	0.46	<0.01
Rel.Age*Borderline	<0.01	-0.26	0.26	1.00	-0.01	-0.27	0.25	0.94
Rel.Age*High	0.06	-0.18	0.29	0.65	0.06	-0.17	0.30	0.60

9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p

Rel.Age	0.09	0.01	0.17	0.03	0.09	0.01	0.17	0.03
Borderline	0.21	0.06	0.35	0.01	0.19	0.04	0.33	0.01
High	0.36	0.22	0.49	<0.01	0.30	0.17	0.44	<0.01
Rel.Age*Borderline	-0.03	-0.28	0.22	0.84	-0.04	-0.29	0.21	0.77
Rel.Age*High	0.21	-0.02	0.45	0.08	0.22	-0.01	0.46	0.06

11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.11	0.03	0.20	0.01	0.11	0.03	0.20	0.01
Borderline	0.29	0.14	0.45	<0.01	0.27	0.11	0.42	<0.01
High	0.28	0.14	0.42	<0.01	0.23	0.08	0.37	<0.01
Rel.Age*Borderline	-0.07	-0.34	0.20	0.61	-0.08	-0.35	0.19	0.55
Rel.Age*High	0.17	-0.07	0.42	0.17	0.18	-0.06	0.43	0.14

13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.10	0.02	0.19	0.02	0.11	0.02	0.20	0.01
Borderline	0.27	0.11	0.43	<0.01	0.24	0.08	0.40	<0.01
High	0.34	0.20	0.49	<0.01	0.29	0.14	0.43	<0.01
Rel.Age*Borderline	-0.09	-0.37	0.18	0.50	-0.11	-0.38	0.17	0.45
Rel.Age*High	0.03	-0.22	0.28	0.83	0.04	-0.22	0.29	0.78

16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.07	-0.02	0.16	0.15	0.07	-0.02	0.17	0.12
Borderline	0.24	0.07	0.41	0.01	0.22	0.05	0.39	0.01
High	0.28	0.11	0.45	<0.01	0.24	0.07	0.41	0.01
Rel.Age*Borderline	-0.15	-0.45	0.15	0.34	-0.16	-0.46	0.15	0.31
Rel.Age*High	-0.01	-0.31	0.28	0.93	-0.01	-0.30	0.29	0.96

25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.09	-0.19	0.02	0.12	-0.08	-0.19	0.03	0.14
Borderline	-0.02	-0.24	0.21	0.89	-0.03	-0.25	0.19	0.78
High	0.33	0.14	0.53	<0.01	0.29	0.10	0.49	<0.01
Rel.Age*Borderline	0.58	0.19	0.96	<0.01	0.56	0.18	0.94	<0.01
Rel.Age*High	0.15	-0.18	0.49	0.37	0.17	-0.17	0.50	0.33

Coefficient (Coef.) represents mean change in standardised parent-report SDQ total difficulties score per 1 year difference in relative age (Rel.Age), or mean change in standardised parent-report SDQ total difficulties score compared to low-risk ADHD group (Borderline vs low/High vs low). "Unadjusted Model" = Age within School Year entered in the regression alone. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. Borderline = SDQ hyperactivity scores at 4 years of age = 6. High = SDQ hyperactivity scores at 4 years of age >=7

Table 4.5: Regression results for SDQ subscales by relative age and PRS scores for ADHD, threshold level p<0.05. Imputed data.

Continuous	**Unadjusted Model**				**Adjusted for covariates**			
			Conduct Problems					
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.01	-0.10	0.07	0.75	-0.01	-0.09	0.07	0.85
PRS	0.08	0.03	0.13	<0.01	0.06	0.01	0.11	0.01
Rel.age*PRS	-0.01	-0.09	0.07	0.78	0.00	-0.08	0.08	0.98
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.03	-0.05	0.11	0.47	0.04	-0.05	0.12	0.38
PRS	0.10	0.06	0.15	<0.01	0.09	0.04	0.13	<0.01
Rel.age*PRS	-0.05	-0.13	0.03	0.26	-0.03	-0.12	0.05	0.41
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.02	-0.10	0.06	0.64	-0.01	-0.09	0.07	0.73
PRS	0.10	0.05	0.15	<0.01	0.08	0.04	0.13	<0.01
Rel.age*PRS	-0.04	-0.12	0.04	0.38	-0.02	-0.10	0.06	0.54
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.09	0.00	0.17	0.05	0.10	0.02	0.18	0.02
PRS	0.09	0.04	0.14	<0.01	0.07	0.02	0.12	0.01
Rel.age*PRS	-0.01	-0.09	0.08	0.84	0.01	-0.08	0.09	0.90
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.04	-0.05	0.12	0.38	0.05	-0.04	0.13	0.27
PRS	0.06	0.01	0.11	0.02	0.04	-0.01	0.09	0.14
Rel.age*PRS	0.04	-0.05	0.12	0.38	0.05	-0.03	0.14	0.24

16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.02	-0.07	0.11	0.69	0.02	-0.07	0.11	0.62
PRS	0.06	0.00	0.11	0.03	0.04	-0.01	0.09	0.13
Rel.age*PRS	0.00	-0.09	0.09	0.96	0.01	-0.08	0.11	0.76

25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.03	-0.14	0.08	0.60	-0.02	-0.13	0.08	0.66
PRS	0.10	0.04	0.17	<0.01	0.09	0.03	0.15	0.01
Rel.age*PRS	0.02	-0.09	0.13	0.75	0.03	-0.08	0.14	0.59
			Emotional Problems					
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.09	0.01	0.17	0.03	0.09	0.01	0.18	0.02
PRS	-0.01	-0.06	0.04	0.69	-0.03	-0.08	0.02	0.24
Rel.age*PRS	0.01	-0.07	0.10	0.75	0.03	-0.05	0.11	0.52

8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.06	-0.03	0.14	0.17	0.05	-0.04	0.13	0.28
PRS	0.02	-0.03	0.06	0.53	0.00	-0.05	0.05	0.99
Rel.age*PRS	0.02	-0.06	0.11	0.61	0.03	-0.05	0.12	0.41

9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.09	0.01	0.17	0.03	0.09	0.01	0.17	0.02
PRS	0.01	-0.04	0.05	0.82	-0.01	-0.06	0.03	0.61
Rel.age*PRS	0.01	-0.07	0.09	0.73	0.03	-0.05	0.11	0.53

11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.10	0.01	0.18	0.02	0.10	0.02	0.19	0.01
PRS	0.02	-0.03	0.07	0.41	0.00	-0.05	0.05	0.97
Rel.age*PRS	0.02	-0.06	0.11	0.57	0.04	-0.04	0.12	0.36

13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.10	0.01	0.18	0.02	0.10	0.02	0.18	0.02

PRS	0.01	-0.04	0.06	0.64	0.00	-0.05	0.05	0.90
Rel.age*PRS	0.01	-0.08	0.09	0.87	0.02	-0.07	0.10	0.70
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.08	-0.01	0.18	0.09	0.08	-0.01	0.18	0.08
PRS	0.00	-0.05	0.06	0.90	-0.01	-0.06	0.04	0.70
Rel.age*PRS	0.03	-0.07	0.12	0.58	0.03	-0.06	0.12	0.45
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.01	-0.09	0.12	0.84	0.01	-0.09	0.12	0.82
PRS	0.06	0.00	0.12	0.05	0.04	-0.02	0.10	0.17
Rel.age*PRS	0.03	-0.08	0.13	0.64	0.03	-0.07	0.14	0.51
Hyperactivity Problems								
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.16	0.08	0.24	<0.01	0.17	0.09	0.25	<0.01
PRS	0.13	0.08	0.17	<0.01	0.10	0.06	0.15	<0.01
Rel.age*PRS	-0.04	-0.12	0.04	0.32	-0.03	-0.11	0.05	0.52
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.21	0.12	0.29	<0.01	0.21	0.13	0.30	<0.01
PRS	0.13	0.09	0.18	<0.01	0.12	0.07	0.16	<0.01
Rel.age*PRS	-0.05	-0.13	0.03	0.25	-0.03	-0.11	0.05	0.41
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.20	0.12	0.28	<0.01	0.20	0.13	0.28	<0.01
PRS	0.14	0.09	0.19	<0.01	0.12	0.07	0.17	<0.01
Rel.age*PRS	-0.08	-0.16	0.00	0.05	-0.07	-0.15	0.01	0.09
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.27	0.19	0.35	<0.01	0.28	0.21	0.36	<0.01
PRS	0.12	0.07	0.16	<0.01	0.10	0.05	0.14	<0.01
Rel.age*PRS	-0.02	-0.10	0.06	0.63	0.00	-0.09	0.08	0.90

13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.17	0.09	0.25	<0.01	0.18	0.10	0.26	<0.01
PRS	0.14	0.09	0.19	<0.01	0.12	0.07	0.17	<0.01
Rel.age*PRS	-0.04	-0.13	0.04	0.34	-0.03	-0.11	0.06	0.52

16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.02	0.17	0.12	0.09	0.00	0.18	0.06
PRS	0.08	0.03	0.14	<0.01	0.06	0.01	0.12	0.02
Rel.age*PRS	0.01	-0.08	0.11	0.80	0.03	-0.07	0.12	0.59

25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.03	-0.14	0.07	0.54	-0.02	-0.13	0.08	0.68
PRS	0.12	0.06	0.18	<0.01	0.10	0.04	0.16	<0.01
Rel.age*PRS	-0.04	-0.14	0.07	0.49	-0.02	-0.13	0.08	0.67

Peer Problems

7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.03	-0.05	0.11	0.43	0.04	-0.04	0.12	0.32
PRS	0.10	0.06	0.15	<0.01	0.09	0.04	0.13	<0.01
Rel.age*PRS	-0.13	-0.21	-0.05	<0.01	-0.11	-0.19	-0.03	0.01

8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.02	0.15	0.11	0.06	-0.02	0.14	0.16
PRS	0.13	0.08	0.17	<0.01	0.11	0.06	0.16	<0.01
Rel.age*PRS	-0.11	-0.20	-0.03	0.01	-0.10	-0.19	-0.02	0.02

9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.10	0.01	0.18	0.02	0.10	0.02	0.18	0.02
PRS	0.07	0.02	0.12	<0.01	0.06	0.01	0.10	0.02
Rel.age*PRS	-0.08	-0.16	0.01	0.07	-0.06	-0.15	0.02	0.12

11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.12	0.03	0.20	0.01	0.12	0.04	0.21	<0.01
PRS	0.08	0.03	0.13	<0.01	0.07	0.02	0.11	0.01

Rel.age*PRS	-0.07	-0.15	0.02	0.12	-0.06	-0.14	0.03	0.19

13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.08	-0.01	0.16	0.07	0.09	0.00	0.17	0.05
PRS	0.10	0.05	0.15	<0.01	0.09	0.04	0.14	<0.01
Rel.age*PRS	-0.12	-0.20	-0.03	0.01	-0.11	-0.19	-0.02	0.01

16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.01	-0.08	0.11	0.79	0.03	-0.07	0.12	0.60
PRS	0.04	-0.02	0.10	0.16	0.03	-0.03	0.08	0.33
Rel.age*PRS	-0.01	-0.11	0.09	0.88	0.00	-0.10	0.10	0.99

25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.02	-0.13	0.08	0.68	0.00	-0.11	0.10	0.94
PRS	0.05	-0.01	0.12	0.11	0.03	-0.03	0.10	0.32
Rel.age*PRS	0.00	-0.11	0.11	0.96	0.01	-0.10	0.12	0.80

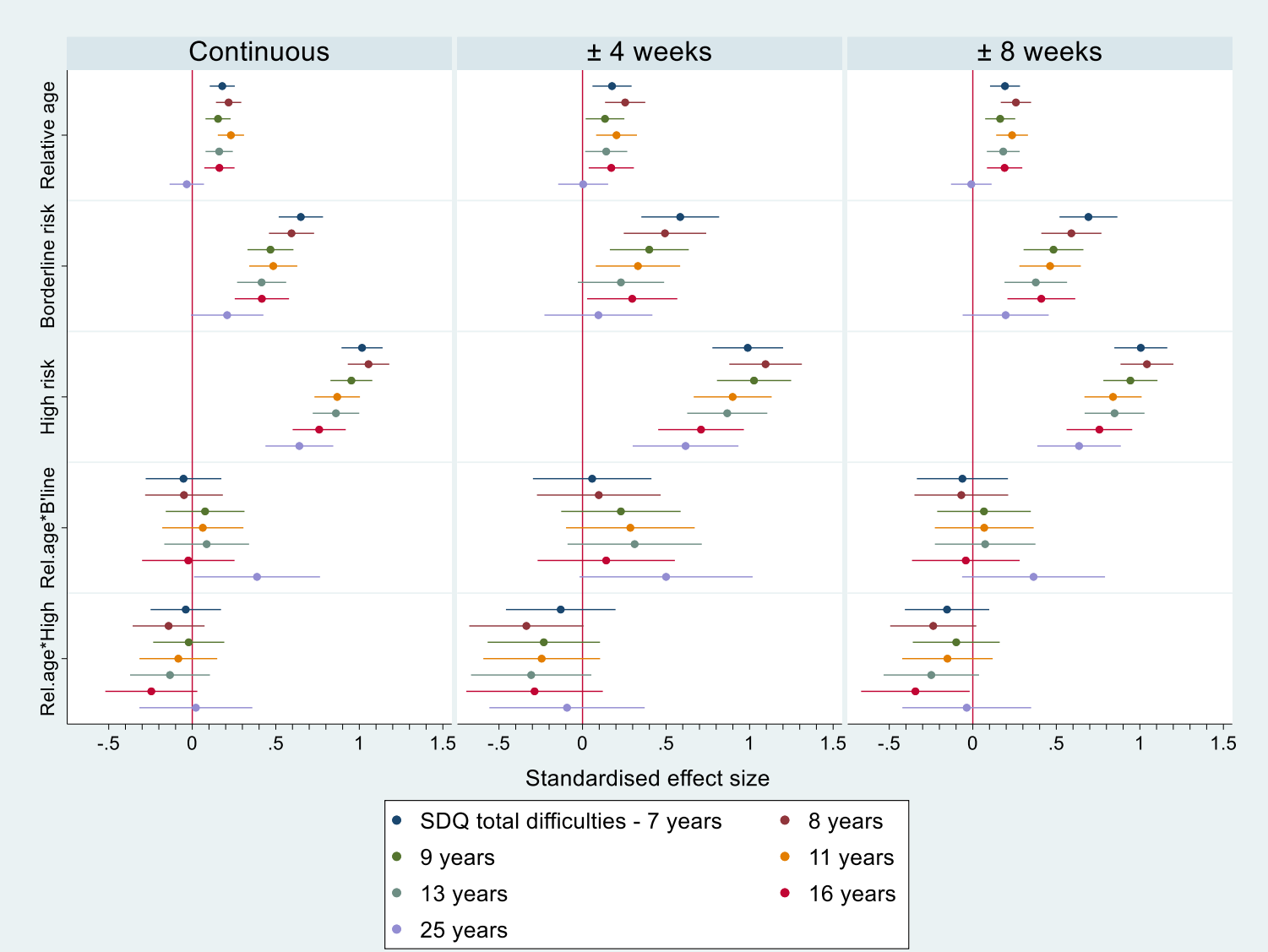
All individuals included (N=6933). Coefficient (Coef.) represents mean change in standardised parent-report SDQ total difficulties score per 1 year difference in relative age (Rel.Age) or mean change in standardised parent-report SDQ total difficulties score per 1 SD unit change in PRS (PRS)). Unadjusted Model" = Age within School Year entered in the regression + principal components. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. PRS p<0.05 = PRS scores for ADHD, threshold level p<0.05

4.5.3 Secondary analyses: Relative age, age 4 ADHD symptom group, and their interaction in the prediction of total mental health difficulties (aged 7-25 years)

As shown in figure 4.9 (and table 4.6), a 1-year decrease in relative age was associated with an average increase of approximately one-sixth of a standard deviation in SDQ total difficulties at age 7 and differences between the oldest and youngest children persist up to age sixteen years, which indicates that relatively young children have poorer parent-rated child mental health. These differences attenuated to the null at 25 years. This pattern of results is identical to that found in chapter 3, with slightly different standardised effect sizes and 95% confidence intervals, due to the difference in number of participants.

As shown in figure 4.1 (and table 4.4) main effects of ADHD symptom group on risk of mental health outcomes were observed throughout development; children classed as being in the borderline risk group for ADHD at 4 years showed elevated parent-rated mental health problems up to sixteen years, compared with children who were in the lower risk ADHD risk group. This was also the case in the high (SDQ >=7) ADHD risk group, where differences were also present at 25 years.

Figure 4.9: Coefficient plots of parent-rated mean standardised SDQ total difficulties, stratified by ADHD symptom group. Effects of relative age (within the school year), ADHD symptom group (SDQ hyperactivity scores at 4 years) and their interactions.



"Borderline risk"/ = Borderline risk group for ADHD symptoms by SDQ 3-band cut-off categorisation (SDQ=6); "High risk" = High risk group for ADHD symptoms (SDQ >=7). Imputed data. Unadjusted models. Standardised effect size: mean change in standardised parent-report SDQ total difficulties score per

1 year difference in relative age (for Rel.Age) or mean change in standardised parent-report SDQ total difficulties score compared to low-risk ADHD group (ADHD symptom group). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born ±4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born ± 8 weeks either side of the September 1st cut-off. N=9172

Table 4.6: Regression results for SDQ total difficulties by relative age, stratified by ADHD trait susceptibility. Imputed data.

	Unadjusted				All covariates			
			Continuous					
7 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.18	0.10	0.25	<0.01	0.18	0.11	0.26	<0.01
Borderline	0.65	0.52	0.78	<0.01	0.61	0.48	0.74	<0.01
High	1.02	0.89	1.14	<0.01	0.93	0.81	1.05	<0.01
Rel.Age*Borderline	-0.05	-0.28	0.17	0.65	-0.07	-0.29	0.15	0.54
Rel.Age*High	-0.04	-0.25	0.17	0.72	-0.03	-0.23	0.18	0.80
8 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.22	0.14	0.29	<0.01	0.21	0.14	0.29	<0.01
Borderline	0.59	0.46	0.73	<0.01	0.55	0.41	0.68	<0.01
High	1.06	0.93	1.18	<0.01	0.96	0.84	1.09	<0.01
Rel.Age*Borderline	-0.05	-0.28	0.18	0.68	-0.06	-0.29	0.17	0.59
Rel.Age*High	-0.14	-0.36	0.07	0.20	-0.13	-0.34	0.08	0.24
9 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.15	0.08	0.23	<0.01	0.16	0.08	0.23	<0.01
Borderline	0.47	0.33	0.61	<0.01	0.43	0.29	0.56	<0.01
High	0.95	0.83	1.08	<0.01	0.87	0.74	0.99	<0.01
Rel.Age*Borderline	0.08	-0.16	0.31	0.52	0.06	-0.17	0.29	0.62
Rel.Age*High	-0.02	-0.23	0.19	0.85	-0.01	-0.22	0.20	0.95
11 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.23	0.15	0.31	<0.01	0.24	0.16	0.31	<0.01
Borderline	0.48	0.34	0.63	<0.01	0.44	0.30	0.58	<0.01
High	0.87	0.73	1.00	<0.01	0.77	0.64	0.91	<0.01
Rel.Age*Borderline	0.06	-0.18	0.31	0.61	0.04	-0.19	0.28	0.72
Rel.Age*High	-0.08	-0.32	0.15	0.48	-0.07	-0.30	0.16	0.57
13 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.16	0.08	0.24	<0.01	0.16	0.08	0.24	<0.01

Borderline	0.42	0.27	0.56	<0.01	0.37	0.23	0.52	<0.01
High	0.86	0.72	1.00	<0.01	0.78	0.64	0.91	<0.01
Rel.Age*Borderline	0.09	-0.17	0.34	0.51	0.07	-0.18	0.32	0.59
Rel.Age*High	-0.13	-0.37	0.11	0.27	-0.12	-0.35	0.12	0.33

16 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.16	0.07	0.25	<0.01	0.16	0.07	0.25	<0.01
Borderline	0.42	0.25	0.58	<0.01	0.39	0.23	0.55	<0.01
High	0.76	0.60	0.92	<0.01	0.70	0.54	0.86	<0.01
Rel.Age*Borderline	-0.02	-0.30	0.25	0.87	-0.04	-0.32	0.23	0.75
Rel.Age*High	-0.25	-0.52	0.03	0.08	-0.23	-0.51	0.04	0.09

25 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.03	-0.14	0.07	0.53	-0.03	-0.13	0.07	0.55
Borderline	0.21	-0.01	0.43	0.06	0.19	-0.03	0.40	0.09
High	0.64	0.44	0.84	<0.01	0.58	0.38	0.78	<0.01
Rel.Age*Borderline	0.39	0.01	0.76	0.04	0.36	-0.01	0.74	0.06
Rel.Age*High	0.02	-0.32	0.36	0.90	0.04	-0.30	0.37	0.82

4 weeks

7 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.18	0.06	0.29	<0.01	0.19	0.08	0.31	<0.01
Borderline	0.58	0.35	0.82	<0.01	0.55	0.32	0.78	<0.01
High	0.99	0.78	1.20	<0.01	0.89	0.68	1.10	<0.01
Rel.Age*Borderline	0.06	-0.30	0.41	0.75	0.01	-0.34	0.36	0.96
Rel.Age*High	-0.13	-0.46	0.20	0.44	-0.11	-0.43	0.21	0.50

8 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.26	0.13	0.38	<0.01	0.27	0.15	0.39	<0.01
Borderline	0.49	0.25	0.74	<0.01	0.46	0.22	0.70	<0.01
High	1.10	0.88	1.31	<0.01	0.99	0.78	1.21	<0.01
Rel.Age*Borderline	0.10	-0.27	0.47	0.61	0.06	-0.31	0.42	0.76
Rel.Age*High	-0.34	-0.68	0.01	0.05	-0.32	-0.66	0.02	0.07

9 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.13	0.02	0.25	0.02	0.15	0.04	0.26	0.01
Borderline	0.40	0.16	0.64	<0.01	0.36	0.13	0.60	<0.01
High	1.03	0.80	1.25	<0.01	0.92	0.70	1.15	<0.01
Rel.Age*Borderline	0.23	-0.13	0.59	0.21	0.18	-0.17	0.53	0.31
Rel.Age*High	-0.23	-0.57	0.10	0.18	-0.21	-0.54	0.12	0.21

11 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.20	0.08	0.33	<0.01	0.22	0.10	0.34	<0.01
Borderline	0.33	0.08	0.58	0.01	0.29	0.04	0.54	0.02
High	0.90	0.67	1.13	<0.01	0.78	0.55	1.01	<0.01
Rel.Age*Borderline	0.29	-0.10	0.67	0.15	0.23	-0.14	0.61	0.22
Rel.Age*High	-0.24	-0.59	0.11	0.17	-0.22	-0.56	0.12	0.21

13 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.14	0.02	0.27	0.03	0.16	0.03	0.28	0.01
Borderline	0.23	-0.03	0.49	0.08	0.19	-0.07	0.44	0.15
High	0.87	0.63	1.11	<0.01	0.75	0.51	0.99	<0.01
Rel.Age*Borderline	0.31	-0.09	0.71	0.13	0.28	-0.12	0.67	0.17
Rel.Age*High	-0.31	-0.67	0.05	0.09	-0.28	-0.64	0.08	0.12

16 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.17	0.04	0.31	0.01	0.18	0.05	0.32	0.01
Borderline	0.30	0.03	0.57	0.03	0.27	<0.01	0.54	0.05
High	0.71	0.45	0.97	<0.01	0.63	0.37	0.89	<0.01
Rel.Age*Borderline	0.14	-0.27	0.55	0.50	0.10	-0.31	0.50	0.63
Rel.Age*High	-0.29	-0.70	0.12	0.17	-0.27	-0.68	0.13	0.19

25 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	<0.01	-0.15	0.15	0.96	0.01	-0.14	0.16	0.88
Borderline	0.10	-0.23	0.42	0.56	0.06	-0.26	0.38	0.70
High	0.62	0.30	0.93	<0.01	0.56	0.25	0.88	<0.01
Rel.Age*Borderline	0.50	-0.02	1.02	0.06	0.47	-0.04	0.99	0.07

Rel.Age*High	-0.09	-0.56	0.37	0.70	-0.08	-0.55	0.38	0.72
			8 weeks					
7 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.19	0.10	0.28	<0.01	0.19	0.11	0.28	<0.01
Borderline	0.69	0.52	0.87	<0.01	0.66	0.49	0.83	<0.01
High	1.01	0.85	1.16	<0.01	0.90	0.75	1.06	<0.01
Rel.Age*Borderline	-0.06	-0.33	0.21	0.66	-0.10	-0.36	0.17	0.48
Rel.age*High	-0.15	-0.41	0.10	0.23	-0.13	-0.38	0.12	0.32
8 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.26	0.17	0.35	<0.01	0.26	0.17	0.35	<0.01
Borderline	0.59	0.41	0.77	<0.01	0.56	0.38	0.74	<0.01
High	1.04	0.88	1.20	<0.01	0.94	0.78	1.10	<0.01
Rel.Age*Borderline	-0.07	-0.35	0.21	0.63	-0.10	-0.38	0.18	0.48
Rel.age*High	-0.24	-0.49	0.02	0.07	-0.21	-0.47	0.04	0.10
9 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.16	0.07	0.25	<0.01	0.17	0.08	0.26	<0.01
Borderline	0.48	0.30	0.66	<0.01	0.45	0.27	0.63	<0.01
High	0.94	0.78	1.11	<0.01	0.84	0.68	1.00	<0.01
Rel.Age*Borderline	0.07	-0.21	0.35	0.64	0.03	-0.24	0.31	0.81
Rel.age*High	-0.10	-0.36	0.16	0.46	-0.07	-0.33	0.19	0.59
11 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.24	0.14	0.33	<0.01	0.24	0.14	0.33	<0.01
Borderline	0.46	0.28	0.65	<0.01	0.43	0.24	0.61	<0.01
High	0.84	0.67	1.01	<0.01	0.73	0.56	0.90	<0.01
Rel.Age*Borderline	0.07	-0.23	0.36	0.65	0.03	-0.26	0.32	0.83
Rel.age*High	-0.15	-0.42	0.12	0.27	-0.12	-0.39	0.15	0.37
13 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.18	0.08	0.28	<0.01	0.18	0.08	0.28	<0.01
Borderline	0.38	0.19	0.56	<0.01	0.34	0.16	0.53	<0.01

High	0.85	0.67	1.03	<0.01	0.75	0.57	0.93	<0.01
Rel.Age*Borderline	0.07	-0.23	0.38	0.63	0.05	-0.25	0.34	0.76
Rel.age*High	-0.25	-0.53	0.04	0.09	-0.22	-0.50	0.06	0.13

16 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.19	0.08	0.30	<0.01	0.19	0.09	0.29	<0.01
Borderline	0.41	0.21	0.61	<0.01	0.39	0.19	0.59	<0.01
High	0.76	0.56	0.95	<0.01	0.68	0.48	0.88	<0.01
Rel.Age*Borderline	-0.04	-0.36	0.28	0.80	-0.08	-0.39	0.24	0.64
Rel.age*High	-0.34	-0.67	-0.02	0.04	-0.32	-0.64	0.01	0.06

25 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.01	-0.13	0.11	0.89	-0.01	-0.13	0.11	0.84
Borderline	0.20	-0.06	0.45	0.13	0.18	-0.08	0.43	0.18
High	0.64	0.39	0.89	<0.01	0.56	0.31	0.81	<0.01
Rel.Age*Borderline	0.36	-0.06	0.79	0.10	0.33	-0.09	0.76	0.12
Rel.age*High	-0.04	-0.42	0.35	0.85	<0.01	-0.39	0.38	0.98

"Continuous" = All individuals included (N=9172). "4 week" = Restricted to individuals born up to 4 weeks either side of the September 1st cut-off (N=1693); 8 weeks = Restricted to individuals born up to 8 weeks either side of the September 1st cut-off Imputed data (N=3380); The numbers contained in the "unadjusted models" column of this table correspond to figure 4.1 Coefficient ("Coef.") represents mean change in standardised parent-report SDQ total difficulties score per 1 year difference in relative age (for Rel.Age) or mean change in standardised parent-report SDQ total difficulties score compared to low-risk ADHD group (borderline vs low; high vs low). "Unadjusted Model" = Age within School Year entered in the regression alone. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. Borderline = SDQ hyperactivity scores at 4 years of age = 6. High = SDQ hyperactivity scores at 4 years of age >=7.

4.5.3.1 Interactions between relative age in the school year and ADHD traits on general mental health problems

As shown in figure 4.9 and table 4.6, no consistent evidence was found for any interaction between relative age and ADHD traits on general mental health problem risk (SDQ total difficulties) for outcomes at any age. However, it is also worth noting that interaction effects between relative age and ADHD traits in the borderline group were not consistently in the same direction, and that most interaction effects between relative age and ADHD traits in the high-risk group were negative in direction.

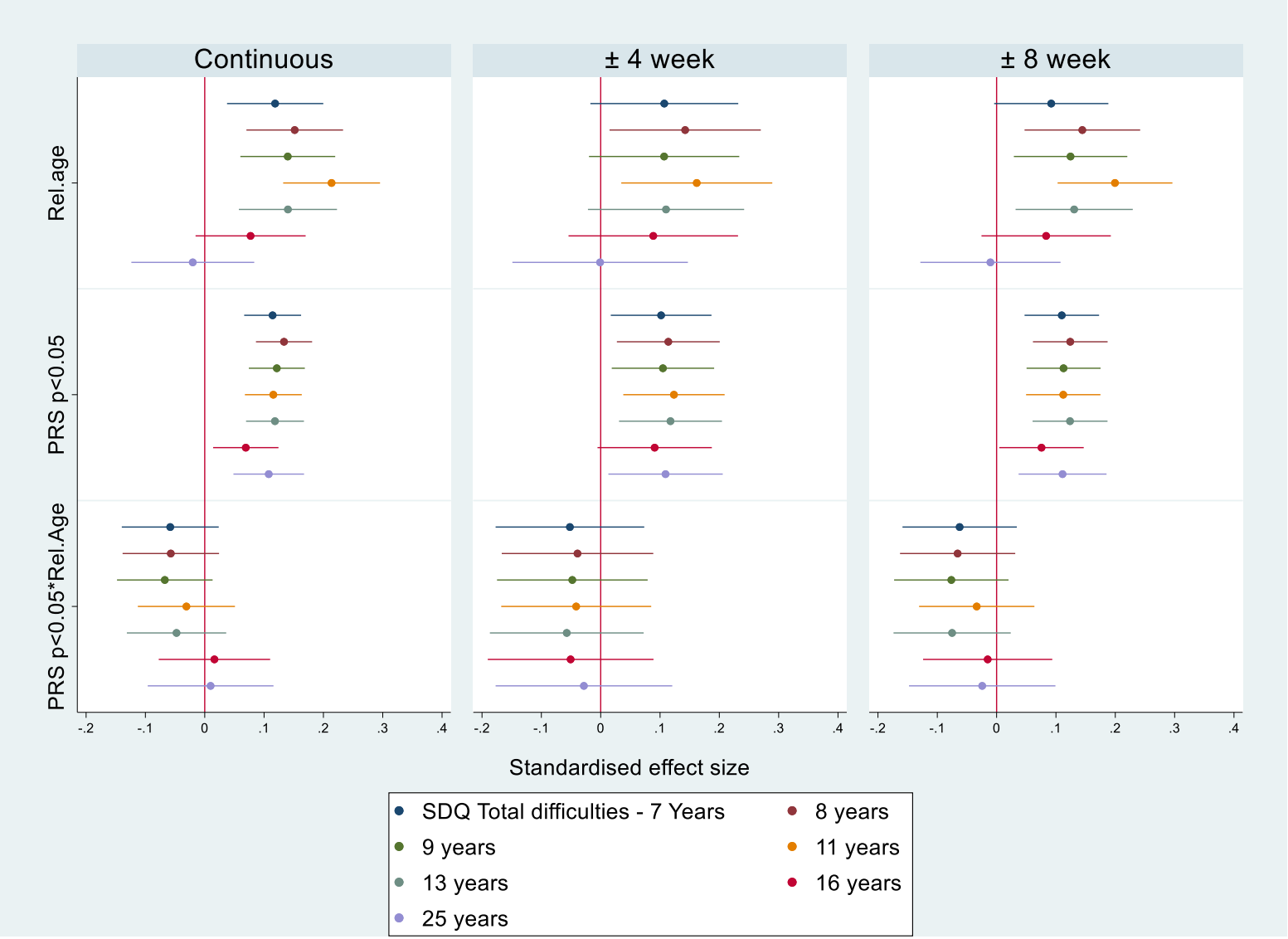
4.5.3.2 Relative age and ADHD PRS: associations with general mental health problems (7-25 years)

Models tested the associations of relative age, ADHD PRS, and their interaction with SDQ total difficulties at each outcome age (7-25 years). Findings are shown in Figure 4.10 for unadjusted models separately by relative age bandwidth. Full model results together with analyses adjusted for covariates are shown in Table 4.7. There was evidence of a positive effect of PRS on risk of mental health problems for SDQ total scores at all ages, including at 25 years. These results indicate that individuals with a higher PRS for ADHD have a higher risk of mental health problems.

4.5.3.3 Interactions between relative age in the school year and ADHD PRS on mental health problems

As shown in table 4.7, there was no evidence for any interaction between relative age and ADHD PRS on general mental health problem risk at any timepoint, with all confidence intervals for interaction coefficients crossing the null. However, a general pattern suggested that the interactions between relative age in the school year and PRS were negative at most timepoints. This implies that relative age effects on mental health were reduced in individuals with a high genetic ADHD risk.

Figure 4.10: – Coefficient plot of parent-rated mean standardised SDQ total difficulties ages 7-25 years: associations with relative age, ADHD polygenic risk and their interaction



"Rel. Age" = Relative age within the school year; "PRS p<0.05" = ADHD polygenic risk alleles at p<0.05 threshold. Imputed data. Unadjusted models. Standardised effect size: mean change in standardised parent-report SDQ total difficulties score per 1 year difference in relative age (Rel.Age), or mean

change in standardised parent-report SDQ total difficulties score per 1 SD unit change in PRS (PRS). "Continuous" = All participants included; "± 4 Weeks" = Restricted to participants born up to 4 weeks either side of September 1st Cut-off; "± 8 weeks" = Restricted to participants born 8 weeks either side of the September 1st cut-off. N=6933

Table 4.7: Regression results for SDQ total difficulties, PRS for ADHD (threshold at p<.05 significance), and subscales by relative age, Imputed data

	Unadjusted Model				All covariates			
	Continuous							
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.12	0.04	0.20	<0.01	0.13	0.05	0.21	<0.01
PRS	0.11	0.07	0.16	<0.01	0.09	0.04	0.13	<0.01
Rel.Age*PRS	-0.06	-0.14	0.02	0.16	-0.04	-0.12	0.04	0.34
8 years								
Rel.Age	0.15	0.07	0.23	<0.01	0.15	0.07	0.23	<0.01
PRS	0.13	0.09	0.18	<0.01	0.11	0.06	0.16	<0.01
Rel.Age*PRS	-0.06	-0.14	0.02	0.17	-0.04	-0.12	0.04	0.35
9 years								
Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.23	<0.01
PRS	0.12	0.07	0.17	<0.01	0.10	0.05	0.14	<0.01
Rel.Age*PRS	-0.07	-0.15	0.01	0.10	-0.05	-0.13	0.03	0.22
11 years								
Rel.Age	0.21	0.13	0.30	<0.01	0.23	0.15	0.31	<0.01
PRS	0.12	0.07	0.16	<0.01	0.09	0.04	0.14	<0.01
Rel.Age*PRS	-0.03	-0.11	0.05	0.46	-0.01	-0.09	0.07	0.78
13 years								
Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.23	<0.01
PRS	0.12	0.07	0.17	<0.01	0.09	0.05	0.14	<0.01
Rel.Age*PRS	-0.05	-0.13	0.04	0.27	-0.03	-0.11	0.05	0.46
16 years								
Rel.Age	0.08	-0.02	0.17	0.10	0.09	<0.01	0.18	0.06
PRS	0.07	0.01	0.12	0.01	0.05	-0.01	0.10	0.09
Rel.Age*PRS	0.02	-0.08	0.11	0.73	0.03	-0.06	0.12	0.51
25 years								
Rel.Age	-0.02	-0.12	0.08	0.70	-0.01	-0.11	0.10	0.89
PRS	0.11	0.05	0.17	<0.01	0.08	0.02	0.14	0.01
Rel.Age*PRS	0.01	-0.10	0.12	0.86	0.03	-0.08	0.13	0.62

					4 weeks				
7 years		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
	Rel.Age	0.11	-0.02	0.23	0.09	0.13	0.01	0.25	0.04
	PRS	0.10	0.02	0.19	0.02	0.08	<0.01	0.17	0.05
	Rel.Age*PRS	-0.05	-0.18	0.07	0.42	-0.04	-0.17	0.08	0.48
8years									
	Rel.Age	0.14	0.01	0.27	0.03	0.16	0.03	0.28	0.02
	PRS	0.11	0.03	0.20	0.01	0.10	0.01	0.18	0.02
	Rel.Age*PRS	-0.04	-0.17	0.09	0.55	-0.03	-0.16	0.09	0.60
9 years									
	Rel.Age	0.11	-0.02	0.23	0.10	0.13	0.01	0.26	0.04
	PRS	0.10	0.02	0.19	0.02	0.09	<0.01	0.17	0.04
	Rel.Age*PRS	-0.05	-0.17	0.08	0.46	-0.04	-0.17	0.08	0.50
11 years									
	Rel.Age	0.16	0.03	0.29	0.01	0.18	0.06	0.31	<0.01
	PRS	0.12	0.04	0.21	0.01	0.11	0.02	0.19	0.01
	Rel.Age*PRS	-0.04	-0.17	0.09	0.52	-0.04	-0.16	0.09	0.57
13 years									
	Rel.Age	0.11	-0.02	0.24	0.10	0.13	<0.01	0.26	0.05
	PRS	0.12	0.03	0.20	0.01	0.10	0.01	0.18	0.02
	Rel.Age*PRS	-0.06	-0.19	0.07	0.39	-0.05	-0.18	0.07	0.41
16 years									
	Rel.Age	0.09	-0.05	0.23	0.22	0.11	-0.03	0.25	0.13
	PRS	0.09	-0.01	0.19	0.06	0.08	-0.02	0.17	0.12
	Rel.Age*PRS	-0.05	-0.19	0.09	0.48	-0.05	-0.18	0.09	0.51
25 years									
	Rel.Age	<0.01	-0.15	0.15	0.99	0.02	-0.13	0.17	0.79
	PRS	0.11	0.01	0.21	0.03	0.09	<0.01	0.19	0.05
	Rel.Age*PRS	-0.03	-0.18	0.12	0.71	-0.02	-0.17	0.12	0.75
					8 weeks				
7 years		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
	Rel.Age	0.09	<0.01	0.19	0.06	0.10	0.01	0.20	0.03
	PRS	0.11	0.05	0.17	<0.01	0.09	0.03	0.15	<0.01

	Rel.Age*PRS	-0.06	-0.16	0.03	0.21	-0.04	-0.14	0.05	0.38
8 years									
	Rel.Age	0.14	0.05	0.24	<0.01	0.15	0.05	0.24	<0.01
	PRS	0.12	0.06	0.19	<0.01	0.11	0.05	0.17	<0.01
	Rel.Age*PRS	-0.07	-0.16	0.03	0.18	-0.05	-0.14	0.05	0.32
9 years									
	Rel.Age	0.12	0.03	0.22	0.01	0.14	0.04	0.23	0.01
	PRS	0.11	0.05	0.18	<0.01	0.10	0.04	0.16	<0.01
	Rel.Age*PRS	-0.08	-0.17	0.02	0.12	-0.06	-0.16	0.03	0.21
11 years									
	Rel.Age	0.20	0.10	0.30	<0.01	0.21	0.12	0.31	<0.01
	PRS	0.11	0.05	0.18	<0.01	0.09	0.03	0.16	<0.01
	Rel.Age*PRS	-0.03	-0.13	0.06	0.50	-0.01	-0.11	0.08	0.76
13 years									
	Rel.Age	0.13	0.03	0.23	0.01	0.14	0.04	0.24	0.01
	PRS	0.12	0.06	0.19	<0.01	0.11	0.04	0.17	<0.01
	Rel.Age*PRS	-0.07	-0.17	0.02	0.14	-0.06	-0.16	0.04	0.23
16 years									
	Rel.Age	0.08	-0.03	0.19	0.13	0.09	-0.01	0.20	0.09
	PRS	0.08	<0.01	0.15	0.04	0.06	-0.01	0.13	0.10
	Rel.Age*PRS	-0.02	-0.12	0.09	0.79	<0.01	-0.11	0.11	0.97
25 years									
	Rel.Age	-0.01	-0.13	0.11	0.86	<0.01	-0.12	0.12	0.98
	PRS	0.11	0.04	0.19	<0.01	0.09	0.02	0.17	0.01
	Rel.Age*PRS	-0.02	-0.15	0.10	0.70	-0.01	-0.13	0.12	0.93

(N=6933) The numbers contained in the "unadjusted models" column of this table correspond to figure 4.2 (unadjusted models). "Continuous" = All participants included. "4 week" = Restricted to individuals born up to 4 weeks either side of the September 1st cut-off (N=1275); 8 weeks = Restricted to individuals born up to 8 weeks either side of the September 1st cut-off (N=2561). Coefficient ("Coef") represents mean change in standardised parent-report SDQ total difficulties score per 1 year difference in relative age (Rel.Age), or mean change in standardised parent-report SDQ total difficulties score per 1 SD unit change in PRS (PRS). "Unadjusted Model" = Age within School Year entered in the regression + principal components. "All covariates" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. PRS p<0.05 = PRS scores for ADHD, PRS threshold level p<0.05

4.5.4 Sensitivity Analyses

4.5.4.1 Adjustments for covariates

Results for all sets of analyses (age 4 ADHD symptom group; ADHD PRS score) were materially unchanged after adjusting for covariates.

4.5.4.2 Relative age bandwidths

As shown in figures 4.1-4.10, most of the identified relative age effects on parent rated SDQ scores were materially unchanged when analysis was restricted to children born 4 or 8 weeks either side of the school entry cut-off, although restricting the bandwidths yielded wider 95% confidence intervals.

4.5.4.3 PRS thresholds

The effects of using different thresholds to define ADHD PRS on associations with SDQ scores, as well as interactions with relative age, resembled those in the analyses presented in this chapter (see tables A4.3-A4.5, in the appendices).

4.5.4.4 Complete-case analysis

The complete-case results were broadly equivalent to those presented above using multiple imputation for the analysis of moderation by ADHD symptoms score. The only differences in the complete-case analysis were the observation of negative interactions between relative age and high ADHD symptom group in children born 4 weeks either side of the cut-off at 8 and 9 years and in children born 8 weeks either side of the cut-off at 8 years. As with the imputed data, the general pattern indicated that the ADHD PRS*relative age interactions were negative at most timepoints. No evidence of differences was found between the complete-case and imputed samples for analyses of moderation by genetic risk. Complete-case findings are presented in tables A4.6-A4.7, in the appendices.

4.5.4.5 Analyses using GEE models

As an alternative approach to multiple imputation, General Estimating Equations (GEE) models of relative age effects on all outcomes were produced. As described in more detail in chapter 2, these modelled relative age effects by measuring how much the average response would change for every one-unit increase in a covariate across the population (Liang & Zeger, 1986). GEE models supported the models that used imputed data. GEE models of ADHD trait risk showed main effects of relative age up to sixteen years, attenuating to the null at 25 years, and main effects of ADHD group (see table A4.8 in the appendices). No evidence of interactions between ADHD symptom group and mental health in these GEE models was found, but most were negative in direction.

In the GEE models of PRS (see table A4.9 in the appendices), main effects were found for relative age only up to 11 years, but followed the same pattern as other results, with wider confidence intervals. Main effects of PRS were observed (standardised effect size: 0.12 [0.08, 0.15]). No evidence of interactions was found.

4.6 Discussion

4.6.1 Summary and interpretation of results

The present study aimed to investigate whether the effect of relative age within the school year on risk of emotional, behavioural and social problems as symptoms of mental health problems varied by pre-school ADHD symptoms and ADHD genetic risk. This chapter aimed to test whether subjective and/or objective measurements of ADHD risk (i.e., parent-rated pre-school symptoms, or ADHD polygenic risk, respectively) interacted with, or provided additive effects towards, the relationship between relative age and mental health. The hypothesis that any association would be stronger for children at risk for a neurodevelopmental disorder (ADHD) than for

those without was tested. A comprehensive set of analyses examined mental health in childhood, adolescence and adulthood, and the robustness of findings to different bandwidth specifications for relative age, adjustment for covariates, different approaches to missing data, and different GWAS thresholds for measuring polygenic risk. Together these analyses provide a consistent answer to the study question. In line with findings in chapter 3, there were main effects of relative age within the school year on parent-rated risk of mental health problems, which is indicative that apparent effects are not simply a reflection of pre-school ADHD. Children who were at high risk for ADHD (as indexed by early symptoms or by genetic risk) before school entry were more likely to have a range of mental health problems in childhood, adolescence, and into adulthood illustrating both considerable continuity and change, consistent with previous literature (Addicoat et al., 2019; Biederman et al., 2012; Riglin, Leppert, et al., 2021).

Homotypic continuity was observed since ADHD problems before school entry predicted ADHD symptoms at later timepoints (see table 4.4 - hyperactivity problems). In addition, ADHD PRS predicted ADHD problems throughout development. However, the study adds further evidence for heterotypic continuities (i.e., that a particular form of psychopathology predicts another form of psychopathology at a later time point) because ADHD symptoms and genetic risk each had strong impacts on a range of problems - not just ADHD problems but also emotional problems, conduct problems, and problems with peers. The considerable number of heterotypic associations between ADHD and other mental health outcomes emphasises the need to identify moderators that can predict which children entering school with (or at high risk of) ADHD problems will continue to

display these or develop new problems later, throughout the school years and beyond.

Turning to the main aim, using an extension to the regression discontinuity approach previously utilised in chapter 3 of the thesis, analyses did not find any evidence for the hypothesis that ADHD risk might exacerbate the impact of young relative age on the majority of mental health outcomes. No evidence of interactions between relative age within the school year and ADHD symptom group or ADHD genetic risk was found in the present analyses. Therefore, the hypothesis that any association between effects of relative age within the school year and mental health problems will be stronger for children at risk for a neurodevelopmental disorder (ADHD) than for those without, was not supported.

The findings that nearly all estimated interactions of relative age and ADHD symptom group, and relative age and ADHD genetic risk were negative in direction were consistent with previous research investigating associations between relative age, ADHD, and mental health outcomes (Kuntsi et al., 2022), however, in the present study, these interactions did not reach conventional significance. This suggests that the impact of ADHD risk is reduced for people born in August, and that the impact of relative age is reduced for people at higher genetic risk for ADHD.

Further secondary analyses examined specific mental health outcomes as captured by the SDQ subscales; a negative interaction was found between relative age and genetic ADHD risk on peer problems, but no other statistical evidence for interactions between relative age and other subscales was found. This indicates that any effect of being young for the school year may be reduced for people who have higher ADHD genetic risk. These consistently negative interactions between relative

age and PRS suggested that the impact of relative age effects is reduced in children with a high genetic ADHD risk, but confidence intervals of interactions between relative age and ADHD risk on mental health were wide and spanned both sides of the null.

4.6.2 Strengths

The current study's main strengths are the use of rich data from a single longitudinal population cohort with ADHD symptoms assessed prior to school entry, and mental health and ADHD data that was collected throughout development. The study also used two different measures of ADHD risk - one assessing symptoms prior to school entry and so more likely to be independent of any relative age effects linked to school, and a second more plausibly objective measurement of ADHD risk (PRS). As explained in the previous chapter, an advantage of using regression discontinuity designs is that controlling for confounders is not as strict a requirement in regression discontinuity designs compared to other designs (Hahn et al., 2001; Moscoe et al., 2015). This is also the first unselected population-based study to look at ADHD risk and the interaction with relative age within the school year on mental health problems across development. Furthermore, this is the first genetically informed study of the interaction between ADHD risk and relative age on mental health problems.

4.6.3 Limitations

The key limitations of this study were participant attrition over time in the ALSPAC cohort leading to substantial data missingness, as well as the possibility of selection bias because of such attrition. Attempts were made to control for the effects of attrition by using imputed data, as well as by using sensitivity analyses that do not rely on imputed data.

The use of the ADHD hyperactivity subscale at 4 years may have limitations because of normative hyperactivity behaviours at that early age (i.e. behaviours that may be perceived as hyperactive but are within the norms of a child's behaviour at a young age; (Ford-Jones, 2015); it is possible that hyperactivity problems within this group may have been overestimated, which in turn may have caused an overinflated number of children in the borderline and high ADHD symptom score risk groups. An alternative approach using SDQ at 7 years to stratify ADHD risk by group was considered, however, it was decided to use the SDQ at 4 years considering that this measurement was more plausibly independent from effects of being young for the year after starting school (Chapter 3). Previous research had also shown that high SDQ scores in the preschool years were strongly predictive of ADHD in adolescence (Rimvall et al., 2014). Most importantly, results were consistent across the two definitions of ADHD risk used in the present study.

Analyses were also limited to broadly defined ADHD risk rather than those with a clinical diagnosis, given the low rates of ADHD diagnoses in the ALSPAC cohort (0.5%, (Powell et al., 2020). In addition, many neurodevelopmental disorder measurements in ALSPAC that were used to predict diagnoses were taken after children had already entered the school system. This would have caused methodological issues such as reverse causation and selection bias, especially if relative age is associated with ADHD diagnosis, which was expected given previous research (Root et al., 2019). The next chapter (chapter 5 - Relative age within the school year and psychiatric and health related outcomes in young people) used data gathered from electronic healthcare records to investigate relative age and diagnosed neurodevelopmental disorder effects on rarer, more serious outcomes.

4.6.4 Implications for theory and practice

The present study aimed to understand whether there was heterogeneity in relative age effects. i.e., the possibility that not all children who are young for the year will be equally affected by their young relative age. This is important theoretically because it might facilitate the identification of potential underpinning mechanisms that explain relative age effects. This is also important for practice because of the potential to expedite more targeted personalised interventions and support for those children who are more affected by young relative age. However, no evidence was found in support of the hypothesis that children at high ADHD risk are especially at risk of relative age effects. This offers some reassurance, but at same time, due to the additive effects of relative age and ADHD risk, it is still true that children with high ADHD risk and who are young for their school year are a very high-risk group for mental health problems. Of these two independent risk factors, ADHD risk is more important and requires appropriate attention. ADHD risk is therefore important to take seriously, even in children who are young for the year, and evidence from this chapter suggests that this association is likely not simply a reflection of developmental immaturity.

Interestingly, there was some tentative evidence to suggest that relative age effects may be less pronounced for children at high ADHD risk, on some aspects of mental health and wellbeing, e.g., peer problems. This could be because younger-in-school children may be more likely to get their ADHD diagnosed and receive support for their ADHD. Previous research found this for children with a clinical diagnosis of ADHD when examining clinical mental health outcomes (depression; Kuntsi et al., 2022). One suggestion in that study was that this result might reflect a lower (severity) threshold for school aged children being referred and diagnosed with

ADHD reflecting their younger age in the school year. However, this cannot be the explanation for findings in the present study because ADHD symptoms were assessed in the general population prior to school entry, not dependent on receiving a clinical diagnosis, and shown also using an independent objective indicator of genetic susceptibility to ADHD. In addition, the wide confidence intervals of interaction effects do not exclude the presence of clinical interaction effects of relative age and ADHD risk on mental health. Studies with a larger number of participants born in September and August with a high risk of ADHD, or meta-analyses of smaller studies will be needed to test this further.

4.6.5 Future research to better understand heterogeneity in relative age effects.

There are two main priorities for future research. First, whilst effects of relative age did not vary by ADHD risk (except for peer problems in childhood), future research should aim to identify other subgroups who may be at greater risk of, or conversely, relatively protected against effects of relative age in the school year. Second, future research should consider testing for heterogeneity in relative age effects either by using larger and more representative studies or conducting meta-analyses of smaller ones.

4.6.5.1 Children with other neurodevelopmental conditions

Future research should test other neurodevelopmental risk groups that may be more (or less) susceptible to effects of relative age within the school year, such as intellectual disabilities (ID) or autism spectrum disorder (ASD) to see if other neurodevelopmental disorders show similar relationships to that of relative age in the school year and ADHD (Chen et al., 2022; Root et al., 2019).

4.6.5.2 Children born prematurely

Future research is also needed on whether other types of neurodevelopmental risk, such as premature birth, are associated with relative age effects on mental health problems. Premature birth is relatively common at around 6% and ALSPAC includes around 900 children born prematurely (Odd, Evans, & Emond, 2019). Premature birth is especially interesting because some children who were born pre-term are at considerably greater risk of neurodevelopmental disorders as well as emotional and behavioural problems, depression, anxiety, and conduct problems, and these risks increase the more extreme the prematurity (Singh et al., 2013). Premature children are also more likely to struggle in school, and especially if their actual birth date and due date were on different sides of the 1st of September cut-off (i.e., their premature birth caused them to be placed into the “incorrect” school year meaning they were also the youngest in the year; (Odd, Evans, & Emond, 2013, 2016).

4.6.5.3 Anthropometric features that might moderate the effects of relative age

The youngest children in a school year are on average physiologically and psychologically less developed than their older peers. But not every child develops in the same way due to different genes, environments, and interactions within and between genes and environments. Physically, there will be variance in children's height and weight, even within those children who are relatively young for the school year. An interesting idea for further research to explore is testing the role of anthropometric variables such as height, weight, and pubertal onset and timing, on the relationship between relative age and mental health problem risk at different ages. Some subgroups of children young for their year may be at greater risk of emotional, behavioural and social difficulties and exposure to bullying behaviours

than others because of physical and psychological differences (Rose, Monda-Amaya, & Espelage, 2010).

4.6.5.4 Testing for heterogeneity of effects of relative age on rarer outcomes, and in individuals with diagnosed ADHD

Future research should aim to test for heterogeneity of relative age effects in individuals with diagnosed ADHD and/or other neurodevelopmental disorders and investigate clinical outcomes using designs that typically gather data from larger number of participants, such as using electronic healthcare records data. This allows for rare and more serious outcomes to be investigated, as well as inclusion of individuals with diagnosed neurodevelopmental disorders, and improved representativeness of children with ADHD seen in clinical practice. The next chapter (chapter 5) aimed to test this further using data gathered from whole-nation Welsh electronic healthcare records – the Secure Anonymised Information Linkage (SAIL) databank, described in further detail in chapter 2 (section 2.3).

4.7 Conclusions

Relative age in the school year and ADHD both contribute independent effects towards risk for mental health difficulties. ADHD is a particularly potent predictor that requires identification and support regardless of children's age in school year. Conversely, young relative age is an additional predictor of risk that is important to consider in planning support for children. Further research will be necessary to identify moderators to the relationship between age in the school year and risk of mental health problems.

Chapter 5: Relative age within the school year and psychiatric and health related outcomes in young people

5.1 Chapter synopsis

Chapters 3 and 4 of the thesis examined the relationship between relative age in the school year and risk of mental health problems in a general population longitudinal cohort and tested the extent to which this relationship was moderated by individual risk of ADHD. The results indicated that the youngest children are more likely to have poorer parent ratings of mental health problems (especially emotional, hyperactivity and social difficulties) relative to their older peers during the school years but not in adulthood. Individual risk of ADHD also contributed towards the risk of poor mental health, as expected. However, there was no evidence that the youngest individuals who are also at high risk of ADHD were more vulnerable to the effects of relative age on emotional, behavioural and social difficulties, and in chapter 4 there was evidence to suggest that the effects of relative age on social difficulties were reduced in children who had a high genetic risk of ADHD. A limitation discussed in the previous chapter was that the ALSPAC cohort may not be representative of individuals with diagnosed ADHD. In addition, heterogeneity of relative age effects in individuals with diagnosed ADHD and/or other neurodevelopmental disorders, and investigating rarer, more serious outcomes, remain relatively unexplored. This chapter aimed to counteract some of these limitations using data gathered from electronic health care records to test associations between relative age and explore adult (16-25 years) mental health disorder diagnoses and other clinical outcomes by age within school year.

5.2 Abstract

Purpose

This chapter aimed to (i) test associations between relative age within the school year and a diagnosis of attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) by age 18, and (ii) to test relative age effects on clinical mental health outcomes (adult anxiety and depression disorders, self-harming, or drug misuse) into young adulthood and whether relative age effects on these outcomes differ according to neurodevelopmental disorder diagnosis.

Method

Data were used from anonymised electronic healthcare records in Wales (SAIL databank) for young adults aged 16-25 years, using a regression discontinuity design. Individuals with a diagnosis of ADHD and/or ASD were matched to individuals without a diagnosis. These samples were used to test for association between relative age effects and neurodevelopmental disorder diagnostic status. Associations between relative age in school year (August vs September births) and ADHD/ASD diagnosis were tested, as well as associations between relative age in the school year and young adult anxiety and depression disorders, self-harming, alcohol misuse, drug misuse, and A&E use, as well as their interactions.

Results: Individuals who were the youngest in their school year were more likely to be diagnosed with ADHD (RR: 1.22 [1.13, 1.32]). No differences by relative age on ASD diagnoses were identified (RR: 1.01 [0.92, 1.10]). No consistent evidence of differences in adult anxiety and depression disorders, self-harming, or drug misuse by relative age in school year in those with a neurodevelopmental disorder were found, and there was no consistent evidence of interactions between relative age and neurodevelopmental disorder on these outcomes. These findings were

supported by sensitivity analyses comparing children born in August and September only.

Conclusion: There was robust evidence for effects of relative age in school year on ADHD diagnosis, but not for adverse psychiatric and related clinical outcomes in adulthood. There is no moderation of age within school year effects on mental health according to neurodevelopmental disorder diagnosis.

5.3 Introduction

As covered in more detail in chapter 1 of the thesis, population cohort studies of school-aged children have identified that the youngest within their academic year group face disadvantages in many mental health and related psychosocial outcomes, including poorer mental health outcomes including diagnoses of anxiety and depression, increased risk of suicide, lower life satisfaction, emotional wellbeing, social skills, and education attainment, greater peer problems, and reduced sports participation and attainment (Ando et al., 2019; Cobley, Baker, et al., 2009; Crawford et al., 2013; Fumarco & Baert, 2019; Fumarco et al., 2020; Goodman et al., 2003; Matsubayashi & Ueda, 2015). There is evidence that relative age in the school year exerts a potential causal influence on anxiety and depression independent of any seasonal effects. For example, Goodman et al. (2003) used large representative population surveys to compare mental health disorder rates by relative age in England, Wales, Scotland, and Northern Ireland – nations with different cut off dates for school entry. The researchers found influences of relative age on psychiatric disorder symptoms and diagnosis (Goodman et al., 2003). These effects were present for children and adolescents, and for different school entry cut-offs.

One recent large-scale English study using electronic healthcare records data strongly supports findings from population-based cohort studies on effects of relative age in the school year on mental health and neurodevelopmental disorders. Root et al (2019) in a large study of 4–15-year-olds found evidence to suggest that the youngest individuals in their academic year group were more likely to be diagnosed with mental health disorders (anxiety and depression) as well as ADHD (Root et al., 2019), but the study did not examine outcomes in young adulthood or test whether

effects of relative age in the school year on mental health differ for children with and without ADHD.

There are two important knowledge gaps that this chapter considers. First, it is unclear whether some individuals who were young in their year and have a known additional risk factor for poor mental health outcomes (i.e., a neurodevelopmental disorder diagnosis) are more susceptible to relative age effects than others. Second, evidence on relative age effects beyond the school years is much sparser.

Crucial to this thesis is the assumption that being young for the school year may not affect individuals equally. One reason for heterogeneity in effects of relative age in the school year might reflect individual variability in developmental maturity. There may be differential effects for individuals diagnosed with neurodevelopmental disorders and those who do not have a diagnosis; young people with neurodevelopmental conditions such as ADHD and ASD are known to be at greater risk of poor psychiatric and related clinical outcomes such as being diagnosed with psychiatric disorders such as anxiety and depression, as well as self-harming, substance misuse and A&E admission (Addicoat et al., 2019; Biederman et al., 2012; Brunkhorst-Kanaan et al., 2021; Butwicka et al., 2017; Hirvikoski et al., 2019; Langley et al., 2023; Rai et al., 2018). Furthermore, evidence from global meta-analyses demonstrates that relatively young individuals are more likely to be diagnosed with ADHD and be prescribed medication for ADHD (risk ratio: 1.27; 95%CI: [1.19, 1.35]; (Holland & Sayal, 2019)) and one prior, yet large (N >9 million) study of relative age in Taiwan suggests younger children in the school year are also more likely to be diagnosed with ASD compared with older peers (OR: 1.23; 95%CI: [1.16, 1.32]) (Chen et al., 2022). Given this, it is important to establish whether

individuals with neurodevelopmental disorders who are also young for their year have particularly poor later mental health outcomes.

Only one reported study has compared effects of relative age in the school year on mental health outcomes in young people by neurodevelopmental disorder diagnosis. Kuntsi et al (2022) investigated whether relative age and ADHD independently or jointly influenced psychiatric outcomes in a large (N = 297,840, of which 6,528 were diagnosed with ADHD) Swedish register-based electronic cohort aged between 15-23 years (Kuntsi et al., 2022). The researchers found that the youngest individuals within the school year that did not have a diagnosis of ADHD were at greater risk for depression diagnosis, substance abuse, and poor education attainment, but not criminality. For individuals diagnosed with ADHD, younger relative age was associated with substance abuse risk and poor education attainment, but not criminality or depression. The study found no interactions for most outcomes with exception of an interaction between relative age and ADHD on depression, suggesting that the effect of young relative age on depression was reduced among the individuals with ADHD. Given the sparsity of evidence to date it is important to replicate these findings and establish whether they generalise to other countries and health care contexts. The previous chapter (chapter 4) considered this question in relation to early ADHD risk in the general population. The current chapter builds on this by examining this for individuals who received a diagnosis of a neurodevelopmental disorder (ADHD and/or ASD) in childhood to compare relative age effects on mental health and related adverse clinical outcomes (diagnoses of anxiety/depression, self-harming, drug and alcohol misuse, and accident and emergency services use) in individuals with and without a diagnosis of neurodevelopmental disorders.

To summarise, previous research shows that relative age is associated with likelihood of neurodevelopmental disorder diagnosis and possibly with psychiatric health outcomes such as depression, suicide, and substance misuse, but it is not fully understood whether effects of relative age in the school year on mental health differ by neurodevelopmental disorder status.

5.3 Methods

5.3.1 Study design and participants

The study population comprised individuals living in Wales (population 3 million), born between 01/01/1991 and 12/31/2000 (N=553,551). Data were analysed from five datasets hosted by the Secure Anonymised Information Linkage (SAIL) Databank in Wales. Further details, and a flowchart of the datasets utilised, exclusions, and the number of participants in each group are provided in chapter 2 (section 2.3). The current study is comprised of three different parts; i: a preliminary whole-population analysis of ADHD and ASD diagnosis rates by relative age, ii: a cohort study that tested risk of adverse clinical outcomes by relative age in individuals who had received a childhood diagnosis of ADHD or ASD and their matched controls, stratified by these groups, and iii: a cohort study investigating the interplay between relative age and neurodevelopmental disorders on adverse outcomes, using two subsamples of SAIL databank participants (ADHD cases & controls/ASD cases & controls). In parts ii) and iii), data were analysed from participants who were selected and matched on week of birth and sex for a previous, unrelated (to relative age effects) case/control study (Langley et al., 2023). Selection into the study sample causes bias if missingness depends on the outcome. Here, selection was dependent on a variable closely related to the exposure (week of birth), sex, and the moderator (ADHD/ASD). Selection did not depend on the outcome (given the exposure and the moderator). Therefore, the selection of participants into case/control groups should not have caused bias in these models. The whole-population analyses in part i) did not match participants.

5.3.2 Exposure, moderation, and outcome measures

Previously derived and validated measures were used in the present analysis (Langley et al., 2023); whilst a brief description is given below, further details on the datasets and outcome measures are presented in chapter 2 of the thesis (chapter 2, section 2.3), and summarised in table 2.1 in chapter 2.

5.3.2.1 Exposure:

The exposure variable was relative age in the school year, determined by month of birth in relation to the academic year (oldest in year Sept = 1; youngest in year Aug = 12). Relative age in the school year was used as a continuous variable (range = 1-12). Analyses were repeated restricting to those born in August and September only, as a sensitivity analysis.

5.3.2.2 Moderator/stratifying variables:

The main stratifying variables of interest were ADHD (case vs control) and separately ASD (case vs control).

5.3.3 Outcome variables:

Psychiatric outcomes were recorded from ages 16-25 years (or the latest that the follow up period allowed). These outcomes were: anxiety/depression disorders, self-harm, alcohol misuse, drug misuse, and accident and emergency services use (hereafter, A&E services use).

5.3.3.1 Anxiety/Depression disorders:

The presence of any Anxiety/Depression disorders, defined as anxiety or depression diagnoses, were predicted by a previously validated algorithm to identify anxiety or depression disorders (John et al., 2020; John et al., 2022).

5.3.3.2 Self-harm:

Self-harming incidents (self-harm) were defined as non-fatal but intentional self-harm, including self-injury, self-poisoning, and suicide attempts, but not suicidal thoughts (Marchant et al., 2020).

5.3.3.3 Drug misuse:

Drug misuse was defined and recorded as the harmful use, or diagnosis of dependence on, psychoactive substances except alcohol or tobacco (Quan et al., 2005; Thompson et al., 2004).

5.3.3.4 Alcohol misuse:

Alcohol misuse was defined and recorded as the harmful use of alcohol, as well as the involvement of alcohol in an admission to hospital care, and diagnoses of alcohol dependence syndrome (Carr et al., 2017; McKenzie et al., 2010).

5.3.3.5 Accident and emergency (A&E) services use

A&E services use was defined as all recorded contacts with A&E departments (John et al., 2020).

5.3.4 Analyses

Loglinear models using a regression discontinuity approach were used to test relative age effects on mental health outcomes.

5.3.4.1 Preliminary analysis: Investigating ADHD and ASD diagnosis rates by relative age in the whole population.

To test whether relative age was associated with neurodevelopmental disorder diagnosis, risk of ADHD and ASD diagnosis by relative age in the full unselected study population was tested. Separate logistic regressions were conducted on the likelihood of selection into the ASD or ADHD case group by month of birth. Odds ratios (ORs) are presented, describing the ratio of odds of an adverse mental health outcome for a one-year difference in relative age. If outcomes are rare (i.e., a prevalence of less than 5% in total population) then the odds ratio is approximately equal to risk ratio, i.e., the ratio of risk of an adverse outcome (Cummings, 2009).

5.3.4.2 Investigating relative age effects on young adult mental health outcomes for children with and without ADHD or ASD

After this initial analysis, associations between relative age, neurodevelopmental disorder diagnosis, and mental health outcomes were then examined. The first step of analysis included relative age in the school year as the predictor, with each mental health variable as an outcome with sex and follow-up time as covariates and analyses stratified by ADHD/ASD status.

The second step used a cohort design (with analyses conducted in subsamples of SAIL) investigating clinical outcomes in ADHD cases and controls, and ASD cases and controls. Interaction terms between ADHD (or ASD) and relative age in the school year were added for each outcome. Our analysis models included main effects of relative age, neurodevelopmental disorder case status and the interaction

between the two. Risk ratios (RR) and 95% confidence intervals (CIs) are presented, describing the change in risk of adverse mental health outcome for a one-year difference in relative age for each ADHD/ASD group.

Two sets of models were fitted; first, one where month of birth is treated as a continuous exposure, and the second restricted to those born in August and September, using month of birth as a binary variable. This was chosen as a sensitivity analysis because for values that lie close to the cut-off, the assumption of no confounding is more plausible (Bor et al., 2014; Oldenburg et al., 2016; Venkataramani et al., 2016).

The data were analysed using IBM SPSS Statistics (version 26) predictive analytics software.

5.4 Results

5.4.1 Descriptive statistics

Sex, relative deprivation (measured by Welsh Index of Multiple Deprivation), follow-up time, and the rates of each adverse psychiatric outcome are presented by month of birth for each ADHD or ASD case/control group, in chapter 2 of the thesis (section 2.6, table 2.6).

5.4.2 Prevalence of neurodevelopmental conditions by relative age in the school year.

Rates of ADHD and ASD by month of birth in the total population sample are summarised in figure 5.1 and table 5.1. As shown in the figure, the prevalence of clinically diagnosed ADHD was highest in August-born children than the average across the school year (per 1 year difference OR: 1.22 [1.13, 1.32]). Rates of ASD did not vary by relative age (per 1 year difference OR: 1.01 [0.92, 1.10]).

Figure 5.1: Neurodevelopmental disorder (neurodevelopmental disorder) rates by Month of Birth (MOB, in relation to school year in Wales) in whole study population

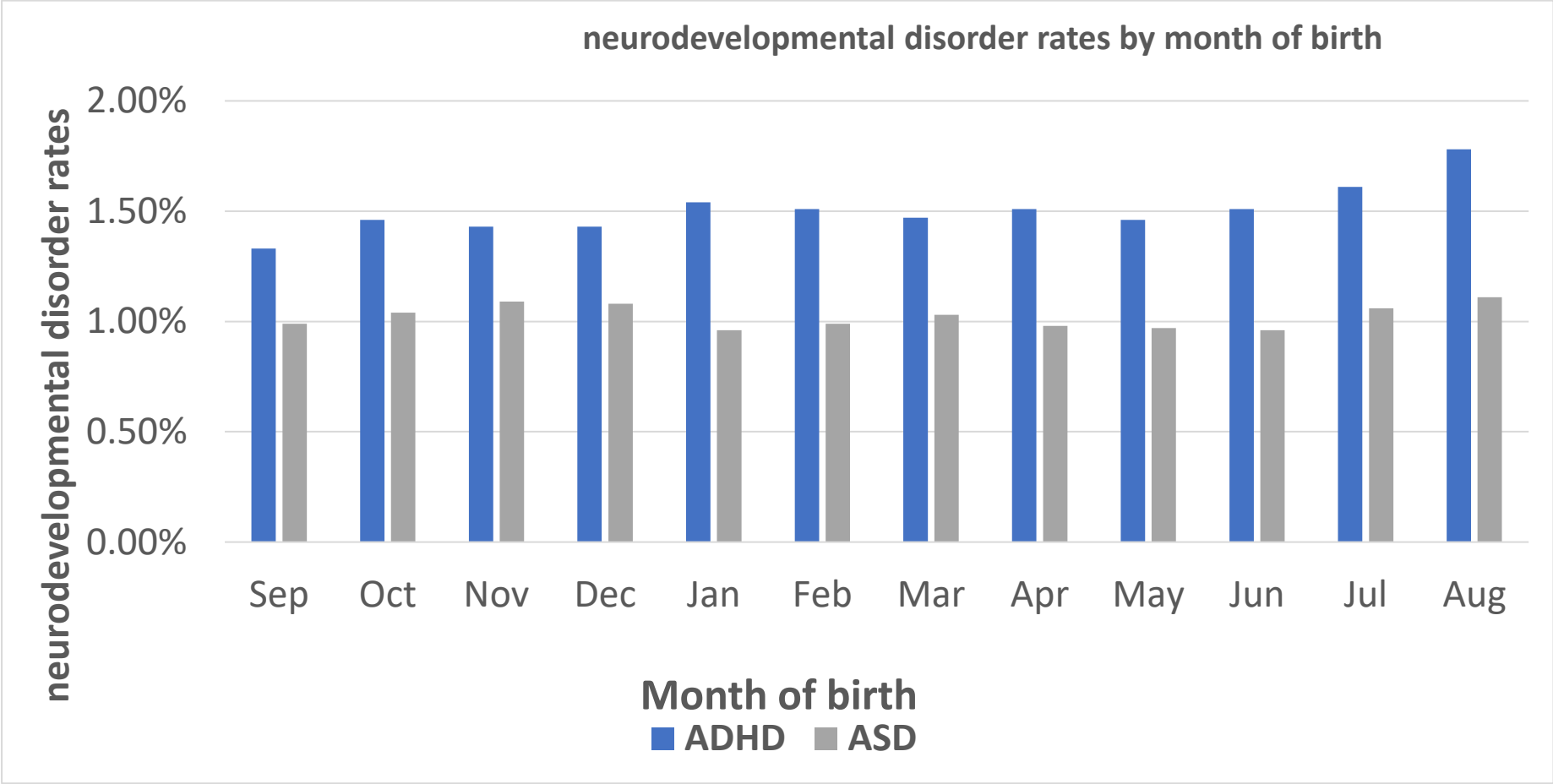


Table 5.1: Neurodevelopmental disorder rates by Month of Birth (MOB) in whole study population

MOB	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Total
N	47540	43931	44232	43491	46926	43324	47929	44962	48309	46752	47927	48228	553551
ADHD	1.33%	1.46%	1.43%	1.43%	1.54%	1.51%	1.47%	1.51%	1.46%	1.51%	1.61%	1.78%	1.51%
ASD	0.99%	1.04%	1.09%	1.08%	0.96%	0.99%	1.03%	0.98%	0.97%	0.96%	1.06%	1.11%	1.02%

5.4.3 Estimating the effects of relative age in the school year on outcomes (anxiety/depression disorders, self-harm, drug misuse, alcohol misuse, and accident and emergency services use), stratified by ADHD case and control groups and ASD case and control groups

Effects of relative age in the school year on Anxiety/Depression disorders, self-harm, drug misuse, alcohol misuse and A&E service use, stratified by group were investigated. In these analyses, ADHD cases, ADHD controls, ASD cases, and ASD controls were treated as independent groups. These results are summarised in figure 5.2, below, and in the appendices (table A5.1). In the main analyses, risk ratios are the ratio of risk of an outcome per one-year decrease in relative age (Rel.age), or ratio of risk of an outcome by presence of a neurodevelopmental disorder (ADHD/ASD) diagnosis (diagnosis vs no diagnosis), assuming a linear association.

5.4.3.1 Relative age in school year impacts on ADHD/ASD associated mental health outcomes

5.4.3.1.1 ADHD controls

Within the ADHD control group, there was a general pattern that month of birth was associated with increased risk of all outcomes. This only reached conventional significance for A&E use (see figure 5.2, panel A).

5.4.3.1.2 ADHD cases

In ADHD cases, RRs of month of birth were close to 1 for all outcomes except for drug misuse, which showed a trend of increased risk by relative age, and alcohol misuse, which appeared to show decreased risk. 95% CIs crossed the null for all outcomes (see figure 5.2, panel B).

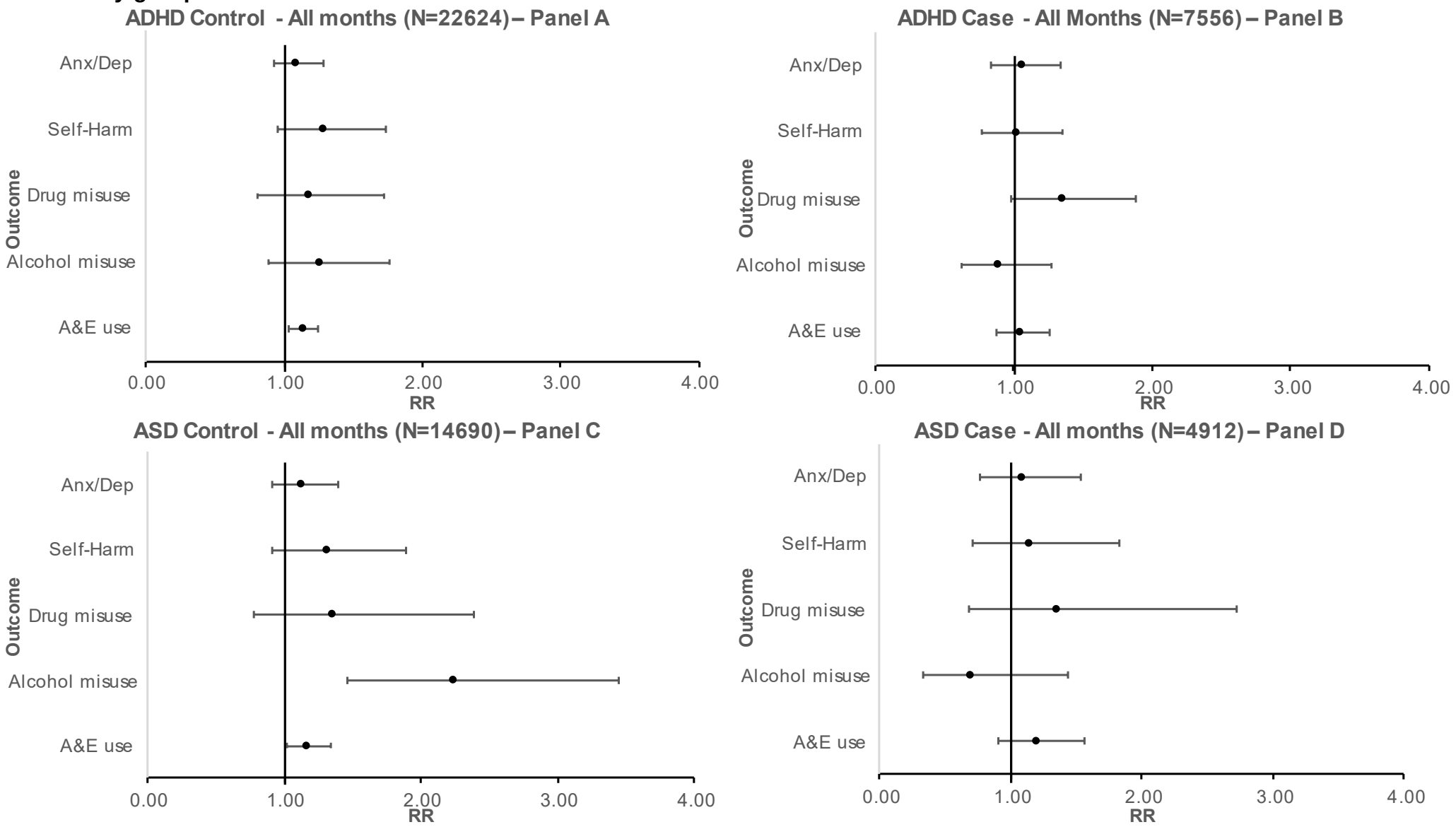
5.4.3.1.3 ASD controls

Within the ASD control group, there was a general pattern that month of birth was associated with increased risk of all outcomes. This reached conventional significance for alcohol misuse and A&E use (see figure 5.2, panel C).

5.4.3.1.4 ASD cases

Month of birth was associated with increased risk of all outcomes except for alcohol misuse, which showed decreased risk. RRs of month of birth were close to 1 and 95% CIs crossed the null for all outcomes (see figure 5.2, panel D).

Figure 5.2: Estimated effects of relative age (per 1 year difference) on psychiatric and related clinical outcomes in young adults, stratified by group.



ADHD controls (A), ADHD cases (B), ASD controls (C), and ASD cases (D).

5.4.4 Estimating the main effects of relative age in the school year and presence of a neurodevelopmental condition on outcomes in ADHD case/control and ASD case/control groups, and interactions between relative age and neurodevelopmental disorder diagnosis.

The main effects of relative age and a presence of a neurodevelopmental condition (ADHD and ASD, respectively) on these outcomes were tested. Effects of relative age in the school year on the outcomes according to presence of a neurodevelopmental condition were then tested by adding interaction terms between ADHD (or ASD) and relative age in the school year for each outcome. These results are summarised in figure 5.3, and full results are presented in table 5.2, below.

5.4.4.1 ADHD

5.4.4.1.1 Relative age in school year impacts on outcomes

There was a general pattern that relative age in the school year was associated with increased risk of all outcomes. This only reached conventional significance for A&E use; for all other outcomes, CIs were wide and spanned the null.

5.4.4.1.2 ADHD impacts on outcomes

As shown previously (Langley et al., 2023), main effects of ADHD on all outcomes relative to the main effects of relative age in the school year were identified.

5.4.4.1.3 Interactions between relative age in the school year and presence of ADHD

No evidence of an interaction between relative age and ADHD on any outcome was found, with all effects crossing the null.

5.4.4.2 ASD

5.4.4.2.1 Relative age in school year impacts on outcomes

There was a general pattern that relative age in the school year was associated with increased risk of all outcomes. This only reached conventional significance for A&E use and alcohol misuse.

5.4.4.2.2 ASD impacts on outcomes

As shown previously (Langley et al., 2023), ASD was associated with increased risk of all outcomes except on A&E use, but effects were in the same direction.

5.4.4.2.3 Interactions between relative age in the school year and presence of ASD

As shown in Figure 5.3 (panel B), a general pattern of negative interaction effects of relative age and ASD was found for all outcomes. All interaction effects were small (i.e., close to 1), and all 95% CIs crossed the null, except for alcohol misuse.

Figure 5.3: Risk of psychiatric and related health outcomes: Interactions of relative age, ADHD, and ASD.

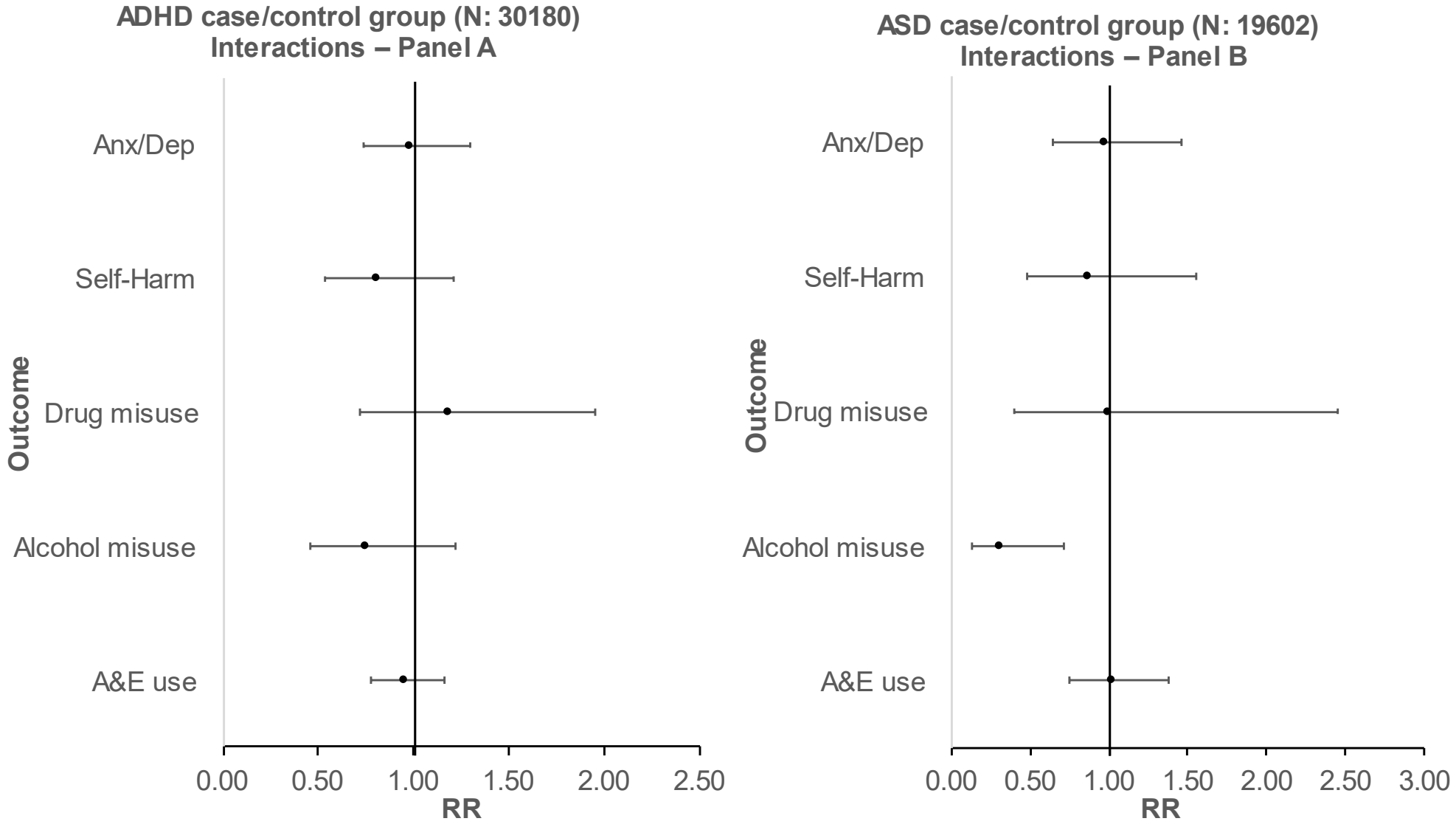


Table 5.2: Relative age in School Year (Rel.age) *neurodevelopmental disorder status interaction model table.

ADHD (N=30180)	Variable	RR	CI	p	ASD (N=19602)	Variable	RR	CI	p
Anx/Dep	Rel.age	1.09	0.93, 1.28	0.31	Anx/Dep	Rel.age	1.12	0.91, 1.39	0.29
	ADHD	2.23	1.87, 2.66	<0.01		ASD	2.04	1.59, 2.62	<0.01
	Interaction	0.98	0.74, 1.30	0.89		Interaction	0.97	0.64, 1.46	0.87
Self-Harm	Rel.age	1.28	0.95, 1.72	0.11	Self-Harm	Rel.age	1.32	0.91, 1.90	0.14
	ADHD	6.06	4.67, 7.86	<0.01		ASD	2.96	2.05, 4.27	<0.01
	Interaction	0.80	0.53, 1.21	0.29		Interaction	0.86	0.48, 1.55	0.62
Drug misuse	Rel.age	1.16	0.79, 1.70	0.44	Drug misuse	Rel.age	1.36	0.78, 2.38	0.29
	ADHD	5.17	3.74, 7.16	<0.01		ASD	1.94	1.09, 3.46	0.02
	Interaction	1.15	0.69, 1.91	0.59		Interaction	0.99	0.40, 2.45	0.99
Alcohol misuse	Rel.age	1.22	0.87, 1.72	0.25	Alcohol misuse	Rel.age	2.24	1.47, 3.44	<0.01
	ADHD	4.32	3.18, 5.87	<0.01		ASD	2.15	1.27, 3.61	<0.01
	Interaction	0.74	0.45, 1.22	0.24		Interaction	0.30	0.13, 0.71	0.01
A&E services use	Rel.age	1.13	1.03, 1.24	0.01	A&E services use	Rel.age	1.17	1.02, 1.34	0.03
	ADHD	1.45	1.28, 1.65	<0.01		ASD	1.04	0.86, 1.25	0.69
	Interaction	0.95	0.77, 1.16	0.60		Interaction	1.02	0.75, 1.38	0.57

Rel.age = main effect of relative age in school year in the model. ADHD/ASD = Main effect of ADHD or ASD in the model. Interaction = interaction term between Rel.age and ADHD/ASD. RR = risk ratio of an outcome per one-year decrease in relative age (Rel.age), or risk ratio of an outcome by presence of a neurodevelopmental disorder (ADHD/ASD) diagnosis (diagnosis vs no diagnosis), assuming a linear association. ADHD cases and controls (left), ASD cases and controls (right). All months (September-August) entered.

5.4.4.3 - Sensitivity analyses

5.4.4.3.1 Prevalence of neurodevelopmental conditions by relative age in school year in the general population: August & September-born children only

These analyses mirror those in section 5.4.2 but restricted to those born in August and September only. The prevalence of ADHD was higher in August-born children (1.78%) than those born in September (1.33%) (OR: 1.38 [1.24, 1.55]). However, the difference in prevalence of ASD between August-born individuals and those born in September was smaller (1.11% vs 0.99%; OR: 1.13 [0.98, 1.29]).

5.4.4.3.2 Estimating the effects of relative age in school year on outcomes, stratified by ADHD case and control groups and ASD case and control groups: August and September only.

These analyses mirror those in section 5.4.3. but restricted to those born in August and September only. Full results are displayed in the appendices (Appendix table A5.2).

Drug use was marginally associated with a younger relative age in the ADHD control group, but this did not reach conventional statistical significance (RR: 1.89 [0.99, 3.61]). RRs were in the same (positive) direction and CIs overlapped with those in the main analysis (RR: 1.18 [0.80, 1.73]). All other results accorded with the main analysis.

5.4.4.3.3 Main effects of relative age in school year: August & September-born children only

These analyses mirror those in section 5.4.4. but restricted to those born in August and September only. Full results are displayed in the appendices (Appendix table A5.3)

A marginal association between relative age in school year on drug misuse was found in the ADHD case/control group (RR: 1.88 [1.00, 3.54]). Whilst this did not reach conventional significance, this was not found in the main analysis (RR:1.16 [0.79, 1.70]); the RRs are different, but both in the same (positive) direction, and their CIs overlap. All other results accorded with the main analysis.

5.4.4.3.4 Main effects of ADHD/ASD: August & September-born children only

All estimates and 95% CIs were consistent with the main analysis.

5.4.4.3.5 Estimating interactions between relative age: August & September-born children only

All estimates and 95% CIs were consistent with the main analysis.

5.5 Discussion

5.5.1 Summary and interpretation of results

The present chapter aimed to examine whether individuals who are relatively young for their school year are at increased risk of anxiety/depression disorders, drug misuse, alcohol misuse, self-harm, and A&E use in young adulthood. The extent to which individuals with neurodevelopmental disorders diagnosed in childhood who are also young for their school year were particularly susceptible to these adverse mental health and related clinical outcomes was also investigated. It has been already widely reported that relative age in the school year influences ADHD diagnosis and to a lesser extent risk for mental health problems (at least in the school years; Root et al., 2019; Holland & Sayal, 2019), but fewer studies have tested whether they influence other neurodevelopmental disorder diagnoses (such as ASD), and whether effects of relative age in the school year persist into young

adulthood or would be more severe in those diagnosed with neurodevelopmental disorders (Chen et al., 2022).

First, data from a large Welsh register-based electronic cohort was used to show that relatively young individuals are more likely to have received an ADHD diagnosis, but not an ASD diagnosis.

Second, in analyses stratified by neurodevelopmental group, being relatively young for the school year appeared to raise risk ratios of all outcomes, but effects were small and only consistently reached conventional statistical significance for A&E service use, in young adults (16–25-year-olds) without a neurodevelopmental disorder (i.e., the controls). In cases, there was a general pattern that month of birth is associated with increased risk of all outcomes in all groups, except for alcohol misuse in both ADHD and ASD cases. Associations were weaker in cases; all RRs were closer to 1 in cases compared to controls, with all 95% CIs crossing the null.

Third, models of subsamples of the SAIL electronic healthcare cohort which examined the effects of relative age, neurodevelopmental group and interactions between relative age and neurodevelopmental disorders on psychiatric outcomes found large main effects of ADHD and ASD on psychiatric outcomes. This accords with previous research elsewhere, including previous analyses in this sample (Addicoat et al., 2019; Biederman et al., 2012; Brunkhorst-Kanaan et al., 2021; Butwicka et al., 2017; Hirvikoski et al., 2019; Langley et al., 2023; Rai et al., 2018).

Finally, all interactions between relative age and adverse outcomes by neurodevelopmental status in the above models were close to 1; all 95% confidence intervals crossed the null, except for a negative interaction between relative age and

ASD on alcohol misuse. Except for that interaction, effects were similar in the ASD and ADHD case/control groups.

Findings extend previous research that have investigated effects of relative age in the school year on psychiatric outcomes by examining outcomes in the transition to adulthood. The current study suggests that risks for depression, anxiety and suicide associated with younger relative age do not extend into the post-school years. The finding that there is no statistical evidence of an effect of relative age on anxiety or depression diagnosis in young adulthood (irrespective of neurodevelopmental status) is in line with findings from the findings in chapter 3 from a prospective longitudinal cohort that effects of relative age in the school year on mental health problem risk attenuate to the null in the general population in young adulthood (Broughton et al., 2023). The current study also extends previous research by adding to the very few studies that have tested heterogeneity in effects of relative age in the school year. There was no statistical evidence of difference in patterns of risk by relative age for mental health and related outcomes in individuals with ADHD or ASD. The present study provides some suggestive evidence that relative age may be associated with elevated risk for broader clinical outcomes in young adulthood, including alcohol misuse and A&E services use (at least in individuals who are not diagnosed with neurodevelopmental disorders), consistent with previous findings (Kuntsi et al, 2022).

The findings of the present study accord with those by Kuntsi et al (2022) who found that relatively young people with ADHD are more likely to be diagnosed with substance use disorders and have a reduced risk of depression relative to controls. our estimated effects were in the same direction and consistent with Kuntsi's findings, but with confidence intervals crossing the null. One reason for this (and the

most likely) is that this study may have been underpowered to detect effects; the study had a smaller sample size (N: 45161) compared with Kuntsi et al.'s study (N: 297840). A second reason may be variation in school entry cut-offs and policies relating to flexibility in school entry between Wales and Sweden, such as a later school entry age in Sweden (Sweden: 6-7 years; UK: 4-5 years; Kuntsi et al., 2022).

5.5.2 Implications

The main implication of these findings is that the effects of being young for the school year on anxiety and depression disorders, self-harming, drug misuse, alcohol misuse, and A&E services use in young adults, if any, are modest in comparison to the effects of neurodevelopmental disorders on these outcomes, (Biederman et al., 2012; Brunkhorst-Kanaan et al., 2021; Butwicka et al., 2017; Hirvikoski et al., 2019; Langley et al., 2023; Rai et al., 2018). The effects of neurodevelopmental disorders on adverse psychiatric and clinical outcomes are pronounced, long-term, and occur irrespective of whether individuals are young or old for their school year. This may be due to a variety of factors that are associated with both neurodevelopmental disorders and with mental health disorders, including (but not limited to) poor peer relationships, bullying, academic competence, and maturity differences (Eyre et al., 2019; Powell et al., 2020; Thapar, Cooper, Eyre, & Langley, 2013).

A timely diagnosis Is particularly important for children with ADHD to receive appropriate treatment and support. Currently, evidence suggests that ADHD diagnosis can be significantly delayed and some children are missed altogether, this is especially the case in girls, and even more so for girls who do not have many externalising mental health problems (Mowlem et al., 2019; Roughan & Stafford, 2019). Given that ADHD risk is important regardless of age in school year, it is

important that an ADHD diagnosis is picked up appropriately regardless of children's age.

Relative age is associated with ADHD diagnosis, and evidence from the previous two chapters in this thesis demonstrates that relative age impacts on mental health outcomes earlier in the life course. Thus, there is some justification for including relatively young children with ADHD as a group that is more susceptible to mental health disorders. This group should be prioritised for resources and interventions to counteract these effects, if moderators of the relationship between relative age and mental health risk are not found in the future. Further research is warranted on identifying more pertinent exacerbating factors of relative age effects on mental health problems for a more efficient use of these resources. Clinicians and teachers should become more aware of relative age effects in the youngest children to reduce inequalities in opportunities that may be caused by the school entry cut-off (Broughton et al., 2023; Norbury et al., 2016).

5.5.3 Strengths of the study

This study is reportedly the first UK-based study to investigate effects of relative age in the school year on health outcomes in ADHD and ASD in young adulthood. A large electronic health care records data-based cohort was used, offering statistically powerful analyses. One advantage of electronic health care records data is that they can be used to study rare and serious clinical outcomes given their sample size and power.

5.5.4 Limitations of the study

This study also has limitations. First, the study is prone to the same drawbacks as many other studies using electronic healthcare records data, including the fact that

there is no systematic timing and no standardised scales to measure disorder and outcome traits consistently over time. Second, clinical samples are associated with several biases. This includes help-seeking bias, e.g. men are less likely to access primary care for mental health problems (Sagar-Ouriaghli, Godfrey, Bridge, Meade, & Brown, 2019), diagnostic bias in primary care and subsequent referral to specialists, e.g. the underdiagnosis of ADHD and ASD in girls (Meyer, Stevenson, & Sonuga-Barke, 2020), and referral biases relating to impact and burden of symptoms on others. For example, teachers and parents are more likely to refer to services when symptoms impact on families or classrooms; similarly, young people with mental health disorders may not get seen by services and will subsequently be missed in health care records (Meyer et al., 2020). However, it is important to note that diagnostic rates for ADHD in the UK are relatively low compared to other nations, so it is likely that not everyone with symptoms that meet diagnostic criteria will be included in the sample (Raman et al., 2018).

In addition, information was limited to what was recorded within these datasets, which included no information on neurodevelopmental disorders besides diagnosis. Therefore, information on symptom severity within case groups could not be ascertained, as well as information on comorbidities such as intellectual disability, diagnoses which are known to be influenced by relative age (Root et al., 2019). This may also be true for the outcome measures. Moreover, precise dates of birth could not be determined to a further extent than week of birth. This necessitated the exclusion of some individuals born close to the school-entry cut-off, i.e., those born in any week commencing 26th- 31st August. As a result, effects of relative age in the school year on outcomes may have been underestimated, but it is worth noting that findings in this chapter agree with those in the previous chapter of this thesis.

Lastly, information was unavailable on whether certain children had been given a delayed school entry. Recent research suggests that the relationship between relative age in the school year and ADHD diagnosis attenuates when relatively young children are held back for a year, but it is important to note that this practice is rare in Wales (Fleming et al., 2022).

5.5.5 Directions for future research

Further studies of possible heterogeneity in relative age effects are warranted. This includes more detailed investigation of developmental variation – when and under what circumstances are relative age effects maintained or attenuated across the school years and beyond. It is also important to consider other groups of children who might be particularly vulnerable. Young people who are born prematurely and are consequently placed in the year above their school year given their expected due date may be particularly susceptible to adverse psychiatric outcomes (Odd et al., 2016). Where robust evidence of effects of relative age in the school year for psychiatric outcomes is found it will also be important to understand how and why these occur. Estimating mediation of effects of relative age in the school year on mental health outcomes is beyond the scope of the study but would also be an interesting direction for future research to take, one route may be to estimate effects of potential underpinning mechanisms of the relationship between relative age, neurodevelopment, and mental health, such as bullying, self-esteem, or education attainment (Crawford et al., 2013; Patalay et al., 2015). Lastly, future research could investigate effects of relative age in the school year across different countries and school systems.

5.6 Conclusion

This study indicates that for most psychiatric outcomes there was some tentative evidence to suggest that risk of likelihood of adverse outcomes were increased by young relative age in the school year, especially in A&E use in clinical health records in young adulthood. In addition, the study indicates that there is no evidence that effects of relative age in the school year exacerbate the known risks of poorer outcomes in those with a diagnosed neurodevelopmental disorder, and that interaction effects, if any, appear to be in the opposite direction, which is in line with previous research. However, relative age in the school year is associated with an early (i.e., in childhood) diagnosis of ADHD, which has considerably and consistently stronger effects on risk of adverse outcomes in young adulthood.

Chapter 6: General discussion

6.1 Recap of aims of PhD thesis

The main aims of this thesis were to investigate whether being relatively young in the school year influences mental health problems (emotional, behavioural, and social difficulties, and hyperactivity) in young people, and to investigate whether early neurodevelopmental vulnerability influences susceptibility to the effects of age within school year on mental health risk. Neurodevelopmental vulnerability was defined as high levels of preschool ADHD symptoms (chapter 4), high genetic susceptibility to ADHD (chapter 4), or a childhood diagnosis of a neurodevelopmental disorder (ADHD/ASD; chapter 5). The present thesis aimed to improve understanding of the interplay between individual risk and the environment (i.e., the effect of being young for the school year) on mental health up to young adulthood. It was predicted that a young age at school entry may be a pertinent exacerbating factor for mental health problems given pre-existing neurodevelopmental differences. Throughout the thesis, a developmental perspective of mental health problems and ADHD was taken to map the course of relative age effects on mental health problems from early childhood (i.e., before entry into school), throughout childhood and adolescence (i.e., during the school years) and into adulthood (i.e., long after the period of compulsory schooling), and how this course was modified by pre-existing neurodevelopmental differences.

Practically, this research is important because it provides evidence on a key policy-relevant question: should children be rigidly assigned to a school entry based on date of birth or should there be greater flexibility in school entry reflecting a child's developmental and neurodevelopmental maturity? In addition, this research is important because it potentially provides evidence that may facilitate the

identification of those who are most at risk for later mental health problems. This subsequently allows for the appropriate targeting of early preventative intervention, if individuals who are relatively young for the school year and have a high risk of neurodevelopmental disorder are found to be especially susceptible to mental health problems.

This chapter will firstly recap the primary aims and objectives of the thesis, then summarise the findings of each results chapter. After this, the chapter will discuss the strengths and limitations of the thesis, then highlight some potential future directions for further research, and finally discuss potential implications and recommendations arising from this body of work.

6.1.1 Recap of primary objectives

There were three primary objectives of the thesis:

The first objective was to utilise a regression discontinuity design to examine the association between relative age in school year and risk of mental health problems in childhood, adolescence, and young adulthood, in a longitudinal population cohort (ALSPAC), using general and specific measurements of mental health problems and depression, respectively, and test the hypothesis that the youngest children in the school year will be at greater risk for these mental health problems.

The second objective was to test the hypothesis that any association between age within school year and mental health problems would be stronger for children with neurodevelopmental vulnerability than for those without, by testing neurodevelopmental vulnerability as a moderator between age within school year and mental health.

The third objective of the thesis was to test links between relative age and adult (16-25

years) mental health disorder diagnoses and other clinical outcomes (hospital admissions/self-harm, drug misuse, alcohol misuse, and accident and emergency services use) in individuals with or without a diagnosis of a neurodevelopmental disorder (ADHD/ASD) in childhood, using data from a whole population cohort with electronic healthcare records data.

6.2 Summary of findings

6.2.1 Chapter 3: Relative age in the school year and risk of mental health problems in childhood, adolescence, and young adulthood

Chapter 3 investigated the impact of relative age in school year on mental health and depression. Data was analysed from a large UK longitudinal population study of young people aged 4 to 25 (ALSPAC, Avon Longitudinal Study of Parents and Children). Throughout data collection in this cohort, young people and their parents completed questionnaires that asked about symptoms of poor mental health (emotional, behavioural and social difficulties, and hyperactivity) in the young person, as well as about depression symptoms specifically. The analysis found that the youngest children had greater parent-rated risk of mental health problems but only during the school years. Before school entry, no evidence of differences in mental health problem risk scores between younger and older children was found. During the school years, the youngest children were more likely to have elevated (i.e., worse) mental health problems as reported by parents, and this difference between the oldest and youngest children was greatest at 11 years of age. However, by the time young people had reached 25 years of age, the effect of relative age on mental health had attenuated to the null. As a secondary analysis, the effect of relative age on SDQ subscales was investigated, and it was found that the hyperactivity problems subscale followed the same pattern as the total difficulties score, in

addition to showing the largest differences by relative age of all subscales; smaller, yet still statistically significant differences by relative age were observed in the emotional problems and peer problems subscales, but no evidence of relative age differences was found for conduct problems. When analysing responses to the SMFQ, which asked specifically about depression symptoms, relative age effects were not consistently observed using self-rated and parent-rated depression. This pattern of relative age effects was consistently reported across multiple regression discontinuity selection bandwidths, across complete case and imputed datasets, and using GEE models as further sensitivity analyses.

6.2.2 Chapter 4: Testing whether the association between relative age and mental health varies according to ADHD risk: evidence from the ALSPAC cohort (ages 7-25 years)

The next step was to investigate whether children who were already at greater risk of developing mental health problems were more susceptible to the effects of relative age on mental health problems. The role of early neurodevelopmental disorder (ADHD) risk on mental health problems was tested in chapter 4. ADHD risk was investigated in two ways; first, by using before-school age parent-report ADHD traits to stratify ADHD risk into risk comparison groups, and second, by investigating genetic vulnerability to ADHD using ADHD polygenic risk.

The reason for using parent-rated hyperactivity at 4 years and polygenic risk scores as indicators was that these were more plausibly not influenced by any effects on ADHD of being young in school, and because ADHD PRS provides an objective measurement of ADHD risk completely independent of any rater-biases that might affect parent, teacher, or self-reported neurodevelopmental disorder symptoms. The key findings in chapter 4 were that, while both subjective and objective measures of ADHD risk contributed effects towards the risk of social, behavioural and emotional

difficulties alongside relative age in the school year, there was no statistical evidence of interactions between relative age and either measure of ADHD risk on mental health problems; 95% confidence intervals were wide and spanned the null. Therefore, there was no evidence that ADHD exacerbates the effects of relative age on mental health problem risk. Whilst not statistically significant, the interactions between ADHD PRS and relative age in predicting later overall mental health problem risk (as measured by SDQ total difficulties) were negative in direction at all outcome measurement timepoints. However, statistically significant negative interactions were found between relative age, ADHD PRS, and social difficulties (SDQ peer problems subscale scores). No evidence of interactions between relative age and other mental health difficulties were found.

It was not possible to investigate more serious clinical outcomes in the ALSPAC cohort, nor was it possible to compare individuals with and without a diagnosed neurodevelopmental disorder, due to a lack of relevant clinical assessment.

6.2.3 Chapter 5: Relative age within the school year and psychiatric and health related outcomes in young people

It was therefore important to consider clinical data from electronic health care records since their strengths can potentially counteract some limitations of longitudinal population cohort designs, such as representativeness, attrition, and non-response bias (Casey et al., 2016). In chapter 5 of the thesis, electronic health record data from across Wales was used to investigate whether age within school year moderated risk of psychiatric and related mental health outcomes in late adolescence and young adulthood in individuals with and without a diagnosis of a neurodevelopmental disorder (ADHD or ASD). These outcomes were included the presence of common mental disorders, self-harm, substance use, and accident and

emergency service use between the ages of 16-25 years. A further aim was to test whether risk for adverse outcomes associated with young relative age differed between individuals who had or had not received a childhood neurodevelopmental disorder diagnosis. The analysis in chapter 5 found that age within school year had a negligible effect on mental health disorder diagnoses and related clinical outcomes in young adulthood, especially when compared to the effects of neurodevelopmental disorders on these adverse outcomes. Furthermore, no robust evidence of differential relative age effects on adult mental health disorders according to neurodevelopment status was identified. These findings were supported by sensitivity analyses comparing children born in August and September only. As in chapter 4, no evidence of interactions between relative age and a diagnosis of ADHD/ASD on adverse mental health outcomes was found.

There was no statistical evidence of an effect of relative age on ASD diagnosis, however, a young age within school year was associated with an increased likelihood of ADHD diagnoses. Therefore, even when effects of relative age on mental health become seemingly negligible in adulthood, relative age effects may persist on other variables that strongly predict mental health.

6.3 Interpretation of findings

6.3.1 Interpretation of relative age effects

Taken together, the results from the present thesis indicate that, firstly, being relatively young in the school year was associated with poorer parent-rated mental health problems as assessed using the SDQ, but not with parent or self-reported depressive symptoms. These effects were most strongly evident for hyperactivity problems, but also evident for emotional problems and problems with peers, but not

conduct problems. Second, evidence of an association between age within school year and risk of mental health problems was only observed in young people who are of school age. Third, the effects of relative age and neurodevelopmental disorder risk contributed independently towards the risk of mental health problems, as there was no statistical evidence of interaction effects between relative age and mental health risk. Last, age within school year is associated with the likelihood of mental health problems in childhood including probability of an ADHD diagnosis, but there was no statistical evidence that age within school year was associated with ASD.

As discussed in chapter 2, regression discontinuity approaches can estimate causal effects of "treatment" (i.e. being relatively old for the school year), when other experimental methods such as randomized controlled trials are not feasible (Moscoe et al., 2015; Thistlethwaite & Campbell, 1960; Venkataramani et al., 2016). A valid causal interpretation of findings relies on the assumption that individuals born on and close to either side of the regression discontinuity cut-off (in this case September 1st), must have similar distributions of potential confounders. If this assumption is plausible, then it can be inferred that individuals close to the cut-off are effectively randomly selected for "treatment".

Throughout this doctoral work, assumption violations of the RD design were tested by checking the distribution of covariates and auxiliary variables included in the regression discontinuity models across the school year (Bor et al., 2014; Hahn et al., 2001; Oldenburg et al., 2016). In both the ALSPAC and SAIL datasets, there was no statistical evidence of a discontinuity in the distribution of any of the potential confounders across the school entry cut-off. The distribution of births across the months of the school year was checked in all studies and these analyses found no evidence of a discontinuous relationship in births across the September 1st threshold.

Therefore, because no evidence was found to indicate a violation of these assumptions, it can be inferred that individuals born close to the cut-off were as effectively randomly selected as possible. Thus, it can be indicated that the increase in risk of mental health problems in the relatively youngest individuals was solely the result of their relatively young age at school entry. Possible mechanisms for this effect are discussed below. The similarity of findings across the three studies, using multiple sensitivity analyses and using two different types of population cohort, adds robustness and coherence. Thus, evidence suggests that there are relative age effects on emotional, behavioural, hyperactivity and peer problems in the school years, but neither study suggested that these continue into young adulthood. The studies contribute to the growing body of literature that indicates that relative age effects on outcomes exist and are not due to other similar variables, such as season of birth (Caye et al., 2020; Fleming et al., 2022; Goodman et al., 2003; Karlstad et al., 2017).

6.3.2 Interpretation of relative age effects findings for specific domains of psychopathology

As discussed, the thesis has shown robust relative age effects on mental health, however, it is also important to consider whether and why relative age effects vary for specific domains of mental health. The following subsection discusses the findings for specific outcomes measured in this thesis.

6.3.2.1 Conduct problems

Previous studies reported inconsistent evidence on whether relative age influences risk of conduct problems, antisocial behaviour or criminality, and this evidence appears to strongly vary depending on groups, contexts and culture; previous studies have reported that individuals born late in the school year were more likely to

commit a crime and be incarcerated, but only within certain subgroups (Peña, 2019) or at certain ages (Dhuey et al., 2019; Landersø, Nielsen, & Simonsen, 2017)), and others do not find associations between relative age and conduct problems or criminal behaviour (Lien, Tambs, Oppedal, Heyerdahl, & Bjertness, 2005; Patalay et al., 2015). In chapters 3 and 4, it was found that parent-rated SDQ conduct problems were not statistically significantly associated with relative age effects, therefore findings in this thesis support the evidence that relative age effects are not associated with the risk of children to engage in externalising behavioural difficulties such as having tantrums, fighting, stealing and related anti-social behavioural problems.

6.3.2.2 Emotional problems

Previous studies have more consistently reported the presence of relative age effects on emotional difficulties (Ando et al., 2019; Patalay et al., 2015). The evidence of this thesis supports this previous research, a young relative age is associated with increased (i.e., worse) parent-rated emotional difficulties symptoms even before entry into school (see table 3.3), and differences in emotional difficulties scores persist up to the age of sixteen years. However, both self-rated and parent-rated depression were not consistently associated with relative age within the school year. This indicates that underlying anxiety symptoms may be driving relative age differences in emotional problem scores because effects of relative age specifically on depressive symptoms were not found.

One possible reason for finding relative age differences in emotional problems before school entry is that the youngest children in the school year may be more anxious in their pre-school settings, and whilst pre-school education may not

organise children into academic year groups, they may still group August-born children with older children within their would-be school year.

6.3.2.3 Peer problems

A young relative age was associated with problems with peers during the school years in the current thesis (see tables 3.3 & 4.4).This is consistent with previous research on relative age effects and peer-related problems which reported that the youngest children face increased peer victimisation and have fewer quality friendships (Fumarco & Baert, 2019; Mühlenweg, 2010). Interestingly, negative interactions between relative age and ADHD PRS on peer problems on mental health problems were found, i.e., that relative age effects on peer problems were less pronounced for relatively young children with a high genetic ADHD risk. This could be because younger-in-school children may be more likely to get their ADHD diagnosed and receive support for their ADHD. Another possible reason for a negative peer problem interaction may be because relatively young children with a higher genetic risk for ADHD may have already been identified as having issues with their friendship groups before or during school, thus they may have already received some form of peer problem related interventions, such as buddy systems. Further research should be conducted on the role of peer problems and bullying as a potential underpinning mechanism of relative age and mental health problem risk.

6.3.2.4. Neurodevelopmental problems/disorder diagnoses

6.3.2.4.1 ADHD

Throughout this thesis, evidence indicates that neurodevelopmental problems are a more important factor in contributing to mental health problems than relative age, however, relative age is associated with ADHD traits as well as receiving a a

diagnosis of a neurodevelopmental disorder, ADHD. This adds support to previous evidence for associations of relative age effects with ADHD symptoms and diagnoses (Caye et al., 2020; Fleming et al., 2022; Halldner et al., 2014; Holland & Sayal, 2019; Root et al., 2019). Parent ratings of hyperactive behaviours (chapters 3 & 4), genetic risk of ADHD in the form of polygenic risk (chapter 4), and diagnoses of ADHD (chapter 5) were associated with mental health problems in young people, and these effects have consistently shown to be either equivalent to (ADHD PRS) or considerably stronger than (parent-rated ADHD risk; ADHD diagnoses) the effects of relative age on mental health problems. Apart from an interaction of relative age and ADHD genetic risk on peer problems at certain ages, no statistically significant evidence for interactions between relative age and ADHD (symptoms, genetic risk, or diagnoses) on outcomes were observed, but effects were in the same direction as previous research investigating the interplay between relative age effects and ADHD on mental health and related outcomes (Kuntsi et al., 2022). This suggests that effects of relative age and ADHD are likely independent, suggesting that interventions to prevent mental health problems in children should aim to target young people with or at high risk of neurodevelopmental disorders, but not to discount the effects of relative age on some neurodevelopmental problems. Teachers, clinicians, and related professionals should take relative age of the child into account when deciding whether to refer children for, and for those children to receive, a diagnosis of ADHD.

6.3.2.4.2 ASD

ASD behaviours and genetic risk were not tested in the present thesis; this was because there were no validated and reliable measures of autistic traits that were taken before school entry in ALSPAC, which is important to maintain temporal

precedence of pre-existing neurodevelopmental traits for causal inference. Furthermore, validated measures of autistic traits were only taken after school entry, and autistic traits were measured inconsistently over the developmental period investigated in this thesis. In chapter 5, effects of relative age were investigated on ASD diagnoses, which showed no statistical evidence of a relationship. This indicates that ASD, at least up to age 18 years, is not influenced by relative age. This differs from the only other study known to investigate relative age and ASD, which found that relative age was associated with receiving a diagnosis of ASD (Chen et al., 2022), OR=1.23 [1.16, 1.33] but effects were nonetheless in the same direction. Further research using a population cohort with validated and reliable autism trait measurements taken before and after school entry will be necessary to establish whether autistic traits and autism genetic risk are influenced by relative age in children and young people. Like ADHD, a diagnosis of ASD was strongly associated with anxiety and depression disorder diagnoses as well as risk of self-harm.

6.3.3 Interpretation of findings in relation to previous research

The findings of chapter 3 and 4 support previous research indicating that relative age in the school year influences emotional problems in children, and that the relatively youngest children show poorer social and emotional development (Crawford et al., 2013; Goodman et al., 2003; Patalay et al., 2015; Root et al., 2019). However, the persistence of parent-rated differences in SDQ scores by relative age up to sixteen years had not been observed in previous studies using ALSPAC data; Crawford et al. (2013) found that parent-rated differences in SDQ scores by relative age are not present beyond the age of nine years of age. However, in both studies, estimates were in the same direction. This may be because chapters 3 and 4 used a more precise measure of relative age (i.e., week of birth, rather than month of birth).

In addition, chapter 3 used imputed data to account for missing data. Lastly, the Crawford study and those in this thesis used different covariates. The findings of chapters 3 and 4 support previous research that found that relative age effects occur in childhood (5-10 years) and adolescence (11-15 years; Goodman et al., 2003).

The hypothesis that any association with relative age within the school year will be stronger for children at risk of ADHD was not supported by findings observed in chapter 4 or chapter 5.

Findings in chapter 5 extend similar previous research investigating effects of relative age in the school year on clinical psychiatric outcomes for individuals who received a diagnosis of a neurodevelopmental disorder (ADHD and/or ASD) in childhood. Differential effects of relative age on clinical outcomes by neurodevelopmental status had been unexplored until recently (Kuntsi et al., 2022), especially when investigating associations between ASD and relative age. The finding that there is no statistical evidence for an effect of relative age on anxiety or depression diagnosis in young adulthood (irrespective of neurodevelopmental status) is in line with findings from chapters 3 & 4 of the thesis. Furthermore, chapter 5 replicated previously well-established findings that younger children in the school year are more likely to be diagnosed with ADHD (Holland & Sayal, 2019; Schnorrbusch, Fabiano, Aloe, & Toro Rodriguez, 2020). The findings in chapter 5 also add to the very few studies that have tested heterogeneity in effects of relative age in the school year, since it was found that individuals with ADHD or ASD do not differ in patterns of risk by relative age for diagnoses of anxiety/depression disorders and related adverse clinical outcomes (Kuntsi et al., 2022). However, findings in chapter 5 contrast with those by Kuntsi et al (2022) who found that relatively young people with ADHD are more likely to be diagnosed with substance use disorders and

have a reduced risk of depression relative to controls. As discussed in chapter 5, variation in school entry cut-offs and policies on school entry between Wales and Sweden, as well as differences in sample size may have accounted for differences in findings. Chapter 5 extends previous clinical record research that has shown relative age effects in younger age groups (Goodman et al., 2003; Root et al., 2019).

6.3.4 Novelty of the studies within this thesis

There are several ways in which the studies contained in this thesis are novel. Prior to the analysis included in chapter 3, it was unknown whether differences in mental health problems by relative age occur prior to starting school. It was also unknown from unselected epidemiological samples whether relative age effects extend into adulthood, and most previous studies had only looked at general mental health symptom screens such as the SDQ. The study in chapter 3 is to my knowledge the first study to map the developmental course of relative age effects on risk of mental health problems from before school entry, through the school years, and to years after compulsory education had ended.

Much attention had been paid to the effects of relative age and ADHD before this thesis (Caye et al., 2020; Holland & Sayal, 2019; Root et al., 2019), but the novelty of chapters 4 and 5 is that they investigated the interplay between ADHD and relative age in the school year with respect to mental health problem traits (chapter 4) and mental health disorders and related clinical outcomes (chapter 5), which has only recently started to be explored (Kuntsi et al, 2022). The study contained in chapter 4 was to my knowledge the first to look at neurodevelopmental disorder trait risk and the interactions between this risk and relative age within the school year on risk of emotional, behavioural and peer problem traits across development. The study contained within chapter 5 is the first UK-based study to investigate effects of

relative age on health outcomes in young adulthood for children with and without ADHD or ASD.

6.4 Strengths and Limitations

6.4.1 Strengths

A key strength of the population cohort studies contained within the present thesis (chapters 3 & 4) is that rich data was used from a single longitudinal population cohort with data collected throughout development. Additionally, both studies used consistent and widely implemented parent and self-report measures of mental health problem and neurodevelopmental disorder risk, which are plausibly less influenced by relative age effects than teacher ratings.

In addition to the use of the validated and reliable measurements of general risk of mental health problem traits (SDQ), the analysis in chapter 3 also utilised validated and reliable measurements of depression symptoms (SMFQ). The use of validated and reliable questionnaires is a strength because assurance is provided that the SDQ and SMFQ measure what they intend to measure (general mental health risk, and depression risk, respectively), stably over time.

Chapter 4 is the first genetically informed study of relative age within the school year on mental health problems risk, and the first study to look at interactions between genetic risk of a neurodevelopmental disorder and relative age within the school year; this is a strength because collider bias and confounding are avoided by using genetic scores. In Chapter 5, data were analysed using a whole population electronic health care records data-based cohort which offered statistically powerful case/control groups. As discussed in chapter 1 (section 1.5.2.4) health record and epidemiological longitudinal cohort studies have different strengths and limitations

(Casey et al., 2016; Gianfrancesco & Goldstein, 2021; Sauer et al., 2022). Together, evidence from electronic health record and epidemiological longitudinal cohort studies may provide important triangulation of evidence that adds transparency and robustness to findings (Hammerton & Munafò, 2021).

6.4.2 Limitations

Some of the limitations specific to each study have been discussed separately in each chapter, but general limitations that apply across the studies in the thesis are discussed here. Firstly, data missingness due to participant attrition may result in bias in longitudinal population cohort studies, such as the ALSPAC cohort used in chapters 3 and 4, due to differences between participants who are retained vs drop out. Attempts were made to mitigate the effects of non-response bias and uncertainty about the missing data by using a multiple imputation approach. Multiple imputation, as highlighted in chapter 2 of the thesis, is a widely implemented and flexible approach to dealing with this ubiquitous problem in research (Sterne et al., 2009). However, if individuals who are at increased risk of mental health problems are more likely to drop out, the use of multiple imputation will not remove all the bias (Lee et al., 2021). Furthermore, there is also the possibility of selection bias because of the exclusion of some participants from analysis altogether, especially in chapter 4, where analysis was restricted to participants who had SDQ hyperactivity measurements at 4 years or to participants who had available PRS data. These exclusions reduce the assumption of plausibility that the data are missing at random, which is essential for valid multiple imputation approaches. To address potential concerns about overreliance on imputed data in chapters 3 and 4, generalized estimating equation (GEE) models were implemented to relate mental health problem risk to relative age, and additional covariates (if adjusting for). Crucially, the

pattern of findings in chapters 3 and 4 did not materially change when these sensitivity analyses were run. Whilst GEE or complete case analyses may not overcome all limitations of multiple imputation, the similarity of findings in these sensitivity analyses to the main analyses suggest that findings are robust to different approaches to sample inclusion and accounting for missing data.

A second limitation of both chapters 3 and 4 was that there was a long gap between some measurements, including a nine-year gap between the last two SDQ measurements, between the ages of 16 and 25, so the precise timing of when relative age effects attenuated to the null after children had left school remained unknown.

A third limitation to consider for chapters 3 and 4 is that these results may only be generalisable to one generation of children in the UK, and more specifically in the geographical area that ALSPAC took place (South West England); other school admissions systems may vary, and school admissions policies in some areas may have become more flexible with regards to school entry for the youngest children in the school year, relative to the time period when ALSPAC child data was collected, due to non-statutory government advice, or policy changes (Department for Education, 2013; Fleming et al., 2022). Whilst previous research has established that relative age effects occur across UK nations with different school entry cut-offs (Goodman et al., 2003), other countries may show different effects because of different policies relating to flexibility with regards to school entry (Holland & Sayal, 2019). Further research will be necessary to replicate findings using data gathered from children born more recently.

The main limitations of chapter 5 are comparable to many other studies using electronic healthcare records data. For example, there was no systematic timing in the SAIL databank, as well as no standardised scales to measure disorder and outcome traits consistently over time (Gianfrancesco & Goldstein, 2021; Pirkis, Nicholas, & Gunnell, 2020). In addition, analysis was restricted to the limited information that was recorded within the specific SAIL dataset used in this study, which did not include any more information on neurodevelopmental disorders or psychiatric outcomes besides the presence or absence of a diagnosis, i.e., there was no further information on the severity of neurodevelopmental disorders, and no information on the impact of diagnosed neurodevelopmental disorders on individuals. This is important considering there is considerable heterogeneity in the severity and impact of neurodevelopmental disorders between individuals (Thapar et al., 2017). Therefore, analyses could not be refined to elucidate whether certain individuals with ASD or ADHD were more vulnerable than others with the same diagnosis to certain adverse outcomes. Moreover, precise dates of birth could not be determined in this dataset, so it was necessary to exclude individuals born closest to the school-entry cut-off. In sum, the studies in the present thesis are not free from the limitations that population cohort and electronic healthcare records studies face, which may be attributed to the fact that secondary data analysis was conducted in all three studies, where the data was not collected for this specific purpose. Nevertheless, the consistency in results that were obtained from these analyses triangulates evidence, allowing for more clear and coherent conclusions to be made.

As discussed earlier in this thesis (section 1.5.2.1), unmeasured environmental and familial confounding is a problem in observational studies (Thapar & Rutter, 2015; 2019). An advantage of the regression discontinuity design is that the assumption of

no unmeasured confounding between exposures and outcomes is likely to hold, enabling causal inference (Moscoe et al., 2015; Oldenburg et al., 2016). However, in this thesis this only applies to relative age, where it is assumed that there are no unmeasured confounders for participants who were born close to the cut-off. Confounding is possible for ADHD (or ASD), and this may have complicated interpretations of the main effect of ADHD/ASD on mental health problem risk/outcomes, either as a result of distortion of effect estimates (overestimation or underestimation of effects of ADHD/ASD), or through attrition (Howe, Tilling, Galobardes, & Lawlor, 2013; Taylor et al., 2018). The main effects of ADHD/ASD could have been confounded by several underlying variables. For example, SES could have confounded main effects of ADHD/ASD because it affects access to support services and thus may have affected the likelihood of receiving a diagnosis (Collishaw et al., 2019; Sellers et al., 2019). UK evidence suggests that children with low SES are more likely to receive a diagnosis of ADHD (Russell, Ford, & Russell, 2018; Russell, Ford, Williams, & Russell, 2016), as well as depression (Freeman et al., 2016; Thapar et al., 2012; Thapar et al., 2022). Evidence of SES effects on ASD is mixed and may be dependent on geographical area (Kelly et al., 2017; Roman-Urrestarazu et al., 2021). Parent ADHD/ASD traits or genetic risk may also have led to inflated estimates of ADHD and mental health problem risk and diagnoses (Agha, Zammit, Thapar, & Langley, 2013; Faraone & Larsson, 2019). Sex may have also confounded ADHD estimates through selection into ADHD or ASD groups, as well as attrition, given the preponderance of males diagnosed (Martin et al., 2018; Mowlem et al., 2019). Parental age is implicated in increased diagnoses of ASD and ADHD and may also be implicated in poor mental health outcomes (Hvolgaard Mikkelsen et al., 2017; Janecka et al., 2017; Zondervan-Zwijnenburg et al., 2020). Interactions

between neurodevelopmental disorders and outcomes could have been altered by the same potential confounding variables, however, relative age in these interactions would still not be affected by confounding. For example, if parent ADHD interacted with relative age in its effect on alcohol use, and parent ADHD causes, it would look as though child ADHD interacted with relative age in their effects on alcohol use. However, the association would be via a confounding-interaction of parent ADHD. Effects of various pre-school-entry covariates that are also known to be associated with ADHD were controlled for (where available), including, but not limited to smoking during pregnancy, premature delivery, low birth weight, maternal education (as a proxy for SES), maternal age (chapters 3 & 4), and sex (all results chapters) (Langley et al., 2012; Singh et al., 2013; Mowlem et al., 2019). Parent ADHD was not controlled for. Virtually all findings were unchanged when comparing unadjusted models to models that adjusted for potential confounders in chapters 3 and 4. Many potential confounders that were available in those chapters were unavailable to measure in chapter 5. However, the main effects of ADHD traits and diagnoses, measured in chapters 4 and 5 respectively, were large (compared to relative age) and were in the same direction.

6.5 Directions for further research

Based on findings and limitations addressed in this thesis, there are several suggestions for future studies that could further scientific understanding of the role of relative age within the school year and risk of mental health problems in childhood and adolescence.

6.5.1 Replication across nations with different school entry cut-offs and policies regarding school entry

Firstly, despite a rapidly growing body of research into relative age effects on mental health problems, more studies are needed to further assess the relationship. This is especially pertinent when comparing effects across different countries, where there is considerable variation in school entry cut-offs and policy relating to flexibility in school entry (Holland & Sayal, 2019). In addition, most previous investigations of relative age effects have been conducted in countries with a high income, with most studies originating from the US and UK (Holland & Sayal, 2019; Schnorrbusch et al., 2020; Urruticoechea et al., 2021). Future research should consider investigating the effects of relative age in the school year across different countries and school systems, especially in lower income countries, where the vast majority of young people live and mental health needs are greater (Kieling et al., 2011). In addition, further research could be conducted on whether there are secular effects of relative age effects on mental health, using data gathered from other population-based cohorts of a younger or older generations of children. For example, the UK includes other cohorts such as the Millennium Cohort Study (Connelly & Platt, 2014) and the 1958 birth cohort (Power & Elliott, 2005).

6.5.2 Identifying potential mechanisms of relative age and mental health

Where robust evidence of effects of relative age within the school year on mental health problems is found, it will also be important to understand how and why these occur; future longitudinal studies are needed to address potential mechanisms through which relative age affects mental health.

6.5.2.1 Identifying potential mechanisms: Bullying

As discussed in chapter 1, younger children in the school year have poorer education attainment and are more likely to be bullied (Crawford et al., 2013;

Mühlenweg, 2010) as well as often having a reduced social network relative to their older peers (Fumarco & Baert, 2019; Mühlenweg, 2010). In addition, children at risk of, or diagnosed with, neurodevelopmental disorders such as ADHD and/or ASD are more likely to experience bullying victimisation (Cappadocia, Weiss, & Pepler, 2012; Efron, Wijaya, Hazell, & Sciberras, 2018). On the other hand, research has indicated that good quality peer relationships and mutual friendships protect against poor mental health outcomes later in life (Collishaw et al., 2016; Powell et al., 2020). Further research is needed to establish the role of peer relationships as a potential mediator of the effect of relative age on mental health.

6.5.2.2 Identifying potential mechanisms: Age of onset of mental health problems

Genetic liability for ADHD has been shown to be associated with earlier mental health disorder onset (Rice, Riglin, Thapar et al., 2019). Age at onset therefore poses an interesting question that was not considered in this thesis, nor to my knowledge has it been covered in other relative age research. ADHD risk and potentially relative age might contribute to earlier age at onset which itself predicts poorer outcomes, including, but not limited to, greater depression severity, lower employment status, medical and psychiatric morbidity, and substance abuse (Lopez-Lopez et al., 2019; Thapar, Collishaw, Pine, & Thapar, 2012; Wilson, Hicks, Foster, McGue, & Iacono, 2015).

6.5.2.3 Schools – an ideal environment for identifying relative age mechanisms?

As explained in chapter 1, schools are environments in which young people spend much of their waking time and provide a consistent and comparatively controlled environment for children to interact with peers, and authority figures (teachers and other staff). Thus, the school environment provides a transformative, central role in

children's social, emotional, and cognitive development throughout childhood and adolescence (Jamal et al., 2013; Langford et al., 2014; Shackleton et al., 2016). The school environment therefore has the potential to play a crucial role in attenuating the risk of mental health problems, in addition to related risk factors including, but not limited to, those caused by being relatively young for the school year. As a result, schools are an ideal place for early preventative interventions for mental health problems to take place (Bonell et al., 2018; Shinde et al., 2018).

Therefore, a logical future direction for further research to take is to attempt to replicate and extend the findings of the current thesis using a whole population schools-based cohort. An example cohort is the School Health Research Network (SHRN) in Wales, a biennial survey that includes measures of adolescent mental health and covers more than 100,000 individuals aged 11-16 years across 200 schools (Hewitt, Roberts, Fletcher, Moore, & Murphy, 2018). The study is one of the largest of its kind worldwide, undertaking school-based assessments of health and wellbeing in all mainstream schools in Wales, with linkage to health records via the SAIL databank. Since 2019, the study has included mental health assessments, including measures of general mental health (the SDQ) and depression (SMFQ). The study would therefore provide excellent power for the comparison of children's outcomes born close to the school entry cut-off date. In addition, further analysis using the SHRN cohort may provide evidence on the effects of relative age in children who have received diagnoses of neurodevelopmental disorders (through linkage with health records). If findings of this thesis are replicated in whole-population schools-based cohorts, then further research could be undertaken to investigate heterogeneity of relative age effects within and across schools using school and regional level data. In other words, the aim would be to identify whether

different schools have larger or smaller relative age effects in their pupils compared to others, and if so, which characteristics of those schools are associated with those differences in relative age effects. There are many factors that could be considered here, including (but not limited to) whether schools are urban or rural, school or class size, diversity, and school connectedness (Bennett, O'Hare, & Lee, 1983; Jamal et al., 2013; Raniti, Rakesh, Patton, & Sawyer, 2022). The translatability to schools in other nations should also be considered, using a schools-based population cohort from a different nation for comparison, for example, the Scottish Schools Health and Wellbeing Improvement Research Network (SHINE). These school-level differences might allow to answer the question of how the education system should be changed to reduce the impact of relative age effects. An alternative direction for future research to consider may be to define and test measures of “school readiness”, i.e., how well prepared a child is cognitively, socially, and emotionally as a way of judging whether to delay school entry (Marti et al., 2018). Concurrently, collaboration with schools, stakeholders, and research advisory groups should be undertaken as a co-production approach to develop evidence-based recommendations for education policy and practice. This would also provide opportunities for qualitative research on the effects of relative age on mental health in school-aged children, which to my knowledge has not been explored.

6.5.3 Identifying other sources of heterogeneity in relative age effects

Further studies of possible individual-level heterogeneity in relative age effects are also necessary. This includes more detailed investigation of the role of developmental variation and relative age in the school year; when and under what conditions are relative age effects maintained or modified across the school years. This subsection will discuss some ideas for this.

6.5.3.1 Premature birth

One suggestion is that future research should aim to identify other groups at risk for mental health disorders who may also be influenced by effects of relative age in the school year. Premature birth is especially interesting in the context of relative age effects because some children born pre-term are at considerably greater risk of neurodevelopmental disorders as well as emotional and behavioural problems, depression, anxiety, and conduct problems, and these risks increase the more extreme the prematurity (Singh et al., 2013). Premature children are also more likely to struggle in school, and especially if they were born in the "wrong" school year given their expected due date, i.e., their actual date of birth crosses the September 1st threshold (Odd et al., 2013, 2016). A future direction for further research might involve investigating whether prematurity heightens relative age effects, particularly if individuals were born in the "wrong" school year given their expected due date. The effects of relative age and prematurity on mental health have only recently started to be explored; Bachmann et al (2022) found that relatively young children in Norway (Cut-off: 1st January) who were born at term (defined here as >=37 weeks) as well as those born prematurely were more likely to be prescribed psychostimulant medication (for ADHD) between the ages of 10 and 23 years (Bachmann, Risnes, Bjørngaard, Schei, & Pape, 2022). The researchers also found relative age effects for antidepressants and antipsychotics at 10-14 years, but not in individuals in older age groups (Bachmann et al., 2022). Future research could be conducted to see if this interaction between relative age and premature birth on mental health also applies to mental health more broadly, such as mental health traits, as well as whether this effect is evident in unselected epidemiological cohorts and the extent to which prematurity affects the relationship between relative age and mental health problems varies across development.

6.5.3.2 Anthropometry

A second source of heterogeneity in relative age effects on mental health problem risk may be via the child's physical characteristics (Copeland, Worthman, Shanahan, Costello, & Angold, 2019). The relatively youngest children in a school year are not only less mature psychologically than their older peers, but also physically. However, not every child develops at the same pace; there will be variability in children's height and weight, even within those children who are relatively young for the school year.

An interesting idea for further research to explore is testing the role of anthropometric variables such as height, weight, and pubertal onset and timing, on the relationship between relative age and mental health problem risk. A related idea for further research is investigating the extent to which physical activity moderates the relationship between relative age and mental health. As discussed in chapter 1, children who are relatively old for the school year are already at a physical and psychological advantage; they are often taller, stronger, and more cognitively developed than younger children, especially in earlier childhood (Cobley, Baker, et al., 2009; Heilmann, Memmert, Weinberg, & Lautenbach, 2022). It is also consistently reported that the oldest children are more likely to be selected for teams in sports that have selection regimes that are tied to the academic year (such as association football in the UK) (Cobley, Abraham, & Baker, 2008; Cobley, Baker, et al., 2009; Smith, Weir, Till, Romann, & Cobley, 2018). As a result of this advantage, the oldest children may be given more opportunities to engage in physical activity through training and competition than the youngest children in their school year. The timing of onset of maturity changes may also be an important risk factor; young people (and especially girls) who begin puberty earlier than their peers are especially vulnerable to mental health and related outcomes (Copeland et al., 2019; Euling et

al., 2008; Graber, 2013). The relationship between relative age in the school year and puberty remains unexplored. Further research could be conducted to investigate whether relative physical maturity (or, conversely, immaturity) modifies relative age effects on mental health problems, or, whether regular physical activity is a moderator for those younger in the year.

6.5.3.3 Identifying potential biomarkers of relative age effects

A further biological approach may be to test for potential biomarkers of stress that may be influenced by relative age within the school year. Reviews of longitudinal studies of children's biological stress response, measured using cortisol levels in saliva and hair during the transition from pre-school to the first year of school, have consistently identified that school entry coincides with an elevated cortisol level in children (Leblond et al., 2022; Parent et al., 2019). An interesting idea for further research would be to test whether younger age within school year is associated with a higher cortisol response relative to their older peers during this transition, and whether it might also take longer for their cortisol levels to recover to levels seen before school entry. If relative age moderates biological response to stress during school transition, then targeted measures to reduce stress in the youngest children might be an appropriate intervention.

6.6 Implications and recommendations

6.6.1 Increased flexibility regarding school entry for the most vulnerable children

The present thesis aimed to assess whether school entry age is associated with later mental health difficulties in specific at-risk groups, with the aim to identify those children who are at highest risk of later mental health problems, and who are therefore a priority for early support and preventative intervention. Identifying a group

of children who would benefit from delaying school entry also has potential individual, family, and societal benefits, and this is an intervention which could be reasonably implemented within the current legislative framework. Currently, guidance in Wales and England indicates that it is possible to delay school entry if there is a ‘compelling reason’. However, decisions on deferred school entry are often left to individual school admission boards, and policy varies between the devolved nations (Department for Education, 2014a, 2014b; 2019; Fleming et al., 2022). Previous authors have suggested school admissions and entry system changes, including delaying school entry (Dee & Sievertsen, 2018) or age-based assessment adjustments (Crawford et al., 2013). Whole-school changes to school admission systems for the general population should not be made based on the research presented in the present thesis alone, given that any changes to established school structures and admission systems need to be based on extensive evidence and will likely be difficult to implement in practice. It is important to consider possible unintended effects of any changes. This is because these changes could cause an increased disruption for local authority planning, schools, teachers, and families. Moreover, additional evidence is required on whether potential whole school-based approaches and interventions, such as age adjustments to grades and examinations, attenuate relative age effects and would be justified. It is important to remember that in any classroom some children will be younger than others, even when combining more than one year group together. Further research will be needed to test whether there are impacts of delayed school entry on children's mental health compared to children who started school ‘on time’, and whether these effects are long-lasting, and who benefits the most from these delays.

Another interesting idea is to school two years together so every child experiences being young for year and old for year, at least at the start of primary school (Bennett et al., 1983). One way to test if this mitigates relative age effects might be to conduct a study of smaller or rural schools where, by necessity, school year groups are combined, possibly through identifying which schools practice mixing age groups within a whole population schools-based cohort (e.g., SHRN or SHINE).

Based on the evidence in this thesis, relative age and ADHD contribute independent effects towards the risk of emotional, behavioural and social problems in children and adolescents, therefore, relatively young children at risk for ADHD are at an increased risk for mental health problems compared to children at risk for ADHD who are not relatively young. One possible intervention might be to place these children into a classroom in the academic year below their chronological age, or at least allow for a greater flexibility for this in countries that traditionally adopt a strict cut-off for school entry, such as in England and Wales. The argument for this is, if held back a year, the brain and behaviour maturity profile of a relatively young child with ADHD might then resemble more closely that of a typically developing child in the academic year group below, which may in turn improve self-esteem, academic achievement, and peer relationships for the held-back child (Shaw et al., 2007). Several charities and pressure groups (e.g., Bliss, the charity for premature babies) offer advice to parents to request delayed entry but note that demonstrating compelling reasons is difficult. Currently, in the UK there is considerable variation between the devolved nations, individual LEAs, and schools in allowing deferred school entry (Department for Education, 2014b). Based on the evidence collected in the present thesis, it may be appropriate for schools, educators, and families to differentiate between children with and without neurodevelopmental disorders in developing a targeted early

preventative intervention to reduce the effects of relative age in children with ADHD, such as delaying school entry. This is because evidence from this body of work indicates that relatively young children at risk for ADHD have a greater risk of emotional, behavioural and peer problems despite a lack of interaction between relative age and ADHD risk, due to both relative age and ADHD risk contributing effects towards the risk of mental health problems (in chapter 4). Furthermore, a young relative age is associated with an increased likelihood of ADHD diagnosis, which has a considerably stronger association with mental health problems than relative age (in chapter 5). It is suggested that teachers and clinicians become more aware of the relationship between relative age and mental health problems, and that local education authorities in England and Wales consider a more flexible approach to school entry, as is currently the case in Scotland (Fleming et al., 2022). However, other factors should additionally be taken into consideration, such as premature birth, and further research will also be needed to investigate whether relative age adds towards, moderates, or even mitigates the effects of these factors on mental health problems. Another important consideration is how ADHD is defined before school entry if this is to be the intervention. The SDQ might be a useful validated measure of emotional, behavioural, social and ADHD problems (especially comparing those at highest risk versus those at lowest risk), but this is not definitive ADHD, compared with ADHD that has been diagnosed by healthcare professionals.

6.6.2 Alternative approaches to increased school entry flexibility

Educators could take age within school year into account when transitioning children into new stages of education, as well as when placing children into classroom sets based on academic ability.

The studies within the present thesis found that age within school year influences on general mental health problems are present after the transition into primary education. As explained in chapter 1, entry into compulsory education is a key milestone in childhood. The transition to a new education setting can be a stressful time for children because it is a major upheaval in social and environmental structure (Campbell, 2013; Evans et al., 2018; Thomson et al., 2017). Furthermore, results in chapter 3 and 4 indicate that effects of relative age on mental health are strongest at around 11-12 years, which coincides with the transition to secondary education in the United Kingdom, as well as typically falling within the developmental period of early adolescence (Evans et al., 2018). So, not only is this period in a child's life marked by large social and biological changes, but also considerable environmental change. Children who are relatively young for their school year may not be as psychologically prepared in relation to their older classmates in dealing with these transitions, both academically and socially (Evans et al., 2018; Rice et al., 2011). One suggestion is for teachers and LEAs to consider delivering additional support to the youngest children in the school year when transitioning those children into a new school, perhaps through short intervention programmes. Studies have shown that a six-week programme on motor competence in pre-school-aged children mitigated relative age effects on motor ability (Mecías-Calvo, Arufe-Giráldez, Cons-Ferreiro, & Navarro-Patón, 2021). Further research is needed on whether this could be applied to mental health problems, and for which age group (i.e., entering primary school or entering secondary school) such an intervention would be most effective.

Furthermore, studies have found that the youngest children in the school year are more likely to be placed in lower ability groups within the classroom, based on their teachers' perceptions of their ability in class (Campbell, 2013, 2014). Classes with

ability grouping have greater relative age effects on teachers' perception of academic ability than those that do not (Campbell, 2014). A potential underlying mechanism of the relationship between relative age within the school year and mental health is teachers' expectations of, and instructions to, those relatively young children. Teachers' behavioural expectations of their youngest pupils may be influenced by perceived cognitive and developmental immaturity relative to their older peers in the classroom, even during times when the relatively young child is behaving in a manner consistent with their chronological age (Campbell, 2014; Caye et al., 2020; Cobley, McKenna, Baker, & Wattie, 2009; Norbury et al., 2016). One suggestion from this is for teachers to not consider in-class ability grouping, especially during the earlier years of schooling.

There will be variability in cognitive processing in childhood, but especially when children enter primary school, including variation in language and executive processing. It has been reported that the youngest children in the school year are perceived to have less developed language skills and executive functions relative to older peers, and that this might influence social, emotional and behaviour skills (Norbury et al., 2016). Moreover, the youngest children are more likely to be diagnosed with intellectual disability (Root et al., 2019). Further research is needed on whether language and executive function development mediates relative age effects on risk of mental health problems. High expectations and complex instructions from teachers to their youngest pupils may potentially hinder their language and executive function development (Norbury et al., 2016). This process may be especially likely to occur in the early years of education, where the difference of up to twelve months is a proportionally greater difference in chronological age. This may lead teachers to disproportionately enter the youngest pupils into lower

academic ability sets (if practiced), as well as refer children to special educational needs support or psychiatric services (Berg & Berg, 2014; Campbell, 2014). Research has also found that being placed in a lower ability group influences education attainment (Campbell, 2013). An alternative, potentially less disruptive approach might be to raise awareness of who is relatively young within the classroom (Norbury et al., 2016), for example by organising the school register by age within school year. This may indirectly facilitate differentiated instruction and assessment.

A more general recommendation is that schools should become more aware of relative age effects on education achievement and mental health on their pupils. One approach for researchers to improve whole school awareness of relative age effects is to co-design and conduct research with schools, parents, and the children themselves in order to obtain their perspectives of teaching, raising, or being the youngest children in the school year, respectively.

This research may be part of a wider process to evaluate the acceptability, feasibility, and effectiveness of changes in policy and practice. Policy and practice changes, including interventions, will likely be complex and multifactorial. Future research should adopt a process evaluation framework to carefully plan, design, analyse and report research, such as the Medical Research Council guidance for developing and evaluating complex interventions (Moore et al., 2015).

6.7 Conclusion

There is now considerably clearer evidence that children entering school who are relatively young for their school year are at greater risk of mental health problems, throughout their time in education, as well as clearer evidence that relatively young

children with (or at high risk of) ADHD constitute a more vulnerable subgroup to mental health problems. Further research will be necessary to build on the evidence found in the present thesis to refine answers to the policy-relevant question of when, and under what circumstances, should relatively young children be allowed a greater flexibility of school entry, and for the development and evaluation of effective and efficient interventions. Alternatively, further research could be conducted to test other solutions proposed in this thesis (e.g., registration changes, interventions at school transition). Whatever approach is taken by future researchers of relative age effects on mental health, it will be necessary for research to evaluate the process of changing current education policy and practice to close the gap in mental health risk determined by the arbitrary cut-off for school entry.

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Appendices

Appendix: Chapter 2

Table A2.1: Summary table of ages of ALSPAC participants at completion of questionnaires.

	Total				August				September			
SDQ Total Difficulties	N	Mean Age (Months)	SD	IQR	N	Mean Age (Months)	SD	IQR	N	Mean Age (Months)	SD	IQR
Timepoint (years)												
4	9243	47.95	1.47	47-48	883	47.83	1.33	47-48	926	47.77	1.47	47-48
7	8296	81.45	1.36	81-82	784	81.27	1.45	81-81	819	81.30	1.11	81-81
8	7881	98.42	3.08	97-99	720	98.21	2.71	97-98	750	97.98	2.45	97-98
9	8109	115.81	1.57	115-116	755	115.59	1.50	115-116	771	115.57	1.37	115-116
11	7374	140.62	1.64	140-141	659	140.46	1.27	140-140	690	140.51	1.49	140-141
13	7059	157.92	2.19	157-158	621	157.95	2.35	157-158	664	157.80	1.95	157-158
16	5644	202.06	4.33	198-205	530	202.46	4.42	198-206	539	202.23	3.93	198-205
25	4681	316.79	6.11	312-322	413	317.08	6.24	311-323	458	316.04	6.19	310-322
Self-rated SMFQ	N	Mean Age (Months)	SD	IQR	N	Mean Age (Months)	SD	IQR	N	Mean Age (Months)	SD	IQR
Timepoint (years)												
10	7430	127.77	3.17	126-129	655	127.85	3.25	126-129	732	127.85	3.05	126-129
13	6720	153.73	2.77	152-155	611	152.97	2.59	151-154	653	153.30	2.84	151-155
14	6042	166.02	2.50	165-167	554	166.40	2.39	165-167	608	166.12	2.27	165-167
16	5064	200.15	2.84	198-202	458	201.86	4.18	198-206	481	201.73	3.73	198-205
17	4446	214.07	4.72	211-216	390	214.28	4.62	212-216	463	214.42	4.59	212-216
18	3335	223.81	5.90	219-229	301	224.06	5.98	218-229	323	222.79	5.75	217-228
21	3413	263.41	6.27	258-269	320	263.32	6.20	257-269	338	262.27	6.24	256-268
22	3969	274.86	6.37	270-280	366	274.70	6.27	268-280	380	273.61	6.34	267-279
23	4025	286.50	6.23	281-292	350	286.44	6.27	280-292	390	285.11	6.13	279-291
25	4,329	309.17	6.12	304-314	384	309.15	6.05	303-315	413	307.95	6.04	302-314

IQR = Interquartile Range; SD = Standard deviation

Appendix: Chapter 3

Table A3.1: Multiple Imputation variables, models used, and percentage of data missing from these variables/models

Variable	Model Used	% Missing
SDQ Maternal Depression (EPDS)	Linear Regression	13.6
SDQ Age of Mother at Birth	Linear Regression	10.1
SDQ Gestation	Linear Regression	3.8
SDQ Birthweight	Linear Regression	4.9
SDQ Birth Size	Linear Regression	0.01
SDQ Alcohol Use in Last 2 Months of Pregnancy	Logistic	10.4
SDQ Caesarean	Logistic	10.4
SDQ Crowding	Logistic	8.4
SDQ Home Ownership	Logistic	7.1
SDQ Mother's Education	Multinomial logistic	12.2
SDQ Parity	Logistic	7.6
SDQ Smoking During Last 2 Months of Pregnancy	Logistic	10.0
SDQ Total Difficulties – 4 Years	Linear Regression. Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	16.2
SDQ Total Difficulties – 7 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status	25.5

	(owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	
SDQ Total Difficulties – 8 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	31.0
SDQ Total Difficulties – 9 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	28.6
SDQ Total Difficulties – 11 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	34.8
SDQ Total Difficulties – 13 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation	37.6

	(weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	
SDQ Total Difficulties – 16 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	50.0
SDQ Total Difficulties –25 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	63.3
Variable	Model Used	% Missing
Self-Rated SMFQ- Maternal Depression (EPDS)	Linear Regression	16.2
Self-Rated SMFQ- Age of Mother at Birth	Linear Regression	13.1
Self-Rated SMFQ- Gestation	Linear Regression	6.8
Self-Rated SMFQ- Birthweight	Linear Regression	7.9
Self-Rated SMFQ- Birth Size	Linear Regression	0.2

Self-Rated SMFQ- Alcohol Use in Last 2 Months of Pregnancy	Logistic	13.5
Self-Rated SMFQ- Caesarean	Logistic	13.5
Self-Rated SMFQ- Crowding	Logistic	11.1
Self-Rated SMFQ- Home Ownership	Logistic	10.1
Self-Rated SMFQ- Mother's Education	Multinomial logistic	14.8
Self-Rated SMFQ- Parity	Logistic	10.4
SDQ Smoking During Last 2 Months of Pregnancy	Logistic	13.1
Self-Rated SMFQ – 10 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	23.5
Self-Rated SMFQ – 13 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	30.2
Self-Rated SMFQ – 14 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status	37.4

	(y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	
Self-Rated SMFQ – 16 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	47.8
Self-Rated SMFQ – 17 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	65.2
Self-Rated SMFQ – 18 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	53.1

Self-Rated SMFQ – 21 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	65.5
Self-Rated SMFQ – 22 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	59.1
Self-Rated SMFQ – 23 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	58.1
Self-Rated SMFQ – 25 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2	58.2

	months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	
Parent-Rated SMFQ- Maternal Depression (EPDS)	Linear Regression	13.4
Parent -Rated SMFQ- Age of Mother at Birth	Linear Regression	9.6
Parent -Rated SMFQ- Gestation	Linear Regression	4.4
Parent -Rated SMFQ- Birthweight	Linear Regression	5.6
Parent -Rated SMFQ- Birth Size	Linear Regression	0
Parent -Rated SMFQ- Alcohol Use in Last 2 Months of Pregnancy	Logistic	9.9
Parent -Rated SMFQ- Caesarean	Logistic	9.9
Parent -Rated SMFQ- Crowding	Logistic	8.4
Parent -Rated SMFQ- Home Ownership	Logistic	7.3
Parent -Rated SMFQ- Mother's Education	Multinomial logistic	11.4
Parent -Rated SMFQ- Parity	Logistic	7.7
Parent Smoking During Last 2 Months of Pregnancy	Logistic	9.5
Parent-Rated SMFQ – 9 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	13.1
Parent-Rated SMFQ – 11 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2	21.4

	months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	
Parent-Rated SMFQ – 13 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	24.7
Parent-Rated SMFQ – 16 Years	Linear Regression Covariates used: maternal depression, Maternal age (years), gestation (weeks), birthweight (g), birth size (singleton/multiple), alcohol use in last 2 months of pregnancy (y/n), smoking in last 2 months of pregnancy (y/n), caesarean status (y/n), crowding, home ownership status (owned/not owned), mother's education (degree/no degree), parity, age at completion of questionnaire (months)	41.3

Table A3.2: Regression results for Self-rated SMFQ by relative age, Imputed data

	Unadjusted			All Covariates		
	Coef.	**95% CI**	**p**	**Coef.**	**95% CI**	**p**
10 Years	0.02	[-0.06, 0.09]	0.64	0.02	[-0.05, 0.10]	0.54
13 Years	0.01	[-0.07, 0.09]	0.84	0.01	[-0.07, 0.09]	0.82
14 Years	0.12	[0.04, 0.20]	<0.01	0.12	[0.04, 0.20]	<0.01
16 Years	0.07	[-0.02, 0.15]	0.12	0.07	[-0.01, 0.15]	0.10
17 Years	-0.08	[-0.18, 0.02]	0.13	-0.06	[-0.17, 0.04]	0.22
18 Years	-0.03	[-0.12, 0.06]	0.47	-0.02	[-0.11, 0.07]	0.63
21 Years	0.04	[-0.06, 0.14]	0.43	0.04	[-0.05, 0.14]	0.38
22 Years	0.07	[-0.03, 0.16]	0.17	0.07	[-0.02, 0.17]	0.13
23 Years	0.02	[-0.08, 0.11]	0.62	0.04	[-0.06, 0.13]	0.45
25 Years	0.14	[0.04, 0.23]	0.01	0.15	[0.05, 0.24]	<0.01

(N=9468) The numbers contained in this table correspond to figure 3.2. Coefficient (Coef.) represents mean change in standardised self-report SMFQ score between children born between 1st September-31st August. "Unadjusted Model" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates.

Table A3.3.

Table A3.3: Regression results for parent-rated SMFQ by relative age, Imputed data.

	Unadjusted			All Covariates		
	Coef.	**95% CI**	**p**	**Coef.**	**95% CI**	**p**
9 Years	0.12	[0.05, 0.19]	<0.01	0.12	[0.05, 0.19]	<0.01
11 Years	0.16	[0.09, 0.23]	<0.01	0.17	[0.09, 0.24]	<0.01
13 Years	0.04	[-0.04, 0.11]	0.36	0.04	[-0.04, 0.11]	0.30
16 Years	0.05	[-0.03, 0.14]	0.23	0.05	[-0.03, 0.14]	0.22

(N=9164) The numbers contained in this table correspond to figure 3.3. Coefficient (Coef.) represents mean change in standardised parent-report SMFQ score per 1 year difference in relative age. "Unadjusted Model" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates

Table A3.4: Regression results for parent-rated SDQ total difficulties scores by relative age, restricted to 4 weeks either side of September 1st cut-off, Imputed data

	Unadjusted			All Covariates		
	Coef.	**95% CI**	**p**	**Coef.**	**95% CI**	**p**
4 Years	-0.02	[-0.12, 0.08]	0.67	0.01	[-0.086, 0.106]	0.84
7 Years	0.13	[0.03, 0.24]	0.01	0.15	[0.054, 0.254]	<0.01
8 Years	0.18	[0.08, 0.29]	<0.01	0.20	[0.095, 0.302]	<0.01
9 Years	0.14	[0.03, 0.24]	<0.01	0.16	[0.056, 0.260]	<0.01
11 Years	0.20	[0.09, 0.30]	<0.01	0.22	[0.117, 0.323]	<0.01
13 Years	0.12	[0.01, 0.23]	0.03	0.14	[0.033, 0.243]	0.01
16 Years	0.11	[-0.01, 0.23]	0.06	0.13	[0.012, 0.244]	0.03
25 Years	0.03	[-0.10, 0.16]	0.67	0.04	[-0.087, 0.168]	0.53

(N=2035) The numbers contained in this table correspond to figure 3.1. Coefficient (Coef.) represents mean change in standardised parent-report SDQ score per 1 year difference in relative age. "Unadjusted Model" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates.

Table A3.5: Regression results for Self-rated SMFQ by relative age, restricted to 4 weeks either side of September 1st cut-off, Imputed data

	Unadjusted			All Covariates		
	Coef.	**95% CI**	**p**	**Coef.**	**95% CI**	**p**
10 Years	0.01	[-0.11, 0.13]	0.88	0.03	[-0.09, 0.15]	0.59
13 Years	-0.05	[-0.16, 0.07]	0.42	-0.04	[-0.16, 0.08]	0.51
14 Years	0.09	[-0.03, 0.20]	0.16	0.08	[-0.03, 0.20]	0.16
16 Years	0.01	[-0.12, 0.13]	0.93	0.01	[-0.11, 0.13]	0.87
17 Years	-0.11	[-0.25, 0.04]	0.14	-0.01	[-0.24, 0.04]	0.17
18 Years	-0.09	[-0.22, 0.04]	0.19	-0.10	[-0.21, 0.05]	0.24
21 Years	0.01	[-0.13, 0.15]	0.85	0.02	[-0.12, 0.15]	0.82
22 Years	0.04	[-0.10, 0.18]	0.58	0.04	[-0.10, 0.18]	0.59
23 Years	0.01	[-0.13, 0.14]	0.92	0.02	[-0.11, 0.15]	0.77
25 Years	0.10	[-0.04, 0.24]	0.15	0.11	[-0.03, 0.24]	0.12

(N=1690) The numbers contained in this table correspond to figure 3.2. Coefficient (Coef.) represents mean change in standardised self-report SMFQ score per 1 year difference in relative age. "Unadjusted Model" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates.

Table A3.6: Regression results for parent-rated SMFQ by relative age, restricted to 4 weeks either side of September 1st cut-off, Imputed data

	Unadjusted			All Covariates		
	Coef.	95% CI	p	Coef.	95% CI	p
9 Years	0.03	[-0.08, 0.15]	0.56	0.05	[-0.06, 0.17]	0.36
11 Years	0.10	[-0.02, 0.22]	0.11	0.11	[-0.01, 0.23]	0.07
13 Years	0.02	[-0.10, 0.14]	0.78	0.03	[-0.09, 0.15]	0.67
16 Years	-0.01	[-0.14, 0.12]	0.83	-0.02	[-0.14, 0.11]	0.80

(N=1642) The numbers contained in this table correspond to figure 3.3. Coefficient (Coef.) represents mean change in standardised parent-report SMFQ score per 1 year difference in relative age. "Unadjusted Model" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates

Table A3.7: Regression results for parent-rated SDQ total difficulties scores by relative age, restricted to 8 weeks either side of September 1st cut-off, Imputed data

	Unadjusted			All Covariates		
	Coef.	95% CI	p	Coef.	95% CI	p
4 Years	-0.03	[-0.10, 0.05]	0.50	-0.01	[-0.08, 0.07]	0.89
7 Years	0.13	[0.05, 0.21]	<0.01	0.15	[0.07, 0.22]	<0.01
8 Years	0.18	[0.10, 0.26]	<0.01	0.19	[0.11, 0.27]	<0.01
9 Years	0.15	[0.07, 0.23]	<0.01	0.16	[0.08, 0.24]	<0.01
11 Years	0.21	[0.13, 0.29]	<0.01	0.22	[0.14, 0.30]	<0.01
13 Years	0.14	[0.05, 0.22]	<0.01	0.14	[0.06, 0.23]	<0.01
16 Years	0.10	[0.00, 0.19]	0.05	0.10	[0.01, 0.20]	0.03
25 Years	-0.00	[-0.11, 0.11]	0.99	0.01	[-0.10, 0.12]	0.91

(N=4042) The numbers contained in this table correspond to figure 3.1. Coefficient (Coef.) represents mean change in standardised parent-report SDQ score per 1 year difference in relative age. "Unadjusted Model" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates.

Table A3.8: Regression results for Self-rated SMFQ by relative age, restricted to 8 weeks either side of September 1st cut-off, Imputed data

	Unadjusted			All Covariates		
	Coef.	**95% CI**	**p**	**Coef.**	**95% CI**	**p**
10 Years	0.01	[-0.08, 0.10]	0.86	0.02	[-0.07, 0.11]	0.70
13 Years	-0.05	[-0.14, 0.05]	0.33	-0.04	[-0.13, 0.05]	0.42
14 Years	0.08	[-0.02, 0.17]	0.11	0.08	[-0.01, 0.17]	0.09
16 Years	0.03	[-0.07, 0.12]	0.61	0.03	[-0.07, 0.13]	0.52
17 Years	-0.10	[-0.22, 0.02]	0.10	-0.09	[-0.20, 0.03]	0.15
18 Years	-0.08	[-0.18, 0.02]	0.13	-0.07	[-0.17, 0.03]	0.18
21 Years	0.03	[-0.09, 0.14]	0.66	0.03	[-0.08, 0.14]	0.61
22 Years	0.04	[-0.07, 0.15]	0.43	0.05	[-0.06, 0.16]	0.39
23 Years	-0.01	[-0.11, 0.10]	0.90	0.01	[-0.10, 0.11]	0.93
25 Years	0.11	[-0.00, 0.22]	0.05	0.12	[0.01, 0.23]	0.03

(N=3383). The numbers contained in this table correspond to figure 3.2. Coefficient (Coef.) represents mean change in standardised self-report SMFQ score per 1 year difference in relative age. "Unadjusted Model" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates.

Table A3.9. Regression results for parent-rated SMFQ by relative age, restricted to 8 weeks either side of September 1st cut-off, Imputed data (N=5297) The numbers contained in this table correspond to figure 3.3. Coefficient (Coef.) represents mean change in standardised parent-report SMFQ score per 1 year difference in relative age. “Unadjusted Model” = Age within School Year entered in the regression alone. “All Covariates” = Model after adjustments for all covariates

	Unadjusted			All Covariates		
	Coef.	**95% CI**	**p**	**Coef.**	**95% CI**	**p**
9 Years	0.07	[-0.02, 0.15]	0.13	0.07	[-0.01, 0.16]	0.09
11 Years	0.12	[0.03, 0.21]	0.01	0.12	[0.04, 0.21]	0.01
13 Years	0.02	[-0.07, 0.11]	0.73	0.02	[-0.07, 0.10]	0.73
16 Years	0.01	[-0.09, 0.11]	0.87	0.01	[-0.09, 0.11]	0.85

Table A3.10: Complete-case analysis regression results: Parent-Rated SDQ (4-25 years)

	Unadjusted				All Covariates			
Total Difficulties	**N**	**Coefficient**	**95% CI**	**p**	**N**	**Coefficient**	**95% CI**	**p**
4 Years	9312	0.02	[-0.04, 0.09]	0.512	7248	0.06	[-0.01, 0.13]	0.11
7 Years	8281	0.15	[0.08, 0.22]	<0.01	6541	0.18	[0.10, 0.25]	<0.01
8 Years	7669	0.17	[0.09, 0.22]	<0.01	5933	0.19	[0.11, 0.27]	<0.01
9 Years	7934	0.15	[0.08, 0.22]	<0.01	6014	0.17	[0.10, 0.25]	<0.01
11 Years	7253	0.21	[0.14, 0.28]	<0.01	5562	0.25	[0.17, 0.33]	<0.01
13 Years	6933	0.15	[0.07, 0.22]	<0.01	5320	0.15	[0.06, 0.23]	0.001
16 Years	5554	0.07	[-0.02, 0.16]	0.108	4365	0.09	[0.00, 0.18]	0.05
25 Years	4076	-0.05	[-0.15, 0.06]	0.282	3233	-0.03	[-0.14, 0.07]	0.52
Conduct Problems								
4 Years	9341	0.01	[-0.06, 0.07]	0.8	7268	0.02	[-0.05, 0.09]	0.54
7 Years	8310	-0.01	[-0.08, 0.06]	0.76	6553	0	[-0.07, 0.08]	0.97
8 Years	7682	0.03	[-0.05, 0.09]	0.48	5940	0.06	[-0.02, 0.14]	0.13
9 Years	7962	-0.02	[-0.09, 0.04]	0.53	6032	0	[-0.08, 0.08]	1
11 Years	7256	0.07	[<0.01, 0.15]	0.05	5561	0.09	[0.01, 0.17]	0.03
13 Years	6958	0.02	[-0.06, 0.09]	0.69	5338	0.03	[-0.05, 0.11]	0.49
16 Years	5598	-0.01	[-0.09 ,0.08]	0.86	4395	0.01	[-0.08, 0.10]	0.81
25 Years	4290	-0.01	[-0.1, 0.1]	0.88	3406	0.02	[-0.09, 0.12]	0.74
Emotional problems								
4 Years	9355	0.09	[0.02, 0.15]	0.01	7271	0.09	[0.02, 0.17]	0.01
7 Years	8300	0.13	[0.06, 0.2]	<0.01	6552	0.14	[0.07, 0.22]	<0.01
8 Years	7679	0.09	[0.02, 0.14]	0.02	5940	0.1	[0.02, 0.18]	0.01
9 Years	7946	0.11	[0.04, 0.18]	<0.01	6026	0.12	[0.04, 0.20]	<0.01
11 Years	7239	0.1	[0.03, 0.18]	0.01	5554	0.14	[0.05, 0.22]	<0.01
13 Years	6961	0.08	[<0.01, 0.16]	0.04	5344	0.07	[-0.01, 0.16]	0.1
16 Years	5587	0.09	[0.01, 0.18]	0.03	4390	0.09	[0.00, 0.18]	0.04
25 Years	4299	-0.05	[-0.15, 0.04]	0.28	3407	-0.03	[-0.14, 0.07]	0.51

Hyperactivity Problems								
4 Years	9347	<0.01	[-0.06, 0.07]	0.897	7269	0.06	[-0.01, 0.13]	0.1
7 Years	8286	0.17	[0.10, 0.24]	<0.01	6548	0.22	[0.15, 0.30]	<0.01
8 Years	7680	0.22	[0.14, 0.28]	<0.01	5936	0.24	[0.16, 0.32]	<0.01
9 Years	7963	0.19	[0.12, 0.26]	<0.01	6037	0.21	[0.14, 0.29]	<0.01
11 Years	7238	0.26	[0.19, 0.33]	<0.01	5555	0.29	[0.21, 0.37]	<0.01
13 Years	6958	0.18	[0.11, 0.25]	<0.01	5340	0.19	[0.11, 0.28]	<0.01
16 Years	5597	0.06	[-0.03, 0.14]	0.175	4396	0.09	[0.00, 0.18]	0.05
25 Years	4294	-0.02	[-0.12, 0.08]	0.677	3406	-0.03	[-0.13, 0.07]	0.55
Peer Problems								
4 Years	9354	-0.03	[-0.09, 0.04]	0.42	7272	-0.03	[-0.10, 0.04]	0.4
7 Years	8305	0.07	[<0.01, 0.14]	0.06	6549	0.07	[-0.01, 0.14]	0.08
8 Years	7678	0.08	[0.01, 0.13]	0.03	5937	0.1	[0.02, 0.18]	0.01
9 Years	7952	0.13	[0.06, 0.2]	<0.01	6025	0.14	[0.06, 0.22]	<0.01
11 Years	7261	0.12	[0.04, 0.19]	<0.01	5564	0.15	[0.07, 0.23]	<0.01
13 Years	6958	0.11	[0.03, 0.18]	0.01	5340	0.1	[0.02, 0.19]	0.02
16 Years	5589	0.02	[-0.07, 0.11]	0.69	4387	0.03	[-0.07, 0.12]	0.58
25 Years	4278	-0.06	[-0.16, 0.05]	0.23	3394	-0.04	[-0.15, 0.06]	0.42

Independent variable: Relative Age (week of birth). Coefficient (Coef.) represents mean change in standardised parent-report SDQ score between children born between 1st September and those born on 31st August (i.e., 1 year difference in age at starting school). "Unadjusted" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates.

Table A3.11: Complete-case analysis regression results: Self-Rated SMFQ (10-25 years)

	Unadjusted				All Covariates			
Age	N	Coefficient	[95% CI]	p	N	Coefficient	[95% CI]	p
10 Years	7245	0.02	[-0.05, 0.10]	0.58	5398	0.03	[-0.06, 0.11]	0.53
13 Years	6607	<.01	[-0.08, 0.08]	0.99	4935	0.01	[-0.08, 0.10]	0.83
14 Years	5925	0.11	[0.02, 0.19]	0.01	4493	0.11	[0.02, 0.21]	0.02
16 Years	4939	0.08	[-0.01, 0.17]	0.08	3780	0.12	[0.02, 0.22]	0.02
17 Years	3299	-0.09	[-0.2, 0.02]	0.11	2534	-0.09	[-0.21, 0.03]]	0.15
18 Years	4444	-0.03	[-0.13, 0.06]	0.48	3357	0.00	[-0.10, 0.11]	0.96
21 Years	3271	0.02	[-0.1, 0.13]	0.79	2506	0.03	[-0.09, 0.15]	0.63
22 Years	3869	0.08	[-0.03, 0.18]	0.15	2880	0.06	[-0.06, 0.18]	0.31
23 Years	3972	-0.02	[-0.12, 0.08]	0.72	2904	-0.03	[-0.15, 0.08]	0.57
25 Years	3962	0.12	[0.02, 0.22]	0.02	2882	0.09	[-0.02, 0.20]	0.12

Independent variable: Relative Age (week of birth), Coefficient (Coef.) represents mean change in standardised self-report SMFQ score per 1 year difference in relative age. "Unadjusted" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates.

Table A3.12: Complete-case analysis regression results: Parent-Rated SMFQ (9-16 years)

	Unadjusted				All Covariates			
Age	N	Coefficient	[95% CI]	p	N	Coefficient	[95% CI]	p
9 Years	7966	0.13	[0.05, 0.20]	<0.01	6036	0.14	[0.07, 0.22]	<0.01
11 Years	7201	0.17	[0.10, 0.25]	<0.01	5526	0.2	[0.12, 0.28]	<0.01
13 Years	6899	0.04	[-0.03, 0.12]	0.25	5295	0.07	[-0.02, 0.15]	0.12
16 Years	5383	0.05	[-0.03, 0.14]	0.21	4224	0.10	[0.01, 0.20]	0.04

Independent variable: Relative Age (week of birth), Coefficient (Coef.) represents mean change in standardised parent-report SMFQ score per 1 year difference in relative age. "Unadjusted" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates.

Table A3.13: Generalized estimating equation (GEE) results for parent-rated SDQ total difficulties

Age	Coef.	p	95% CI
4 Years	0.02	0.63	[-0.05, 0.08]
7 Years	0.13	<0.01	[0.07, 0.20]
8 Years	0.17	<0.01	[0.10, 0.23]
9 Years	0.15	<0.01	[0.08, 0.21]
11 Years	0.20	<0.01	[0.14, 0.27]
13 Years	0.12	<0.01	[0.06, 0.19]
16 Years	0.06	0.08	[-0.01, 0.13]
25 Years	-0.04	0.37	[-0.12, 0.04]

(N=11116). Coefficient (Coef.) represents mean change in standardised parent-report SDQ score per 1 year difference in relative age.

Table A3.14: Generalized estimating equation (GEE) results for self-rated SMFQ scores (N=9468).

Age	Coef.	p	95% CI
10 years	0.02	0.63	[-0.06, 0.09]
13 years	-0.01	0.88	[-0.09, 0.08]
14 years	0.10	0.03	[0.01, 0.19]
16 years	0.04	0.42	[-0.06, 0.14]
17 years	-0.10	0.06	[-0.21, 0.01]
18 years	-0.05	0.31	[-0.15, 0.05]
21 years	-0.01	0.83	[-0.12, 0.10]
22 years	0.03	0.57	[-0.07, 0.14]
23 years	-0.02	0.77	[-0.12, 0.09]
25 years	0.11	0.04	[0.01, 0.22]

Coefficient (Coef.) represents mean change in standardised self-report SMFQ score per 1 year difference in relative age.

Table A3.15: Generalized estimating equation (GEE) results for parent-rated SMFQ scores (N=9164).

Age	Coef.	p	95% CI
9 years	0.12	0.00	[0.05, 0.19]
11 years	0.04	0.32	[-0.04, 0.12]
13 years	-0.08	0.04	[-0.16, 0.00]
16 years	-0.08	0.09	[-0.16, 0.01]

Coefficient (Coef.) represents mean change in standardised parent-report SMFQ score per 1 year difference in relative age.

Table A3.16: Effects of relative age, sex, and their interactions on mental health problems.

SDQ	Unadjusted				All Covariates			
4 Years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Relative Age	0.03	-0.06	0.12	0.58	0.12	0.00	0.24	0.05
Sex	-0.19	-0.27	-0.12	<0.01	-0.20	-0.30	-0.10	<0.01
Sex*relative age	-0.01	-0.14	0.13	0.94	0.01	-0.16	0.17	0.93
7 Years								
Relative Age	0.22	0.12	0.31	<0.01	0.29	0.17	0.41	<0.01
Sex	-0.15	-0.23	-0.06	<0.01	-0.12	-0.22	-0.02	0.02
Sex*relative age	-0.14	-0.28	-0.01	0.04	-0.14	-0.31	0.02	0.10
8 Years								
Relative Age	0.19	0.09	0.29	<0.01	0.30	0.18	0.42	<0.01
Sex	-0.21	-0.29	-0.12	<0.01	-0.11	-0.21	-0.01	0.03
Sex*relative age	-0.04	-0.18	0.11	0.60	-0.13	-0.30	0.04	0.13
9 Years								
Relative Age	0.22	0.12	0.32	<0.01	0.39	0.27	0.50	<0.01
Sex	-0.10	-0.18	-0.01	0.02	-0.02	-0.12	0.07	0.64
Sex*relative age	-0.13	-0.27	0.01	0.07	-0.27	-0.43	-0.10	<0.01
11 Years								
Relative Age	0.25	0.15	0.36	<0.01	0.44	0.32	0.56	<0.01
Sex	-0.15	-0.23	-0.06	<0.01	-0.04	-0.14	0.07	0.48
Sex*relative age	-0.09	-0.24	0.06	0.23	-0.28	-0.45	-0.10	<0.01
13 Years								
Relative Age	0.16	0.05	0.26	<0.01	0.31	0.18	0.44	<0.01
Sex	-0.14	-0.23	-0.05	<0.01	-0.02	-0.13	0.09	0.72
Sex*relative age	-0.02	-0.18	0.13	0.76	-0.26	-0.44	-0.08	0.01
16 Years								
Relative Age	0.00	-0.13	0.12	0.95	0.15	0.01	0.29	0.04
Sex	-0.03	-0.13	0.07	0.59	0.01	-0.11	0.13	0.87
Sex*relative age	0.15	-0.03	0.32	0.10	0.01	-0.18	0.21	0.90
25 Years								
Relative Age	-0.01	-0.15	0.14	0.92	0.06	-0.10	0.22	0.48
Sex	0.16	0.04	0.27	0.01	0.13	0.00	0.26	0.05

Sex*relative age	-0.08	-0.28	0.12	0.42	-0.09	-0.31	0.13	0.42
Self-rated SMFQ								
10 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
relative age	0.02	-0.09	0.13	0.71	0.06	-0.07	0.19	0.39
Sex	-0.07	-0.15	0.02	0.13	-0.07	-0.18	0.03	0.18
Sex*relative age	0.00	-0.15	0.15	0.99	-0.03	-0.21	0.15	0.74
13 years								
relative age	-0.01	-0.12	0.11	0.92	0.06	-0.07	0.19	0.38
Sex	0.19	0.10	0.28	<0.01	0.24	0.13	0.35	<0.01
Sex*relative age	0.02	-0.14	0.17	0.84	-0.11	-0.30	0.07	0.23
14 years								
relative age	0.06	-0.05	0.18	0.30	0.12	-0.02	0.26	0.09
Sex	0.31	0.21	0.40	<0.01	0.36	0.25	0.48	<0.01
Sex*relative age	0.12	-0.05	0.28	0.16	-0.02	-0.21	0.18	0.86
16 years								
relative age	0.08	-0.06	0.21	0.27	0.13	-0.03	0.30	0.12
Sex	0.47	0.37	0.58	<0.01	0.46	0.33	0.59	<0.01
Sex*relative age	0.01	-0.16	0.19	0.87	-0.04	-0.26	0.17	0.70
17 years								
relative age	0.09	-0.09	0.27	0.32	0.02	-0.19	0.24	0.84
Sex	0.53	0.40	0.66	<0.01	0.41	0.25	0.57	<0.01
Sex*relative age	-0.27	-0.49	-0.04	0.02	-0.18	-0.44	0.09	0.20
18 years								
relative age	0.00	-0.14	0.14	0.97	0.10	-0.06	0.27	0.23
Sex	0.33	0.22	0.44	<0.01	0.33	0.19	0.46	<0.01
Sex*relative age	-0.04	-0.23	0.15	0.67	-0.12	-0.34	0.11	0.31
21 years								
relative age	-0.06	-0.24	0.13	0.53	0.11	-0.11	0.33	0.34
Sex	0.16	0.02	0.29	0.02	0.24	0.07	0.40	0.01
Sex*relative age	0.12	-0.11	0.35	0.30	-0.09	-0.37	0.18	0.50
22 years								
relative age	0.02	-0.15	0.20	0.78	0.11	-0.10	0.32	0.31

Sex	0.19	0.06	0.31	<0.01	0.24	0.08	0.40	<0.01
Sex*relative age	0.09	-0.12	0.31	0.40	-0.06	-0.32	0.21	0.68
23 years								
relative age	-0.01	-0.18	0.16	0.94	0.07	-0.14	0.28	0.51
Sex	0.22	0.09	0.34	<0.01	0.21	0.05	0.37	0.01
Sex*relative age	-0.01	-0.22	0.20	0.92	-0.09	-0.35	0.17	0.50
25 years								
relative age	0.09	-0.08	0.26	0.32	0.09	-0.12	0.30	0.39
Sex	0.30	0.18	0.43	<0.01	0.31	0.15	0.46	<0.01
Sex*relative age	0.07	-0.14	0.28	0.52	-0.03	-0.29	0.23	0.82

Parent-rated SMFQ								
9 Years (N=7966)	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
relative age	0.11	0.01	0.21	0.02	0.22	0.10	0.34	<0.01
Sex	-0.04	-0.12	0.04	0.33	0.01	-0.09	0.11	0.79
Sex*relative age	0.02	-0.12	0.17	0.75	-0.11	-0.28	0.06	0.20
11 Years								
relative age	0.12	0.01	0.22	0.03	0.26	0.13	0.38	<0.01
Sex	-0.02	-0.11	0.07	0.63	0.02	-0.09	0.12	0.76
Sex*relative age	0.11	-0.04	0.26	0.16	-0.06	-0.24	0.11	0.48
13 Years								
relative age	-0.02	-0.13	0.09	0.70	0.10	-0.03	0.23	0.12
Sex	0.03	-0.06	0.12	0.57	0.09	-0.02	0.20	0.11
Sex*relative age	0.13	-0.02	0.29	0.09	-0.05	-0.23	0.13	0.59
16 Years								
relative age	-0.03	-0.15	0.09	0.63	0.09	-0.06	0.23	0.25
Sex	0.19	0.08	0.29	<0.01	0.20	0.08	0.32	<0.01
Sex*relative age	0.17	0.00	0.35	0.05	0.11	-0.10	0.31	0.31

Complete case analysis. Refer to tables A3.10-A3.12 for Ns. "Unadjusted" = Age within School Year entered in the regression alone. "All Covariates" = Model after adjustments for all covariates. Coefficient (Coef.) represents mean change in standardised outcome (parent-report SDQ, self-report SMFQ, parent-report SMFQ) per 1 year difference in relative age (relative age), or effect of sex (0 = Male, 1=Female)

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Appendix: Chapter 4

Table A4.1: Multiple Imputation variables, models used, and percentage of data missing from these variables/models – ADHD traits

Variable	Model used	% Missing
Low risk		
SDQ Total - 7 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	17.50
SDQ Total - 8 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	25.71
SDQ Total - 9 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	25.41
SDQ Total - 11 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	30.69
SDQ Total - 13 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	33.57
SDQ Total - 16 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	45.14
SDQ Total - 25 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	59.36
Maternal Depression	Linear Regression	9.22
Age of Mother at Birth	Linear Regression	4.35
Borderline risk		
SDQ Total - 7 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	20.76
SDQ Total - 8 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	30.81
SDQ Total - 9 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	29.62
SDQ Total - 11 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	37.19

SDQ Total - 13 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	39.35
SDQ Total - 16 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	53.19
SDQ Total - 25 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	63.35
Maternal Depression	Linear Regression	7.46
Age of Mother at Birth	Linear Regression	5.19
High risk		
SDQ Total - 7 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	21.85
SDQ Total - 8 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	28.96
SDQ Total - 9 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	29.05
SDQ Total - 11 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	36.59
SDQ Total - 13 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	39.59
SDQ Total - 16 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	53.13
SDQ Total - 25 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	66.50
Maternal Depression	Linear Regression	10.03
Age of Mother at Birth	Linear Regression	5.91
Overall		
SDQ Total - 7 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	18.38
SDQ Total - 8 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	26.64

SDQ Total - 9 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	26.30
SDQ Total - 11 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	32.10
SDQ Total - 13 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	34.92
SDQ Total - 16 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	46.97
SDQ Total - 25 Years	Linear Regression - Covariates used: Maternal depression, Sex, Maternal age (years), Age at completion of questionnaire (years)	60.67
Maternal Depression	Linear Regression	9.15
Age of Mother at Birth	Linear Regression	4.63

Table A4.2: Multiple Imputation variables, models used, and percentage of data missing from these variables/models – PRS

Variable	Model used	% Missing
SDQ Total - 7 Years	Linear Regression - Covariates used: Maternal depression, Sex, 5 principal components of ancestry, Maternal age (years), Age at completion of questionnaire (years)	20.78
SDQ Total - 8 Years	Linear Regression - Covariates used: Maternal depression, Sex, 5 principal components of ancestry, Maternal age (years), Age at completion of questionnaire (years)	24.10
SDQ Total - 9 Years	Linear Regression - Covariates used: Maternal depression, Sex, 5 principal components of ancestry, Maternal age (years), Age at completion of questionnaire (years)	20.67
SDQ Total - 11 Years	Linear Regression - Covariates used: Maternal depression, Sex, 5 principal components of ancestry, Maternal age (years), Age at completion of questionnaire (years)	26.25
SDQ Total - 13 Years	Linear Regression - Covariates used: Maternal depression, Sex, 5 principal components of ancestry, Maternal age (years), Age at completion of questionnaire (years)	29.16
SDQ Total - 16 Years	Linear Regression - Covariates used: Maternal depression, Sex, 5 principal components of ancestry, Maternal age (years), Age at completion of questionnaire (years)	41.67
SDQ Total - 25 Years	Linear Regression - Covariates used: Maternal depression, Sex, 5 principal components of ancestry, Maternal age (years), Age at completion of questionnaire (years)	56.79
Maternal Depression	Linear Regression	12.45
Age of Mother at Birth	Linear Regression	8.97

Table A4.3: Regression results for SDQ subscales by relative age, stratified by ADHD symptoms at age 4 years. Imputed data. Restricted to individuals born up to 4 weeks either side of the September 1st cut-off.

	Unadjusted				Adjusted			
	Conduct problems							
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.01	-0.12	0.13	0.93	0.02	-0.11	0.14	0.81
Borderline	0.44	0.19	0.69	<0.01	0.42	0.17	0.67	<0.01
High	0.75	0.53	0.98	<0.01	0.69	0.47	0.92	<0.01
Rel.Age*Borderline	0.14	-0.24	0.52	0.47	0.11	-0.27	0.48	0.58
Rel.Age*High	-0.22	-0.57	0.13	0.22	-0.21	-0.56	0.14	0.24
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.08	-0.05	0.21	0.24	0.09	-0.04	0.22	0.18
Borderline	0.41	0.14	0.67	<0.01	0.37	0.11	0.64	0.01
High	0.84	0.60	1.08	<0.01	0.78	0.54	1.02	<0.01
Rel.Age*Borderline	0.03	-0.37	0.43	0.87	0.01	-0.39	0.41	0.97
Rel.Age*High	-0.30	-0.67	0.07	0.11	-0.29	-0.65	0.08	0.12
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.03	-0.15	0.09	0.62	-0.02	-0.14	0.10	0.75
Borderline	0.31	0.06	0.56	0.01	0.28	0.04	0.53	0.03
High	0.81	0.59	1.03	<0.01	0.75	0.53	0.97	<0.01
Rel.Age*Borderline	0.21	-0.17	0.59	0.29	0.18	-0.19	0.56	0.34
Rel.Age*High	-0.26	-0.60	0.08	0.14	-0.25	-0.58	0.09	0.15
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.09	-0.04	0.22	0.19	0.10	-0.02	0.23	0.11
Borderline	0.33	0.05	0.61	0.02	0.29	0.02	0.57	0.04
High	0.64	0.40	0.88	<0.01	0.56	0.32	0.79	<0.01
Rel.Age*Borderline	0.19	-0.22	0.60	0.36	0.16	-0.24	0.57	0.43
Rel.Age*High	-0.26	-0.63	0.10	0.16	-0.25	-0.61	0.11	0.18
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.01	-0.12	0.15	0.84	0.02	-0.11	0.15	0.74
Borderline	0.11	-0.15	0.38	0.40	0.08	-0.19	0.34	0.57
High	0.67	0.44	0.90	<0.01	0.59	0.36	0.83	<0.01
Rel.Age*Borderline	0.29	-0.11	0.70	0.16	0.28	-0.13	0.68	0.18

Rel.Age*High	-0.28	-0.64	0.08	0.12	-0.27	-0.62	0.09	0.14
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.04	-0.10	0.18	0.55	0.05	-0.09	0.19	0.47
Borderline	0.25	-0.02	0.52	0.07	0.23	-0.04	0.50	0.10
High	0.49	0.22	0.76	<0.01	0.43	0.15	0.70	<0.01
Rel.Age*Borderline	0.15	-0.28	0.59	0.48	0.12	-0.31	0.55	0.59
Rel.Age*High	-0.25	-0.66	0.16	0.24	-0.23	-0.64	0.17	0.26
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.03	-0.12	0.18	0.69	0.03	-0.12	0.19	0.66
Borderline	0.31	-0.03	0.65	0.07	0.28	-0.06	0.62	0.10
High	0.34	0.02	0.66	0.04	0.29	-0.03	0.61	0.07
Rel.Age*Borderline	0.08	-0.47	0.63	0.77	0.06	-0.49	0.61	0.83
Rel.Age*High	-0.11	-0.59	0.37	0.66	-0.10	-0.58	0.37	0.67
			Emotional problems					
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.15	0.02	0.27	0.02	0.15	0.03	0.28	0.02
Borderline	0.16	-0.09	0.42	0.20	0.14	-0.10	0.39	0.26
High	0.33	0.10	0.55	<0.01	0.27	0.05	0.50	0.02
Rel.Age*Borderline	0.11	-0.27	0.49	0.56	0.08	-0.30	0.46	0.68
Rel.Age*High	-0.12	-0.47	0.23	0.51	-0.11	-0.45	0.24	0.55
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.22	0.09	0.34	<0.01	0.21	0.09	0.34	<0.01
Borderline	0.18	-0.08	0.45	0.18	0.17	-0.09	0.43	0.20
High	0.51	0.28	0.74	<0.01	0.46	0.23	0.69	<0.01
Rel.Age*Borderline	-0.02	-0.42	0.37	0.91	-0.05	-0.44	0.34	0.80
Rel.Age*High	-0.34	-0.70	0.02	0.06	-0.33	-0.68	0.02	0.07
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.09	-0.04	0.22	0.18	0.09	-0.04	0.22	0.16
Borderline	0.12	-0.14	0.38	0.38	0.10	-0.15	0.36	0.43
High	0.34	0.11	0.58	<0.01	0.29	0.06	0.52	0.01
Rel.Age*Borderline	0.19	-0.20	0.59	0.34	0.16	-0.23	0.55	0.43
Rel.Age*High	-0.13	-0.49	0.23	0.48	-0.12	-0.47	0.24	0.52
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p

Rel.Age	0.08	-0.05	0.21	0.21	0.09	-0.04	0.22	0.19
Borderline	0.06	-0.20	0.33	0.63	0.05	-0.22	0.31	0.73
High	0.42	0.17	0.67	<0.01	0.37	0.12	0.62	<0.01
Rel.Age*Borderline	0.22	-0.18	0.62	0.28	0.19	-0.21	0.58	0.36
Rel.Age*High	-0.23	-0.62	0.15	0.24	-0.22	-0.61	0.16	0.25
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.06	-0.07	0.19	0.36	0.05	-0.08	0.18	0.42
Borderline	0.08	-0.20	0.35	0.58	0.06	-0.21	0.33	0.65
High	0.31	0.06	0.55	0.01	0.27	0.03	0.51	0.03
Rel.Age*Borderline	0.21	-0.21	0.63	0.33	0.20	-0.22	0.61	0.35
Rel.Age*High	-0.10	-0.46	0.27	0.61	-0.08	-0.45	0.28	0.66
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.13	-0.01	0.27	0.07	0.12	-0.01	0.26	0.08
Borderline	0.11	-0.16	0.37	0.43	0.10	-0.16	0.37	0.43
High	0.27	0.01	0.54	0.05	0.27	0.00	0.53	0.05
Rel.Age*Borderline	0.11	-0.30	0.51	0.61	0.08	-0.32	0.49	0.68
Rel.Age*High	-0.20	-0.62	0.21	0.34	-0.20	-0.61	0.21	0.34
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.01	-0.16	0.14	0.88	-0.02	-0.17	0.13	0.82
Borderline	0.07	-0.26	0.41	0.66	0.06	-0.27	0.39	0.72
High	0.32	0.02	0.63	0.04	0.32	0.02	0.62	0.04
Rel.Age*Borderline	0.21	-0.28	0.70	0.40	0.20	-0.28	0.69	0.41
Rel.Age*High	-0.08	-0.54	0.39	0.74	-0.08	-0.54	0.38	0.73
			Hyperactivity problems					
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.22	0.11	0.33	<0.01	0.24	0.13	0.35	<0.01
Borderline	0.75	0.53	0.97	<0.01	0.71	0.49	0.94	<0.01
High	1.22	1.01	1.43	<0.01	1.12	0.92	1.33	<0.01
Rel.Age*Borderline	-0.12	-0.46	0.22	0.50	-0.15	-0.49	0.18	0.37
Rel.Age*High	-0.20	-0.52	0.11	0.21	-0.19	-0.50	0.13	0.24
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.27	0.15	0.38	<0.01	0.28	0.17	0.40	<0.01
Borderline	0.53	0.29	0.77	<0.01	0.50	0.26	0.74	<0.01

High	1.19	0.98	1.39	<0.01	1.09	0.89	1.30	<0.01
Rel.Age*Borderline	0.20	-0.16	0.56	0.27	0.17	-0.18	0.53	0.34
Rel.Age*High	-0.23	-0.56	0.09	0.16	-0.22	-0.53	0.10	0.19
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.19	0.08	0.31	<0.01	0.21	0.10	0.33	<0.01
Borderline	0.40	0.17	0.63	<0.01	0.37	0.14	0.60	<0.01
High	1.19	0.98	1.40	<0.01	1.09	0.88	1.30	<0.01
Rel.Age*Borderline	0.30	-0.05	0.65	0.10	0.26	-0.09	0.60	0.14
Rel.Age*High	-0.27	-0.59	0.05	0.09	-0.25	-0.57	0.06	0.12
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.28	0.16	0.39	<0.01	0.30	0.19	0.41	<0.01
Borderline	0.34	0.10	0.59	0.01	0.30	0.07	0.54	0.01
High	1.10	0.87	1.32	<0.01	0.97	0.75	1.19	<0.01
Rel.Age*Borderline	0.35	-0.03	0.72	0.07	0.30	-0.06	0.66	0.11
Rel.Age*High	-0.33	-0.67	0.01	0.06	-0.30	-0.63	0.04	0.08
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.22	0.10	0.34	<0.01	0.24	0.12	0.36	<0.01
Borderline	0.31	0.06	0.56	0.02	0.27	0.02	0.52	0.04
High	1.08	0.85	1.30	<0.01	0.95	0.73	1.17	<0.01
Rel.Age*Borderline	0.26	-0.12	0.65	0.18	0.22	-0.15	0.60	0.25
Rel.Age*High	-0.41	-0.76	-0.07	0.02	-0.39	-0.72	-0.05	0.03
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.19	0.06	0.33	0.01	0.21	0.08	0.34	<0.01
Borderline	0.39	0.12	0.66	0.01	0.35	0.08	0.62	0.01
High	0.94	0.68	1.20	<0.01	0.84	0.59	1.10	<0.01
Rel.Age*Borderline	0.11	-0.31	0.53	0.62	0.07	-0.35	0.49	0.75
Rel.Age*High	-0.42	-0.82	-0.01	0.05	-0.39	-0.80	0.01	0.06
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.03	-0.12	0.17	0.71	0.04	-0.10	0.19	0.58
Borderline	0.26	-0.05	0.56	0.10	0.22	-0.08	0.52	0.15
High	0.76	0.45	1.07	<0.01	0.68	0.37	0.98	<0.01
Rel.Age*Borderline	0.27	-0.21	0.75	0.26	0.24	-0.24	0.72	0.32
Rel.Age*High	-0.09	-0.55	0.38	0.72	-0.07	-0.53	0.39	0.77

	Peer problems							
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.08	-0.05	0.20	0.24	0.08	-0.04	0.21	0.19
Borderline	0.15	-0.10	0.41	0.24	0.13	-0.12	0.39	0.30
High	0.20	-0.03	0.44	0.09	0.14	-0.09	0.38	0.23
Rel.Age*Borderline	0.03	-0.35	0.42	0.86	0.01	-0.37	0.39	0.97
Rel.Age*High	0.20	-0.16	0.57	0.27	0.22	-0.14	0.58	0.23
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.11	-0.02	0.24	0.09	0.12	-0.01	0.25	0.08
Borderline	0.21	-0.06	0.47	0.13	0.19	-0.08	0.45	0.17
High	0.37	0.14	0.60	<0.01	0.31	0.07	0.54	0.01
Rel.Age*Borderline	0.08	-0.31	0.48	0.68	0.06	-0.34	0.45	0.77
Rel.Age*High	-0.07	-0.43	0.30	0.72	-0.06	-0.42	0.31	0.77
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.06	-0.07	0.19	0.35	0.07	-0.06	0.20	0.28
Borderline	0.27	0.01	0.52	0.04	0.25	0.00	0.50	0.05
High	0.36	0.12	0.60	<0.01	0.30	0.06	0.54	0.01
Rel.Age*Borderline	-0.04	-0.42	0.34	0.84	-0.07	-0.45	0.31	0.72
Rel.Age*High	0.19	-0.18	0.55	0.32	0.20	-0.17	0.56	0.29
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.07	-0.07	0.20	0.33	0.08	-0.06	0.21	0.25
Borderline	0.17	-0.10	0.43	0.22	0.15	-0.12	0.41	0.28
High	0.26	0.01	0.52	0.04	0.20	-0.06	0.46	0.13
Rel.Age*Borderline	0.06	-0.35	0.48	0.77	0.03	-0.38	0.45	0.88
Rel.Age*High	0.16	-0.23	0.54	0.43	0.17	-0.22	0.56	0.39
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.05	-0.09	0.18	0.52	0.06	-0.08	0.19	0.40
Borderline	0.13	-0.16	0.42	0.38	0.10	-0.19	0.38	0.50
High	0.26	0.00	0.52	0.05	0.18	-0.08	0.45	0.17
Rel.Age*Borderline	0.10	-0.34	0.54	0.67	0.07	-0.37	0.51	0.76
Rel.Age*High	-0.02	-0.43	0.38	0.92	0.00	-0.41	0.40	0.98
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.04	-0.10	0.18	0.57	0.05	-0.09	0.19	0.47

Borderline	0.06	-0.22	0.33	0.69	0.04	-0.24	0.32	0.80
High	0.13	-0.15	0.41	0.36	0.08	-0.21	0.36	0.59
Rel.Age*Borderline	0.03	-0.41	0.46	0.90	0.01	-0.43	0.44	0.98
Rel.Age*High	0.14	-0.27	0.56	0.50	0.15	-0.26	0.57	0.47
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.11	-0.26	0.04	0.16	-0.10	-0.25	0.05	0.19
Borderline	-0.12	-0.46	0.22	0.50	-0.14	-0.48	0.20	0.42
High	0.24	-0.06	0.53	0.11	0.20	-0.09	0.50	0.18
Rel.Age*Borderline	0.76	0.23	1.29	0.01	0.74	0.21	1.27	0.01
Rel.Age*High	0.21	-0.25	0.66	0.37	0.21	-0.24	0.66	0.36

Coefficient (Coef.) represents mean change in standardised parent-report SDQ subscale score per 1 year difference in relative age (rel.age), or mean change in standardised parent-report SDQ subscale score compared to low-risk ADHD group (Borderline vs low ADHD risk/High vs low ADHD risk). "Unadjusted Model" = Age within School Year entered in the regression alone. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. Borderline = SDQ hyperactivity scores at 4 years of age = 6. High = SDQ hyperactivity scores at 4 years of age >=7

Table A4.4: Regression results for SDQ subscales by relative age, stratified by ADHD symptoms at age 4 years. Imputed data. Restricted to individuals born up to 8 weeks either side of the September 1st cut-off.

	Unadjusted				Adjusted			
	Conduct problems							
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.05	-0.05	0.14	0.34	0.05	-0.05	0.14	0.33
Borderline	0.43	0.24	0.62	<0.01	0.41	0.23	0.60	<0.01
High	0.74	0.57	0.91	<0.01	0.68	0.51	0.85	<0.01
Rel.Age*Borderline	0.11	-0.18	0.41	0.45	0.09	-0.21	0.38	0.56
Rel.Age*High	-0.15	-0.43	0.12	0.28	-0.14	-0.41	0.14	0.34
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.11	0.01	0.21	0.03	0.11	0.01	0.21	0.03
Borderline	0.42	0.22	0.61	<0.01	0.39	0.20	0.58	<0.01
High	0.77	0.60	0.95	<0.01	0.70	0.53	0.87	<0.01
Rel.Age*Borderline	-0.01	-0.31	0.30	0.97	-0.03	-0.33	0.28	0.85
Rel.Age*High	-0.15	-0.44	0.14	0.31	-0.13	-0.42	0.16	0.38
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.02	-0.12	0.07	0.66	-0.02	-0.11	0.08	0.73
Borderline	0.35	0.17	0.53	<0.01	0.32	0.14	0.50	<0.01
High	0.67	0.51	0.83	<0.01	0.60	0.44	0.76	<0.01
Rel.Age*Borderline	0.14	-0.15	0.43	0.33	0.12	-0.17	0.41	0.42
Rel.Age*High	-0.02	-0.29	0.24	0.87	0.00	-0.27	0.26	0.99
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.12	0.02	0.22	0.02	0.12	0.02	0.22	0.02
Borderline	0.34	0.14	0.54	<0.01	0.30	0.10	0.51	<0.01
High	0.59	0.41	0.76	<0.01	0.50	0.33	0.68	<0.01
Rel.Age*Borderline	0.12	-0.20	0.45	0.45	0.10	-0.22	0.42	0.54
Rel.Age*High	-0.19	-0.48	0.10	0.20	-0.16	-0.45	0.12	0.27
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.04	-0.06	0.14	0.45	0.04	-0.07	0.14	0.48
Borderline	0.14	-0.05	0.34	0.16	0.11	-0.09	0.30	0.27
High	0.60	0.43	0.78	<0.01	0.53	0.35	0.70	<0.01
Rel.Age*Borderline	0.20	-0.12	0.51	0.22	0.18	-0.13	0.49	0.26

Rel.Age*High	-0.20	-0.48	0.08	0.17	-0.17	-0.45	0.11	0.23
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.06	-0.06	0.17	0.32	0.06	-0.05	0.17	0.32
Borderline	0.22	0.00	0.44	0.05	0.21	-0.01	0.42	0.06
High	0.45	0.25	0.66	<0.01	0.39	0.18	0.60	<0.01
Rel.Age*Borderline	0.12	-0.23	0.47	0.49	0.09	-0.25	0.44	0.61
Rel.Age*High	-0.22	-0.56	0.12	0.20	-0.20	-0.53	0.14	0.25
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.00	-0.13	0.12	0.95	-0.01	-0.13	0.11	0.89
Borderline	0.29	0.02	0.57	0.04	0.28	0.00	0.55	0.05
High	0.34	0.09	0.59	0.01	0.29	0.04	0.54	0.02
Rel.Age*Borderline	0.12	-0.32	0.57	0.59	0.10	-0.35	0.55	0.66
Rel.Age*High	-0.02	-0.42	0.38	0.92	0.00	-0.40	0.40	1.00
			Emotional problems					
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.13	0.03	0.22	0.01	0.12	0.03	0.22	0.01
Borderline	0.22	0.04	0.41	0.02	0.22	0.04	0.40	0.02
High	0.39	0.22	0.55	<0.01	0.33	0.17	0.49	<0.01
Rel.Age*Borderline	0.02	-0.27	0.31	0.90	-0.01	-0.30	0.28	0.94
Rel.Age*High	-0.15	-0.42	0.11	0.26	-0.13	-0.39	0.14	0.34
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.20	0.10	0.30	<0.01	0.19	0.09	0.29	<0.01
Borderline	0.22	0.02	0.41	0.03	0.21	0.02	0.41	0.03
High	0.49	0.33	0.66	<0.01	0.44	0.27	0.61	<0.01
Rel.Age*Borderline	-0.14	-0.44	0.16	0.37	-0.17	-0.46	0.13	0.27
Rel.Age*High	-0.28	-0.56	0.00	0.05	-0.26	-0.54	0.01	0.06
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.09	-0.01	0.19	0.07	0.09	-0.01	0.19	0.07
Borderline	0.11	-0.08	0.30	0.24	0.11	-0.08	0.29	0.25
High	0.41	0.24	0.57	<0.01	0.35	0.19	0.52	<0.01
Rel.Age*Borderline	0.12	-0.18	0.43	0.42	0.10	-0.20	0.40	0.52
Rel.Age*High	-0.15	-0.42	0.12	0.27	-0.13	-0.40	0.14	0.35
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p

Rel.Age	0.11	0.01	0.21	0.04	0.11	0.01	0.21	0.04
Borderline	0.14	-0.05	0.34	0.16	0.14	-0.06	0.33	0.17
High	0.45	0.26	0.63	<0.01	0.39	0.20	0.57	<0.01
Rel.Age*Borderline	0.08	-0.23	0.39	0.61	0.05	-0.26	0.35	0.77
Rel.Age*High	-0.21	-0.51	0.10	0.18	-0.18	-0.48	0.12	0.24
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.11	0.01	0.22	0.03	0.10	0.00	0.21	0.05
Borderline	0.18	-0.02	0.37	0.08	0.18	-0.01	0.38	0.07
High	0.42	0.25	0.60	<0.01	0.39	0.21	0.57	<0.01
Rel.Age*Borderline	0.05	-0.27	0.37	0.77	0.03	-0.29	0.34	0.87
Rel.Age*High	-0.20	-0.48	0.09	0.18	-0.18	-0.46	0.11	0.22
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.15	0.04	0.26	0.01	0.15	0.04	0.26	0.01
Borderline	0.14	-0.07	0.34	0.18	0.15	-0.05	0.35	0.13
High	0.41	0.21	0.61	<0.01	0.39	0.19	0.59	<0.01
Rel.Age*Borderline	0.01	-0.31	0.33	0.95	-0.02	-0.33	0.30	0.92
Rel.Age*High	-0.34	-0.67	-0.01	0.05	-0.32	-0.65	0.01	0.06
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.02	-0.14	0.11	0.80	-0.02	-0.15	0.10	0.69
Borderline	0.12	-0.13	0.37	0.35	0.12	-0.13	0.37	0.35
High	0.40	0.16	0.64	<0.01	0.36	0.13	0.60	<0.01
Rel.Age*Borderline	0.16	-0.24	0.56	0.43	0.14	-0.26	0.54	0.49
Rel.Age*High	-0.11	-0.50	0.27	0.56	-0.09	-0.47	0.29	0.66
			Hyperactivity problems					
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.26	0.18	0.35	<0.01	0.27	0.18	0.35	<0.01
Borderline	0.86	0.69	1.02	<0.01	0.82	0.65	0.98	<0.01
High	1.22	1.06	1.37	<0.01	1.13	0.97	1.28	<0.01
Rel.Age*Borderline	-0.22	-0.48	0.05	0.11	-0.24	-0.50	0.02	0.08
Rel.Age*High	-0.25	-0.50	-0.01	0.04	-0.24	-0.48	0.01	0.06
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.28	0.19	0.38	<0.01	0.29	0.20	0.38	<0.01
Borderline	0.65	0.47	0.84	<0.01	0.62	0.44	0.80	<0.01

High	1.15	0.99	1.30	<0.01	1.06	0.90	1.21	<0.01
Rel.Age*Borderline	0.00	-0.28	0.27	0.98	-0.02	-0.30	0.25	0.86
Rel.Age*High	-0.21	-0.46	0.04	0.10	-0.19	-0.44	0.06	0.13
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.24	0.15	0.33	<0.01	0.25	0.16	0.33	<0.01
Borderline	0.58	0.40	0.75	<0.01	0.54	0.37	0.71	<0.01
High	1.07	0.92	1.23	<0.01	0.98	0.82	1.13	<0.01
Rel.Age*Borderline	0.04	-0.23	0.31	0.78	0.02	-0.25	0.29	0.90
Rel.Age*High	-0.16	-0.41	0.09	0.22	-0.14	-0.39	0.11	0.27
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.29	0.20	0.38	<0.01	0.29	0.20	0.38	<0.01
Borderline	0.50	0.32	0.68	<0.01	0.46	0.28	0.64	<0.01
High	0.97	0.80	1.13	<0.01	0.86	0.70	1.03	<0.01
Rel.Age*Borderline	0.09	-0.20	0.37	0.54	0.06	-0.21	0.34	0.65
Rel.Age*High	-0.16	-0.43	0.10	0.22	-0.15	-0.40	0.11	0.27
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.22	0.12	0.31	<0.01	0.22	0.13	0.31	<0.01
Borderline	0.44	0.26	0.63	<0.01	0.40	0.22	0.58	<0.01
High	0.97	0.80	1.13	<0.01	0.86	0.70	1.02	<0.01
Rel.Age*Borderline	0.07	-0.23	0.36	0.66	0.04	-0.24	0.33	0.76
Rel.Age*High	-0.27	-0.54	-0.01	0.04	-0.25	-0.51	0.01	0.06
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.18	0.07	0.28	<0.01	0.18	0.07	0.28	<0.01
Borderline	0.50	0.29	0.71	<0.01	0.47	0.26	0.68	<0.01
High	0.87	0.67	1.07	<0.01	0.78	0.58	0.98	<0.01
Rel.Age*Borderline	-0.04	-0.37	0.30	0.83	-0.06	-0.40	0.27	0.71
Rel.Age*High	-0.36	-0.69	-0.04	0.03	-0.34	-0.67	-0.02	0.04
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.01	-0.13	0.10	0.82	-0.01	-0.13	0.10	0.82
Borderline	0.30	0.06	0.54	0.02	0.27	0.03	0.51	0.03
High	0.68	0.44	0.91	<0.01	0.59	0.36	0.82	<0.01
Rel.Age*Borderline	0.22	-0.17	0.61	0.27	0.20	-0.20	0.59	0.33
Rel.Age*High	0.05	-0.33	0.44	0.78	0.08	-0.31	0.46	0.69

				Peer problems				
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.03	-0.06	0.13	0.48	0.04	-0.06	0.13	0.45
Borderline	0.26	0.08	0.45	0.01	0.24	0.06	0.43	0.01
High	0.23	0.05	0.40	0.01	0.16	-0.02	0.33	0.07
Rel.Age*Borderline	-0.05	-0.35	0.24	0.72	-0.08	-0.37	0.21	0.59
Rel.Age*High	0.17	-0.12	0.46	0.24	0.19	-0.10	0.48	0.19
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.09	-0.01	0.19	0.08	0.09	-0.01	0.18	0.09
Borderline	0.29	0.09	0.49	<0.01	0.27	0.08	0.47	0.01
High	0.36	0.18	0.53	<0.01	0.29	0.12	0.47	<0.01
Rel.Age*Borderline	-0.02	-0.33	0.29	0.90	-0.04	-0.35	0.27	0.80
Rel.Age*High	0.01	-0.27	0.30	0.92	0.03	-0.25	0.31	0.85
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.09	-0.01	0.18	0.08	0.09	-0.01	0.19	0.07
Borderline	0.23	0.05	0.42	0.01	0.21	0.03	0.40	0.02
High	0.32	0.15	0.49	<0.01	0.26	0.09	0.43	<0.01
Rel.Age*Borderline	-0.07	-0.37	0.22	0.63	-0.10	-0.39	0.20	0.52
Rel.Age*High	0.21	-0.06	0.48	0.13	0.23	-0.05	0.50	0.10
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.11	0.01	0.21	0.03	0.11	0.01	0.22	0.03
Borderline	0.27	0.07	0.46	0.01	0.25	0.05	0.44	0.01
High	0.25	0.07	0.43	0.01	0.18	0.00	0.36	0.05
Rel.Age*Borderline	-0.10	-0.42	0.22	0.55	-0.12	-0.44	0.20	0.46
Rel.Age*High	0.13	-0.16	0.42	0.38	0.15	-0.14	0.44	0.32
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.11	0.00	0.21	0.05	0.11	0.01	0.21	0.04
Borderline	0.25	0.04	0.45	0.02	0.22	0.02	0.43	0.04
High	0.29	0.11	0.48	<0.01	0.23	0.04	0.41	0.02
Rel.Age*Borderline	-0.09	-0.42	0.24	0.61	-0.11	-0.44	0.22	0.52
Rel.Age*High	0.00	-0.30	0.30	0.99	0.02	-0.29	0.32	0.92
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.07	-0.04	0.19	0.19	0.08	-0.03	0.19	0.17

Borderline	0.22	0.01	0.43	0.04	0.20	-0.01	0.41	0.06
High	0.25	0.05	0.46	0.02	0.21	0.00	0.42	0.05
Rel.Age*Borderline	-0.15	-0.49	0.19	0.39	-0.17	-0.51	0.18	0.34
Rel.Age*High	-0.01	-0.34	0.32	0.94	0.00	-0.33	0.33	1.00
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.09	-0.21	0.03	0.16	-0.09	-0.21	0.04	0.16
Borderline	-0.03	-0.29	0.23	0.83	-0.05	-0.31	0.22	0.73
High	0.30	0.06	0.54	0.01	0.25	0.01	0.49	0.04
Rel.Age*Borderline	0.61	0.18	1.04	0.01	0.59	0.17	1.02	0.01
Rel.Age*High	0.19	-0.20	0.57	0.34	0.21	-0.17	0.59	0.28

Coefficient (Coef.) represents mean change in standardised parent-report SDQ subscale score per 1 year difference in relative age (rel.age), or mean change in standardised parent-report SDQ subscale score compared to low-risk ADHD group (Borderline vs low ADHD risk/High vs low ADHD risk) "Unadjusted Model" = Age within School Year entered in the regression alone. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. Borderline = SDQ hyperactivity scores at 4 years of age = 6. High = SDQ hyperactivity scores at 4 years of age >=7

Table A4.5: Regression results for SDQ subscales by relative age and PRS scores for ADHD, threshold level p<0.05 ("PRS p<0.05"). Imputed data. Restricted to individuals born up to 4 weeks either side of the September 1st cut-off

	Unadjusted Model				Adjusted for covariates			
Conduct problems								
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.02	-0.15	0.11	0.80	-0.01	-0.13	0.12	0.93
PRS	0.10	0.02	0.19	0.02	0.09	0.01	0.18	0.04
Rel.age*PRS	-0.03	-0.16	0.10	0.69	-0.02	-0.15	0.11	0.74
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.03	-0.16	0.10	0.68	-0.01	-0.14	0.12	0.85
PRS	0.10	0.02	0.19	0.02	0.09	0.01	0.18	0.04
Rel.age*PRS	-0.03	-0.16	0.10	0.66	-0.03	-0.15	0.10	0.68
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.07	-0.19	0.06	0.30	-0.05	-0.18	0.08	0.43
PRS	0.10	0.02	0.19	0.02	0.09	0.01	0.18	0.03
Rel.age*PRS	0.00	-0.12	0.13	0.99	0.00	-0.12	0.13	0.97
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.01	-0.12	0.14	0.89	0.03	-0.10	0.16	0.64
PRS	0.12	0.03	0.20	0.01	0.10	0.02	0.19	0.02
Rel.age*PRS	-0.03	-0.16	0.10	0.67	-0.03	-0.16	0.10	0.68
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.00	-0.13	0.14	0.94	0.02	-0.11	0.15	0.74
PRS	0.05	-0.03	0.14	0.23	0.04	-0.05	0.12	0.39
Rel.age*PRS	0.05	-0.08	0.18	0.41	0.06	-0.07	0.18	0.39
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.04	-0.10	0.18	0.57	0.05	-0.08	0.19	0.43
PRS	0.06	-0.03	0.15	0.18	0.05	-0.04	0.14	0.26
Rel.age*PRS	-0.02	-0.16	0.11	0.74	-0.02	-0.16	0.12	0.77
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.00	-0.15	0.15	0.99	0.01	-0.14	0.16	0.87
PRS	0.08	-0.01	0.18	0.08	0.07	-0.02	0.17	0.12
Rel.age*PRS	0.02	-0.12	0.17	0.75	0.03	-0.12	0.17	0.71
Emotional Problems								

7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.12	-0.01	0.25	0.07	0.13	0.01	0.26	0.04
PRS	0.01	-0.07	0.10	0.78	0.00	-0.09	0.08	0.97
Rel.age*PRS	0.01	-0.11	0.14	0.85	0.02	-0.11	0.14	0.78
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.09	-0.04	0.23	0.17	0.10	-0.04	0.23	0.16
PRS	-0.01	-0.10	0.08	0.82	-0.02	-0.11	0.07	0.66
Rel.age*PRS	0.05	-0.08	0.18	0.48	0.05	-0.08	0.18	0.42
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.10	-0.02	0.23	0.11	0.12	-0.01	0.24	0.07
PRS	-0.01	-0.10	0.07	0.80	-0.02	-0.11	0.06	0.59
Rel.age*PRS	0.05	-0.07	0.18	0.41	0.06	-0.07	0.18	0.36
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.03	-0.10	0.16	0.67	0.04	-0.09	0.18	0.50
PRS	0.03	-0.05	0.12	0.45	0.02	-0.07	0.11	0.65
Rel.age*PRS	0.04	-0.09	0.17	0.52	0.05	-0.08	0.18	0.45
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.06	-0.07	0.19	0.36	0.07	-0.06	0.20	0.30
PRS	0.02	-0.07	0.11	0.68	0.01	-0.08	0.09	0.89
Rel.age*PRS	0.03	-0.10	0.16	0.67	0.03	-0.09	0.16	0.61
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.08	0.21	0.36	0.08	-0.06	0.22	0.27
PRS	0.02	-0.07	0.12	0.66	0.01	-0.08	0.10	0.85
Rel.age*PRS	-0.02	-0.16	0.12	0.74	-0.02	-0.16	0.12	0.79
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.01	-0.14	0.16	0.88	0.02	-0.13	0.18	0.76
PRS	0.06	-0.03	0.16	0.21	0.05	-0.04	0.15	0.28
Rel.age*PRS	-0.01	-0.16	0.14	0.92	0.00	-0.15	0.14	0.96
			Hyperactivity Problems					
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.12	0.00	0.25	0.06	0.14	0.02	0.27	0.02
PRS	0.11	0.03	0.20	0.01	0.09	0.01	0.18	0.03
Rel.age*PRS	-0.06	-0.18	0.07	0.38	-0.05	-0.17	0.07	0.43

8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.19	0.06	0.32	<0.01	0.20	0.07	0.33	<0.01
PRS	0.12	0.03	0.20	0.01	0.11	0.02	0.19	0.02
Rel.age*PRS	-0.04	-0.17	0.08	0.49	-0.04	-0.17	0.08	0.51
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.17	0.04	0.29	0.01	0.18	0.06	0.31	<0.01
PRS	0.13	0.04	0.22	<0.01	0.12	0.03	0.20	0.01
Rel.age*PRS	-0.10	-0.23	0.02	0.11	-0.10	-0.23	0.02	0.11
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.27	0.14	0.39	<0.01	0.28	0.16	0.41	<0.01
PRS	0.12	0.03	0.20	0.01	0.10	0.02	0.19	0.01
Rel.age*PRS	-0.04	-0.17	0.08	0.49	-0.04	-0.17	0.08	0.53
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.19	0.06	0.32	<0.01	0.21	0.08	0.34	<0.01
PRS	0.15	0.07	0.24	<0.01	0.14	0.05	0.22	<0.01
Rel.age*PRS	-0.07	-0.19	0.06	0.31	-0.06	-0.19	0.06	0.31
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.12	-0.02	0.25	0.10	0.13	-0.01	0.27	0.06
PRS	0.09	-0.01	0.18	0.07	0.08	-0.02	0.17	0.11
Rel.age*PRS	-0.05	-0.19	0.10	0.53	-0.04	-0.18	0.10	0.55
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.01	-0.14	0.17	0.87	0.03	-0.12	0.18	0.69
PRS	0.12	0.03	0.21	0.01	0.11	0.01	0.20	0.03
Rel.age*PRS	-0.04	-0.19	0.10	0.55	-0.04	-0.19	0.10	0.57
				Peer Problems				
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.03	-0.10	0.16	0.70	0.04	-0.09	0.17	0.57
PRS	0.04	-0.05	0.13	0.41	0.03	-0.06	0.12	0.51
Rel.age*PRS	-0.06	-0.19	0.07	0.39	-0.06	-0.18	0.07	0.40
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.06	0.21	0.29	0.08	-0.06	0.21	0.25
PRS	0.12	0.03	0.21	0.01	0.11	0.02	0.20	0.02
Rel.age*PRS	-0.08	-0.22	0.05	0.22	-0.08	-0.21	0.05	0.24

9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.06	-0.08	0.19	0.41	0.07	-0.06	0.20	0.30
PRS	0.03	-0.06	0.12	0.47	0.02	-0.07	0.11	0.61
Rel.age*PRS	-0.04	-0.17	0.10	0.59	-0.03	-0.17	0.10	0.61
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.06	0.21	0.30	0.09	-0.05	0.22	0.22
PRS	0.07	-0.02	0.16	0.13	0.06	-0.03	0.15	0.19
Rel.age*PRS	-0.05	-0.19	0.08	0.44	-0.05	-0.19	0.08	0.46
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.02	-0.11	0.16	0.73	0.04	-0.10	0.18	0.56
PRS	0.08	-0.01	0.17	0.08	0.07	-0.02	0.16	0.13
Rel.age*PRS	-0.14	-0.28	-0.01	0.04	-0.14	-0.28	-0.01	0.04
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.00	-0.15	0.14	0.99	0.01	-0.13	0.16	0.89
PRS	0.07	-0.02	0.17	0.14	0.06	-0.03	0.16	0.19
Rel.age*PRS	-0.03	-0.17	0.11	0.68	-0.03	-0.17	0.11	0.68
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.05	-0.20	0.10	0.50	-0.03	-0.18	0.11	0.65
PRS	0.05	-0.05	0.15	0.32	0.04	-0.06	0.14	0.43
Rel.age*PRS	-0.02	-0.18	0.13	0.76	-0.02	-0.17	0.13	0.78

N=1275. Coefficient (Coef.) represents mean change in standardised parent-report SDQ score per 1 year difference in relative age (Rel.Age) or mean change in standardised parent-report SDQ subscale score per 1 SD unit change in PRS (PRS) Unadjusted Model" = Age within School Year entered in the regression + principal components. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. PRS $p<0.05$ = PRS scores for ADHD, threshold level $p<0.05$

Table A4.6: Regression results for SDQ subscales by relative age and PRS scores for ADHD, threshold level p<0.05 ("PRS p<0.05"). Imputed data. Restricted to individuals born up to 8 weeks either side of the September 1st cut-off Imputed data

	Unadjusted model				Adjusted for covariates			
Conduct Problems								
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.01	-0.09	0.11	0.89	0.01	-0.09	0.11	0.80
PRS	0.09	0.03	0.15	0.01	0.08	0.01	0.14	0.02
Rel.age*PRS	-0.02	-0.12	0.08	0.67	-0.01	-0.11	0.09	0.86
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.04	-0.06	0.14	0.47	0.05	-0.05	0.14	0.37
PRS	0.10	0.04	0.16	<0.01	0.09	0.02	0.15	0.01
Rel.age*PRS	-0.05	-0.15	0.05	0.33	-0.04	-0.14	0.06	0.45
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.02	-0.12	0.07	0.65	-0.01	-0.11	0.08	0.79
PRS	0.10	0.03	0.16	<0.01	0.09	0.02	0.15	0.01
Rel.age*PRS	-0.03	-0.13	0.07	0.54	-0.02	-0.12	0.07	0.66
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.03	0.17	0.15	0.09	-0.01	0.19	0.09
PRS	0.10	0.04	0.17	<0.01	0.09	0.03	0.15	0.01
Rel.age*PRS	-0.02	-0.12	0.08	0.66	-0.01	-0.11	0.09	0.82
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.01	-0.09	0.11	0.81	0.02	-0.08	0.12	0.67
PRS	0.06	0.00	0.12	0.07	0.04	-0.02	0.11	0.18
Rel.age*PRS	0.02	-0.08	0.12	0.75	0.03	-0.07	0.13	0.59
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.04	-0.07	0.15	0.50	0.04	-0.06	0.15	0.42
PRS	0.07	0.00	0.14	0.04	0.06	-0.01	0.13	0.09
Rel.age*PRS	-0.03	-0.14	0.08	0.56	-0.02	-0.13	0.09	0.73
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.02	-0.15	0.10	0.74	-0.02	-0.14	0.11	0.76
PRS	0.10	0.03	0.18	0.01	0.09	0.02	0.17	0.02
Rel.age*PRS	0.00	-0.12	0.13	0.96	0.02	-0.11	0.14	0.81
Emotional Problems								

7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.03	0.17	0.17	0.08	-0.02	0.17	0.13
PRS	0.01	-0.05	0.07	0.75	0.00	-0.07	0.06	0.94
Rel.age*PRS	-0.01	-0.11	0.08	0.79	0.00	-0.09	0.10	0.95
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.03	0.18	0.16	0.07	-0.04	0.17	0.20
PRS	0.01	-0.05	0.08	0.75	0.00	-0.06	0.07	0.96
Rel.age*PRS	0.00	-0.09	0.10	0.92	0.02	-0.08	0.12	0.70
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.09	-0.01	0.19	0.07	0.09	0.00	0.19	0.05
PRS	0.02	-0.04	0.08	0.58	0.01	-0.05	0.07	0.83
Rel.age*PRS	0.00	-0.10	0.09	0.93	0.01	-0.09	0.10	0.84
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.03	0.17	0.15	0.08	-0.01	0.18	0.09
PRS	0.03	-0.04	0.09	0.44	0.01	-0.05	0.07	0.76
Rel.age*PRS	0.03	-0.06	0.13	0.49	0.05	-0.04	0.15	0.29
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.10	0.01	0.20	0.04	0.11	0.01	0.20	0.04
PRS	0.03	-0.03	0.10	0.31	0.02	-0.04	0.09	0.47
Rel.age*PRS	-0.01	-0.11	0.09	0.80	0.00	-0.10	0.10	1.00
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.08	-0.03	0.19	0.17	0.09	-0.03	0.20	0.13
PRS	0.01	-0.06	0.08	0.75	0.00	-0.07	0.07	1.00
Rel.age*PRS	0.00	-0.11	0.11	0.98	0.02	-0.09	0.12	0.78
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.01	-0.11	0.13	0.90	0.01	-0.11	0.13	0.86
PRS	0.07	-0.01	0.14	0.07	0.06	-0.02	0.13	0.14
Rel.age*PRS	-0.01	-0.13	0.11	0.84	0.00	-0.12	0.12	0.97
			Hyperactivity Problems					
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.14	0.04	0.24	<0.01	0.15	0.06	0.25	<0.01
PRS	0.11	0.05	0.18	<0.01	0.10	0.03	0.16	<0.01
Rel.age*PRS	-0.04	-0.14	0.06	0.41	-0.03	-0.12	0.07	0.58

8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.19	0.09	0.29	<0.01	0.19	0.09	0.29	<0.01
PRS	0.12	0.05	0.18	<0.01	0.11	0.04	0.17	<0.01
Rel.age*PRS	-0.04	-0.14	0.06	0.43	-0.03	-0.13	0.07	0.58
9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.19	0.09	0.28	<0.01	0.20	0.10	0.29	<0.01
PRS	0.11	0.05	0.17	<0.01	0.10	0.04	0.16	<0.01
Rel.age*PRS	-0.07	-0.16	0.03	0.16	-0.06	-0.15	0.04	0.24
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.27	0.17	0.37	<0.01	0.28	0.18	0.37	<0.01
PRS	0.10	0.04	0.16	<0.01	0.09	0.03	0.15	<0.01
Rel.age*PRS	-0.02	-0.12	0.08	0.70	-0.01	-0.10	0.09	0.89
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.16	0.06	0.26	<0.01	0.17	0.07	0.26	<0.01
PRS	0.13	0.07	0.19	<0.01	0.12	0.05	0.18	<0.01
Rel.age*PRS	-0.04	-0.14	0.06	0.40	-0.03	-0.13	0.07	0.53
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.08	-0.03	0.19	0.16	0.08	-0.02	0.19	0.12
PRS	0.07	0.00	0.14	0.04	0.06	-0.01	0.13	0.08
Rel.age*PRS	0.00	-0.12	0.11	0.93	0.01	-0.10	0.12	0.90
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.01	-0.14	0.11	0.83	-0.01	-0.13	0.12	0.92
PRS	0.11	0.04	0.18	<0.01	0.09	0.02	0.17	0.01
Rel.age*PRS	-0.04	-0.16	0.08	0.48	-0.03	-0.15	0.09	0.64
				Peer Problems				
7 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.02	-0.12	0.07	0.63	-0.02	-0.11	0.08	0.74
PRS	0.08	0.02	0.14	0.01	0.07	0.01	0.13	0.03
Rel.age*PRS	-0.10	-0.20	0.00	0.04	-0.09	-0.18	0.01	0.07
8 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.05	-0.05	0.15	0.36	0.04	-0.06	0.14	0.42
PRS	0.13	0.07	0.20	<0.01	0.12	0.06	0.19	<0.01
Rel.age*PRS	-0.13	-0.23	-0.03	0.01	-0.12	-0.22	-0.02	0.02

9 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.07	-0.03	0.17	0.15	0.08	-0.02	0.18	0.11
PRS	0.07	0.01	0.13	0.04	0.06	0.00	0.12	0.07
Rel.age*PRS	-0.10	-0.20	0.00	0.05	-0.09	-0.19	0.01	0.08
11 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.10	-0.01	0.20	0.07	0.10	0.00	0.21	0.05
PRS	0.08	0.02	0.15	0.01	0.07	0.01	0.14	0.03
Rel.age*PRS	-0.08	-0.18	0.03	0.15	-0.06	-0.17	0.04	0.22
13 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.08	-0.02	0.18	0.11	0.09	-0.01	0.19	0.09
PRS	0.11	0.04	0.18	<0.01	0.10	0.03	0.17	<0.01
Rel.age*PRS	-0.15	-0.26	-0.05	<0.01	-0.15	-0.25	-0.04	0.01
16 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	0.01	-0.10	0.12	0.83	0.02	-0.09	0.13	0.72
PRS	0.06	-0.02	0.13	0.12	0.05	-0.02	0.12	0.20
Rel.age*PRS	-0.01	-0.13	0.10	0.81	-0.01	-0.12	0.11	0.91
25 years	Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
Rel.age	-0.03	-0.15	0.09	0.61	-0.02	-0.14	0.10	0.75
PRS	0.06	-0.01	0.14	0.10	0.05	-0.02	0.13	0.18
Rel.age*PRS	-0.03	-0.16	0.09	0.61	-0.02	-0.14	0.10	0.76

(N=2561). Coefficient (Coef.) represents mean change in standardised parent-report SDQ score per 1 year difference in relative age (Rel.Age) or mean change in standardised parent-report SDQ score per 1 SD unit change in PRS (PRS). Unadjusted Model" = Age within School Year entered in the regression + principal components. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. PRS p<0.05 = PRS scores for ADHD, threshold level p<0.05

Table A4.7: Regression results SDQ total difficulties, relative age and PRS scores for ADHD, all thresholds. Imputed data.

		Unadjusted model				Adjusted Model			
PRS <0.001		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.12	0.04	0.20	<0.01	0.13	0.05	0.21	<0.01
	PRS	0.08	0.04	0.13	<0.01	0.07	0.03	0.12	<0.01
	Rel.Age*PRS	-0.04	-0.12	0.04	0.31	-0.05	-0.12	0.03	0.25
8years	Rel.Age	0.15	0.07	0.23	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.11	0.06	0.16	<0.01	0.10	0.05	0.14	<0.01
	Rel.Age*PRS	-0.07	-0.15	0.01	0.09	-0.08	-0.16	<0.01	0.06
9 years	Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.09	0.04	0.13	<0.01	0.08	0.03	0.12	<0.01
	Rel.Age*PRS	-0.05	-0.13	0.03	0.23	-0.05	-0.13	0.03	0.19
11 years	Rel.Age	0.21	0.13	0.29	<0.01	0.23	0.15	0.31	<0.01
	PRS	0.08	0.03	0.13	<0.01	0.07	0.02	0.11	0.01
	Rel.Age*PRS	-0.02	-0.11	0.06	0.56	-0.03	-0.11	0.05	0.50
13 years	Rel.Age	0.14	0.05	0.22	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.08	0.03	0.13	<0.01	0.07	0.02	0.11	0.01
	Rel.Age*PRS	-0.03	-0.11	0.05	0.48	-0.03	-0.11	0.05	0.43
16 years	Rel.Age	0.07	-0.02	0.17	0.12	0.09	-0.01	0.18	0.07
	PRS	0.09	0.04	0.15	<0.01	0.08	0.03	0.14	<0.01
	Rel.Age*PRS	-0.04	-0.14	0.05	0.35	-0.04	-0.14	0.05	0.36
25 years	Rel.Age	-0.02	-0.13	0.08	0.66	-0.01	-0.11	0.10	0.88
	PRS	0.10	0.04	0.16	<0.01	0.08	0.02	0.14	0.01
	Rel.Age*PRS	-0.07	-0.17	0.03	0.20	-0.06	-0.16	0.04	0.22
PRS <0.005		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.12	0.04	0.20	0.01	0.13	0.05	0.21	<0.01
	PRS	0.10	0.05	0.15	<0.01	0.08	0.04	0.13	<0.01
	Rel.Age*PRS	-0.06	-0.14	0.02	0.16	-0.05	-0.12	0.03	0.25
8years	Rel.Age	0.15	0.07	0.23	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.13	0.08	0.17	<0.01	0.11	0.07	0.16	<0.01
	Rel.Age*PRS	-0.07	-0.16	0.01	0.07	-0.07	-0.14	0.01	0.11
9 years	Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.23	<0.01

	PRS	0.10	0.05	0.14	<0.01	0.08	0.03	0.13	<0.01
	Rel.Age*PRS	-0.04	-0.12	0.04	0.30	-0.03	-0.11	0.05	0.44
11 years	Rel.Age	0.21	0.13	0.29	<0.01	0.22	0.14	0.30	<0.01
	PRS	0.10	0.05	0.14	<0.01	0.08	0.03	0.12	<0.01
	Rel.Age*PRS	-0.03	-0.11	0.05	0.44	-0.02	-0.10	0.06	0.62
13 years	Rel.Age	0.14	0.05	0.22	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.12	0.07	0.16	<0.01	0.10	0.05	0.15	<0.01
	Rel.Age*PRS	-0.06	-0.15	0.02	0.12	-0.05	-0.13	0.03	0.19
16 years	Rel.Age	0.07	-0.02	0.17	0.12	0.09	-0.01	0.18	0.07
	PRS	0.09	0.04	0.15	<0.01	0.08	0.02	0.13	0.01
	Rel.Age*PRS	-0.02	-0.11	0.07	0.70	-0.01	-0.10	0.08	0.90
25 years	Rel.Age	-0.02	-0.13	0.08	0.67	-0.01	-0.11	0.10	0.89
	PRS	0.08	0.02	0.14	0.01	0.06	0.00	0.11	0.06
	Rel.Age*PRS	-0.02	-0.13	0.08	0.64	-0.01	-0.11	0.09	0.85
PRS p<0.01		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.12	0.04	0.20	0.01	0.13	0.05	0.21	<0.01
	PRS	0.09	0.05	0.14	<0.01	0.07	0.03	0.12	<0.01
	Rel.Age*PRS	-0.02	-0.11	0.06	0.56	-0.01	-0.09	0.07	0.75
8years	Rel.Age	0.15	0.07	0.23	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.13	0.08	0.17	<0.01	0.11	0.06	0.15	<0.01
	Rel.Age*PRS	-0.05	-0.13	0.03	0.21	-0.04	-0.12	0.04	0.31
9 years	Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.22	<0.01
	PRS	0.11	0.06	0.16	<0.01	0.09	0.04	0.14	<0.01
	Rel.Age*PRS	-0.04	-0.12	0.04	0.38	-0.03	-0.10	0.05	0.53
11 years	Rel.Age	0.21	0.13	0.29	<0.01	0.22	0.15	0.30	<0.01
	PRS	0.11	0.07	0.16	<0.01	0.09	0.04	0.14	<0.01
	Rel.Age*PRS	-0.02	-0.10	0.07	0.71	0.00	-0.08	0.08	0.93
13 years	Rel.Age	0.14	0.05	0.22	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.13	0.08	0.17	<0.01	0.10	0.06	0.15	<0.01
	Rel.Age*PRS	-0.05	-0.13	0.04	0.27	-0.04	-0.12	0.04	0.38
16 years	Rel.Age	0.07	-0.02	0.17	0.12	0.09	-0.01	0.18	0.07
	PRS	0.11	0.05	0.16	<0.01	0.09	0.03	0.14	<0.01
	Rel.Age*PRS	0.00	-0.09	0.09	0.98	0.01	-0.08	0.10	0.83

25 years	Rel.Age	-0.02	-0.13	0.08	0.66	-0.01	-0.11	0.10	0.87
	PRS	0.09	0.04	0.15	<0.01	0.07	0.01	0.13	0.02
	Rel.Age*PRS	-0.01	-0.12	0.09	0.78	0.00	-0.10	0.10	0.99
PRS p<0.05		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.12	0.04	0.20	<0.01	0.13	0.05	0.21	<0.01
	PRS	0.11	0.07	0.16	<0.01	0.09	0.04	0.13	<0.01
	Rel.Age*PRS	-0.06	-0.14	0.02	0.16	-0.04	-0.12	0.04	0.34
8years	Rel.Age	0.15	0.07	0.23	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.13	0.09	0.18	<0.01	0.11	0.06	0.16	<0.01
	Rel.Age*PRS	-0.06	-0.14	0.02	0.17	-0.04	-0.12	0.04	0.35
9 years	Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.12	0.07	0.17	<0.01	0.10	0.05	0.14	<0.01
	Rel.Age*PRS	-0.07	-0.15	0.01	0.10	-0.05	-0.13	0.03	0.22
11 years	Rel.Age	0.21	0.13	0.30	<0.01	0.23	0.15	0.31	<0.01
	PRS	0.12	0.07	0.16	<0.01	0.09	0.04	0.14	<0.01
	Rel.Age*PRS	-0.03	-0.11	0.05	0.46	-0.01	-0.09	0.07	0.78
13 years	Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.12	0.07	0.17	<0.01	0.09	0.05	0.14	<0.01
	Rel.Age*PRS	-0.05	-0.13	0.04	0.27	-0.03	-0.11	0.05	0.46
16 years	Rel.Age	0.08	-0.02	0.17	0.10	0.09	0.00	0.18	0.06
	PRS	0.07	0.01	0.12	0.01	0.05	-0.01	0.10	0.09
	Rel.Age*PRS	0.02	-0.08	0.11	0.73	0.03	-0.06	0.12	0.51
25 years	Rel.Age	-0.02	-0.12	0.08	0.70	-0.01	-0.11	0.10	0.89
	PRS	0.11	0.05	0.17	<0.01	0.08	0.02	0.14	0.01
	Rel.Age*PRS	0.01	-0.10	0.12	0.86	0.03	-0.08	0.13	0.62
PRS p<0.10		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.12	0.04	0.20	0.01	0.13	0.05	0.21	<0.01
	PRS	0.09	0.05	0.14	<0.01	0.07	0.03	0.12	<0.01
	Rel.Age*PRS	-0.02	-0.11	0.06	0.56	-0.01	-0.09	0.07	0.75
8years	Rel.Age	0.15	0.07	0.23	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.13	0.08	0.17	<0.01	0.11	0.06	0.15	<0.01
	Rel.Age*PRS	-0.05	-0.13	0.03	0.21	-0.04	-0.12	0.04	0.31
9 years	Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.22	<0.01

	PRS	0.11	0.06	0.16	<0.01	0.09	0.04	0.14	<0.01
	Rel.Age*PRS	-0.04	-0.12	0.04	0.38	-0.03	-0.10	0.05	0.53
11 years	Rel.Age	0.21	0.13	0.29	<0.01	0.22	0.15	0.30	<0.01
	PRS	0.11	0.07	0.16	<0.01	0.09	0.04	0.14	<0.01
	Rel.Age*PRS	-0.02	-0.10	0.07	0.71	0.00	-0.08	0.08	0.93
13 years	Rel.Age	0.14	0.05	0.22	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.13	0.08	0.17	<0.01	0.10	0.06	0.15	<0.01
	Rel.Age*PRS	-0.05	-0.13	0.04	0.27	-0.04	-0.12	0.04	0.38
16 years	Rel.Age	0.07	-0.02	0.17	0.12	0.09	-0.01	0.18	0.07
	PRS	0.11	0.05	0.16	<0.01	0.09	0.03	0.14	<0.01
	Rel.Age*PRS	0.00	-0.09	0.09	0.98	0.01	-0.08	0.10	0.83
25 years	Rel.Age	-0.02	-0.13	0.08	0.66	-0.01	-0.11	0.10	0.87
	PRS	0.09	0.04	0.15	<0.01	0.07	0.01	0.13	0.02
	Rel.Age*PRS	-0.01	-0.12	0.09	0.78	0.00	-0.10	0.10	0.99
PRS p<0.5		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.12	0.04	0.20	<0.01	0.13	0.05	0.21	<0.01
	PRS	0.12	0.07	0.16	<0.01	0.09	0.04	0.13	<0.01
	Rel.Age*PRS	-0.06	-0.14	0.02	0.14	-0.04	-0.12	0.03	0.27
8years	Rel.Age	0.15	0.07	0.23	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.13	0.09	0.18	<0.01	0.11	0.07	0.16	<0.01
	Rel.Age*PRS	-0.07	-0.15	0.01	0.08	-0.06	-0.14	0.02	0.17
9 years	Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.10	0.06	0.15	<0.01	0.08	0.03	0.12	<0.01
	Rel.Age*PRS	-0.03	-0.11	0.05	0.49	-0.01	-0.09	0.06	0.73
11 years	Rel.Age	0.21	0.13	0.29	<0.01	0.23	0.15	0.31	<0.01
	PRS	0.10	0.05	0.15	<0.01	0.07	0.03	0.12	<0.01
	Rel.Age*PRS	-0.02	-0.10	0.07	0.72	0.00	-0.08	0.08	0.98
13 years	Rel.Age	0.14	0.06	0.22	<0.01	0.15	0.07	0.23	<0.01
	PRS	0.13	0.08	0.18	<0.01	0.10	0.06	0.15	<0.01
	Rel.Age*PRS	-0.06	-0.14	0.02	0.16	-0.05	-0.13	0.04	0.27
16 years	Rel.Age	0.08	-0.02	0.17	0.10	0.09	-0.05	0.23	0.23
	PRS	0.07	0.02	0.13	0.01	0.12	0.02	0.22	0.02
	Rel.Age*PRS	0.02	-0.08	0.11	0.74	-0.06	-0.21	0.08	0.37

25 years	Rel.Age	-0.02	-0.13	0.08	0.66	0.00	-0.15	0.14	0.96
	PRS	0.12	0.06	0.18	<0.01	0.14	0.04	0.24	0.01
	Rel.Age*PRS	-0.03	-0.14	0.08	0.60	-0.09	-0.24	0.06	0.24

All individuals included (N=6933). Coefficient (Coef.) represents mean change in standardised parent-report SDQ total difficulties score per 1 year difference in relative age (Rel.Age), or mean change in standardised parent-report SDQ total difficulties score per 1 SD unit change in PRS ("Unadjusted Model" = Age within School Year entered in the regression + principal components. "Adjusted" = Model after additional adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age.

Table A4.8: SDQ total difficulties - Regression results, relative age and PRS scores for ADHD, all thresholds. Imputed data. Restricted to individuals born up to 4 weeks either side of the September 1st cut-off

		Unadjusted model				Adjusted model			
PRS p <0.001		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.11	-0.01	0.24	0.08	0.13	0.01	0.26	0.03
	PRS	0.10	0.01	0.18	0.03	0.07	-0.01	0.15	0.09
	Rel.Age*PRS	-0.08	-0.21	0.04	0.20	-0.07	-0.19	0.05	0.26
8 years	Rel.Age	0.15	0.02	0.28	0.02	0.16	0.03	0.29	0.01
	PRS	0.11	0.03	0.20	0.01	0.09	0.01	0.18	0.03
	Rel.Age*PRS	-0.09	-0.22	0.04	0.16	-0.09	-0.21	0.04	0.18
9 years	Rel.Age	0.11	-0.01	0.24	0.08	0.14	0.01	0.26	0.03
	PRS	0.11	0.02	0.19	0.01	0.09	0.00	0.17	0.05
	Rel.Age*PRS	-0.10	-0.23	0.03	0.13	-0.09	-0.22	0.03	0.15
11 years	Rel.Age	0.17	0.04	0.29	0.01	0.19	0.06	0.31	<0.01
	PRS	0.11	0.02	0.19	0.01	0.08	0.00	0.17	0.05
	Rel.Age*PRS	-0.07	-0.20	0.05	0.26	-0.06	-0.19	0.06	0.32
13 years	Rel.Age	0.12	-0.02	0.25	0.08	0.14	0.01	0.26	0.04
	PRS	0.13	0.04	0.21	<0.01	0.10	0.02	0.19	0.02
	Rel.Age*PRS	-0.07	-0.20	0.06	0.28	-0.07	-0.20	0.06	0.29
16 years	Rel.Age	0.09	-0.05	0.23	0.21	0.11	-0.03	0.25	0.13
	PRS	0.14	0.04	0.23	<0.01	0.12	0.02	0.21	0.01
	Rel.Age*PRS	-0.09	-0.23	0.05	0.19	-0.08	-0.22	0.05	0.23
25 years	Rel.Age	0.01	-0.14	0.15	0.94	0.03	-0.12	0.17	0.73
	PRS	0.15	0.06	0.25	<0.01	0.13	0.04	0.23	0.01
	Rel.Age*PRS	-0.12	-0.27	0.03	0.12	-0.11	-0.26	0.04	0.15
PRS <0.005		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.11	-0.01	0.23	0.08	0.13	0.01	0.25	0.03
	PRS	0.10	0.01	0.18	0.02	0.08	0.00	0.16	0.07
	Rel.Age*PRS	-0.10	-0.22	0.03	0.13	-0.08	-0.20	0.04	0.20
8years	Rel.Age	0.15	0.02	0.27	0.03	0.16	0.03	0.28	0.01
	PRS	0.10	0.02	0.19	0.02	0.09	0.01	0.17	0.04
	Rel.Age*PRS	-0.06	-0.18	0.07	0.36	-0.05	-0.17	0.07	0.43
9 years	Rel.Age	0.11	-0.01	0.24	0.08	0.14	0.01	0.26	0.03

	PRS	0.10	0.01	0.18	0.02	0.08	0.00	0.16	0.06
	Rel.Age*PRS	-0.07	-0.19	0.05	0.27	-0.06	-0.18	0.07	0.38
11 years	Rel.Age	0.16	0.04	0.29	0.01	0.18	0.06	0.31	<0.01
	PRS	0.11	0.02	0.19	0.01	0.09	0.01	0.17	0.03
	Rel.Age*PRS	-0.08	-0.20	0.05	0.21	-0.06	-0.19	0.06	0.30
13 years	Rel.Age	0.11	-0.02	0.24	0.10	0.13	0.00	0.26	0.05
	PRS	0.12	0.04	0.21	0.01	0.10	0.02	0.19	0.02
	Rel.Age*PRS	-0.10	-0.22	0.03	0.12	-0.09	-0.21	0.03	0.15
16 years	Rel.Age	0.09	-0.05	0.23	0.22	0.11	-0.03	0.25	0.13
	PRS	0.11	0.02	0.20	0.02	0.09	0.00	0.18	0.05
	Rel.Age*PRS	-0.07	-0.21	0.07	0.32	-0.06	-0.19	0.08	0.41
25 years	Rel.Age	0.00	-0.14	0.15	0.96	0.02	-0.12	0.17	0.74
	PRS	0.11	0.02	0.20	0.02	0.10	0.00	0.19	0.04
	Rel.Age*PRS	-0.08	-0.23	0.07	0.27	-0.07	-0.22	0.08	0.35
PRS p<0.01		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.11	-0.02	0.23	0.09	0.13	0.01	0.25	0.03
	PRS	0.10	0.01	0.18	0.03	0.08	-0.01	0.16	0.07
	Rel.Age*PRS	-0.07	-0.20	0.05	0.27	-0.05	-0.17	0.07	0.40
8years	Rel.Age	0.14	0.02	0.27	0.03	0.16	0.03	0.28	0.02
	PRS	0.10	0.02	0.19	0.02	0.09	0.00	0.17	0.04
	Rel.Age*PRS	-0.06	-0.18	0.07	0.37	-0.05	-0.17	0.08	0.45
9 years	Rel.Age	0.11	-0.02	0.24	0.09	0.13	0.01	0.26	0.04
	PRS	0.11	0.02	0.19	0.01	0.09	0.01	0.18	0.03
	Rel.Age*PRS	-0.07	-0.19	0.06	0.29	-0.05	-0.18	0.07	0.40
11 years	Rel.Age	0.16	0.04	0.29	0.01	0.18	0.06	0.31	<0.01
	PRS	0.12	0.03	0.20	0.01	0.10	0.02	0.19	0.02
	Rel.Age*PRS	-0.05	-0.18	0.07	0.41	-0.04	-0.16	0.08	0.54
13 years	Rel.Age	0.11	-0.02	0.24	0.10	0.13	0.00	0.26	0.05
	PRS	0.13	0.04	0.21	<0.01	0.11	0.02	0.19	0.01
	Rel.Age*PRS	-0.07	-0.20	0.05	0.25	-0.07	-0.19	0.06	0.30
16 years	Rel.Age	0.09	-0.05	0.23	0.22	0.11	-0.03	0.25	0.13
	PRS	0.14	0.04	0.23	<0.01	0.12	0.03	0.21	0.01
	Rel.Age*PRS	-0.07	-0.20	0.07	0.32	-0.06	-0.19	0.08	0.42

25 years	Rel.Age	0.00	-0.15	0.15	0.98	0.02	-0.12	0.17	0.76
	PRS	0.12	0.03	0.21	0.01	0.10	0.01	0.20	0.03
	Rel.Age*PRS	-0.07	-0.22	0.08	0.35	-0.06	-0.20	0.09	0.44
PRS p<0.05		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.11	-0.02	0.23	0.09	0.13	0.01	0.25	0.04
	PRS	0.10	0.02	0.19	0.02	0.08	0.00	0.17	0.05
	Rel.Age*PRS	-0.05	-0.18	0.07	0.42	-0.04	-0.17	0.08	0.48
8years	Rel.Age	0.14	0.01	0.27	0.03	0.16	0.03	0.28	0.02
	PRS	0.11	0.03	0.20	0.01	0.10	0.01	0.18	0.02
	Rel.Age*PRS	-0.04	-0.17	0.09	0.55	-0.03	-0.16	0.09	0.60
9 years	Rel.Age	0.11	-0.02	0.23	0.10	0.13	0.01	0.26	0.04
	PRS	0.10	0.02	0.19	0.02	0.09	0.00	0.17	0.04
	Rel.Age*PRS	-0.05	-0.17	0.08	0.46	-0.04	-0.17	0.08	0.50
11 years	Rel.Age	0.16	0.03	0.29	0.01	0.18	0.06	0.31	<0.01
	PRS	0.12	0.04	0.21	0.01	0.11	0.02	0.19	0.01
	Rel.Age*PRS	-0.04	-0.17	0.09	0.52	-0.04	-0.16	0.09	0.57
13 years	Rel.Age	0.11	-0.02	0.24	0.10	0.13	0.00	0.26	0.05
	PRS	0.12	0.03	0.20	0.01	0.10	0.01	0.18	0.02
	Rel.Age*PRS	-0.06	-0.19	0.07	0.39	-0.05	-0.18	0.07	0.41
16 years	Rel.Age	0.09	-0.05	0.23	0.22	0.11	-0.03	0.25	0.13
	PRS	0.09	-0.01	0.19	0.06	0.08	-0.02	0.17	0.12
	Rel.Age*PRS	-0.05	-0.19	0.09	0.48	-0.05	-0.18	0.09	0.51
25 years	Rel.Age	0.00	-0.15	0.15	0.99	0.02	-0.13	0.17	0.79
	PRS	0.11	0.01	0.21	0.03	0.09	0.00	0.19	0.05
	Rel.Age*PRS	-0.03	-0.18	0.12	0.71	-0.02	-0.17	0.12	0.75
PRS p<0.10		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.11	-0.02	0.23	0.09	0.13	0.01	0.25	0.03
	PRS	0.10	0.01	0.18	0.03	0.08	-0.01	0.16	0.07
	Rel.Age*PRS	-0.07	-0.20	0.05	0.27	-0.05	-0.17	0.07	0.40
8years	Rel.Age	0.14	0.02	0.27	0.03	0.16	0.03	0.28	0.02
	PRS	0.10	0.02	0.19	0.02	0.09	0.00	0.17	0.04
	Rel.Age*PRS	-0.06	-0.18	0.07	0.37	-0.05	-0.17	0.08	0.45
9 years	Rel.Age	0.11	-0.02	0.24	0.09	0.13	0.01	0.26	0.04

	PRS	0.11	0.02	0.19	0.01	0.09	0.01	0.18	0.03
	Rel.Age*PRS	-0.07	-0.19	0.06	0.29	-0.05	-0.18	0.07	0.40
11 years	Rel.Age	0.16	0.04	0.29	0.01	0.18	0.06	0.31	<0.01
	PRS	0.12	0.03	0.20	0.01	0.10	0.02	0.19	0.02
	Rel.Age*PRS	-0.05	-0.18	0.07	0.41	-0.04	-0.16	0.08	0.54
13 years	Rel.Age	0.11	-0.02	0.24	0.10	0.13	0.00	0.26	0.05
	PRS	0.13	0.04	0.21	<0.01	0.11	0.02	0.19	0.01
	Rel.Age*PRS	-0.07	-0.20	0.05	0.25	-0.07	-0.19	0.06	0.30
16 years	Rel.Age	0.09	-0.05	0.23	0.22	0.11	-0.03	0.25	0.13
	PRS	0.14	0.04	0.23	<0.01	0.12	0.03	0.21	0.01
	Rel.Age*PRS	-0.07	-0.20	0.07	0.32	-0.06	-0.19	0.08	0.42
25 years	Rel.Age	0.00	-0.15	0.15	0.98	0.02	-0.12	0.17	0.76
	PRS	0.12	0.03	0.21	0.01	0.10	0.01	0.20	0.03
	Rel.Age*PRS	-0.07	-0.22	0.08	0.35	-0.06	-0.20	0.09	0.44
PRS p<0.5		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.13	0.01	0.25	0.03	0.09	0.00	0.19	0.06
	PRS	0.10	0.02	0.18	0.02	0.11	0.05	0.17	<0.01
	Rel.Age*PRS	-0.05	-0.17	0.07	0.40	-0.05	-0.14	0.05	0.32
8years	Rel.Age	0.16	0.03	0.28	0.02	0.14	0.05	0.24	<0.01
	PRS	0.10	0.01	0.19	0.02	0.12	0.06	0.18	<0.01
	Rel.Age*PRS	-0.04	-0.17	0.09	0.53	-0.05	-0.15	0.04	0.27
9 years	Rel.Age	0.13	0.01	0.26	0.04	0.13	0.03	0.22	0.01
	PRS	0.07	-0.01	0.16	0.09	0.09	0.03	0.15	<0.01
	Rel.Age*PRS	0.00	-0.12	0.12	0.99	-0.02	-0.12	0.07	0.65
11 years	Rel.Age	0.19	0.06	0.31	<0.01	0.20	0.10	0.30	<0.01
	PRS	0.09	0.01	0.18	0.04	0.10	0.04	0.16	<0.01
	Rel.Age*PRS	-0.02	-0.15	0.10	0.71	-0.01	-0.10	0.09	0.88
13 years	Rel.Age	0.13	0.00	0.26	0.05	0.13	0.03	0.23	0.01
	PRS	0.11	0.03	0.20	0.01	0.14	0.08	0.20	<0.01
	Rel.Age*PRS	-0.07	-0.19	0.06	0.31	-0.09	-0.18	0.01	0.09
16 years	Rel.Age	0.11	-0.03	0.25	0.14	0.08	-0.03	0.19	0.14
	PRS	0.10	0.00	0.19	0.05	0.09	0.02	0.17	0.01
	Rel.Age*PRS	-0.06	-0.20	0.08	0.44	-0.02	-0.13	0.09	0.77

25 years	Rel.Age	0.02	-0.13	0.16	0.82	-0.01	-0.13	0.10	0.81
	PRS	0.12	0.02	0.21	0.02	0.12	0.05	0.20	<0.01
	Rel.Age*PRS	-0.08	-0.23	0.07	0.29	-0.06	-0.19	0.06	0.32

(N=1275) Imputed data Coefficient (Coef.) represents mean change in standardised parent-report SDQ total difficulties score per 1 year difference in relative age (Rel.Age), or mean change in standardised parent-report SDQ total difficulties score per 1 SD unit change in PRS (PRS). Unadjusted Model" = Age within School Year entered in the regression + principal components. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression.

Table A4.9: Regression results, relative age and PRS scores for ADHD, all thresholds. Imputed data. Restricted to individuals born up to 8 weeks either side of the September 1st cut-off Imputed data

		Unadjusted model				Adjusted model			
PRS <0.001		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.09	0.00	0.19	0.06	0.10	0.01	0.20	0.03
	PRS <0.001	0.10	0.03	0.16	<0.01	0.07	0.01	0.13	0.02
	Rel.Age*PRS <0.001	-0.06	-0.16	0.04	0.22	-0.05	-0.14	0.05	0.34
8 years	Rel.Age	0.14	0.05	0.24	<0.01	0.14	0.05	0.24	<0.01
	PRS <0.001	0.12	0.06	0.18	<0.01	0.10	0.04	0.16	<0.01
	Rel.Age*PRS <0.001	-0.10	-0.20	0.00	0.05	-0.09	-0.18	0.01	0.08
9 years	Rel.Age	0.13	0.03	0.22	0.01	0.14	0.04	0.23	<0.01
	PRS <0.001	0.10	0.04	0.16	<0.01	0.08	0.02	0.14	0.01
	Rel.Age*PRS <0.001	-0.08	-0.18	0.02	0.11	-0.07	-0.16	0.03	0.17
11 years	Rel.Age	0.20	0.10	0.29	<0.01	0.21	0.11	0.30	<0.01
	PRS <0.001	0.10	0.03	0.16	<0.01	0.07	0.01	0.14	0.02
	Rel.Age*PRS <0.001	-0.05	-0.15	0.04	0.28	-0.04	-0.14	0.06	0.41
13 years	Rel.Age	0.13	0.03	0.23	0.01	0.14	0.04	0.24	0.01
	PRS <0.001	0.12	0.06	0.18	<0.01	0.10	0.04	0.16	<0.01
	Rel.Age*PRS <0.001	-0.07	-0.17	0.03	0.15	-0.06	-0.16	0.03	0.21
16 years	Rel.Age	0.08	-0.03	0.19	0.15	0.09	-0.02	0.20	0.10
	PRS <0.001	0.13	0.06	0.20	<0.01	0.11	0.04	0.18	<0.01
	Rel.Age*PRS <0.001	-0.09	-0.20	0.02	0.12	-0.07	-0.18	0.03	0.18
25 years	Rel.Age	-0.01	-0.13	0.11	0.88	0.00	-0.12	0.12	1.00
	PRS <0.001	0.15	0.07	0.22	<0.01	0.13	0.05	0.20	<0.01
	Rel.Age*PRS <0.001	-0.12	-0.24	0.00	0.05	-0.11	-0.22	0.01	0.08
PRS <0.005		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.09	-0.01	0.19	0.07	0.10	0.01	0.20	0.03
	PRS	0.10	0.04	0.16	<0.01	0.08	0.02	0.14	0.01
	Rel.Age*PRS	-0.07	-0.17	0.02	0.13	-0.06	-0.15	0.03	0.22
8years	Rel.Age	0.14	0.04	0.24	<0.01	0.14	0.05	0.24	<0.01
	PRS	0.12	0.06	0.19	<0.01	0.11	0.05	0.17	<0.01
	Rel.Age*PRS	-0.10	-0.20	0.00	0.04	-0.09	-0.18	0.01	0.07
9 years	Rel.Age	0.12	0.03	0.22	0.01	0.14	0.04	0.23	<0.01

	PRS	0.10	0.03	0.16	<0.01	0.08	0.02	0.14	0.01
	Rel.Age*PRS	-0.07	-0.17	0.02	0.14	-0.06	-0.15	0.04	0.22
11 years	Rel.Age	0.20	0.10	0.29	<0.01	0.21	0.11	0.30	<0.01
	PRS	0.10	0.04	0.16	<0.01	0.09	0.03	0.15	0.01
	Rel.Age*PRS	-0.06	-0.16	0.03	0.20	-0.05	-0.14	0.05	0.33
13 years	Rel.Age	0.13	0.03	0.23	0.01	0.14	0.04	0.23	0.01
	PRS	0.13	0.06	0.19	<0.01	0.11	0.05	0.17	<0.01
	Rel.Age*PRS	-0.10	-0.20	-0.01	0.04	-0.09	-0.19	0.00	0.06
16 years	Rel.Age	0.08	-0.03	0.19	0.14	0.09	-0.02	0.20	0.09
	PRS	0.11	0.04	0.18	<0.01	0.10	0.03	0.17	0.01
	Rel.Age*PRS	-0.06	-0.17	0.05	0.28	-0.05	-0.15	0.06	0.40
25 years	Rel.Age	-0.01	-0.13	0.11	0.87	0.00	-0.12	0.12	1.00
	PRS	0.11	0.04	0.18	<0.01	0.09	0.02	0.17	0.01
	Rel.Age*PRS	-0.08	-0.20	0.04	0.21	-0.06	-0.18	0.06	0.31
PRS p<0.01		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.09	-0.01	0.19	0.06	0.10	0.01	0.20	0.03
	PRS	0.10	0.04	0.16	<0.01	0.08	0.02	0.14	0.01
	Rel.Age*PRS	-0.05	-0.14	0.05	0.32	-0.03	-0.13	0.06	0.49
8years	Rel.Age	0.14	0.04	0.24	<0.01	0.14	0.05	0.24	<0.01
	PRS	0.13	0.07	0.20	<0.01	0.12	0.06	0.18	<0.01
	Rel.Age*PRS	-0.10	-0.19	0.00	0.05	-0.08	-0.18	0.01	0.09
9 years	Rel.Age	0.12	0.03	0.22	0.01	0.14	0.04	0.23	0.01
	PRS	0.11	0.05	0.18	<0.01	0.10	0.04	0.16	<0.01
	Rel.Age*PRS	-0.07	-0.16	0.03	0.17	-0.05	-0.15	0.04	0.26
11 years	Rel.Age	0.20	0.10	0.29	<0.01	0.21	0.11	0.30	<0.01
	PRS	0.12	0.06	0.18	<0.01	0.10	0.04	0.16	<0.01
	Rel.Age*PRS	-0.04	-0.14	0.06	0.41	-0.03	-0.12	0.07	0.59
13 years	Rel.Age	0.13	0.03	0.23	0.01	0.14	0.04	0.23	0.01
	PRS	0.14	0.08	0.21	<0.01	0.13	0.07	0.19	<0.01
	Rel.Age*PRS	-0.09	-0.19	0.01	0.07	-0.08	-0.17	0.02	0.10
16 years	Rel.Age	0.08	-0.03	0.19	0.14	0.09	-0.02	0.20	0.09
	PRS	0.13	0.06	0.20	<0.01	0.12	0.05	0.19	<0.01
	Rel.Age*PRS	-0.05	-0.15	0.06	0.40	-0.03	-0.14	0.07	0.54

25 years	Rel.Age	-0.01	-0.13	0.11	0.86	0.00	-0.12	0.12	0.98
	PRS	0.12	0.05	0.20	<0.01	0.11	0.04	0.18	<0.01
	Rel.Age*PRS	-0.06	-0.18	0.06	0.33	-0.04	-0.16	0.08	0.47
PRS p<0.05		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.09	0.00	0.19	0.06	0.10	0.01	0.20	0.03
	PRS	0.11	0.05	0.17	<0.01	0.09	0.03	0.15	<0.01
	Rel.Age*PRS	-0.06	-0.16	0.03	0.21	-0.04	-0.14	0.05	0.38
8years	Rel.Age	0.14	0.05	0.24	<0.01	0.15	0.05	0.24	<0.01
	PRS	0.12	0.06	0.19	<0.01	0.11	0.05	0.17	<0.01
	Rel.Age*PRS	-0.07	-0.16	0.03	0.18	-0.05	-0.14	0.05	0.32
9 years	Rel.Age	0.12	0.03	0.22	0.01	0.14	0.04	0.23	0.01
	PRS	0.11	0.05	0.18	<0.01	0.10	0.04	0.16	<0.01
	Rel.Age*PRS	-0.08	-0.17	0.02	0.12	-0.06	-0.16	0.03	0.21
11 years	Rel.Age	0.20	0.10	0.30	<0.01	0.21	0.12	0.31	<0.01
	PRS	0.11	0.05	0.18	<0.01	0.09	0.03	0.16	<0.01
	Rel.Age*PRS	-0.03	-0.13	0.06	0.50	-0.01	-0.11	0.08	0.76
13 years	Rel.Age	0.13	0.03	0.23	0.01	0.14	0.04	0.24	0.01
	PRS	0.12	0.06	0.19	<0.01	0.11	0.04	0.17	<0.01
	Rel.Age*PRS	-0.07	-0.17	0.02	0.14	-0.06	-0.16	0.04	0.23
16 years	Rel.Age	0.08	-0.03	0.19	0.13	0.09	-0.01	0.20	0.09
	PRS	0.08	0.00	0.15	0.04	0.06	-0.01	0.13	0.10
	Rel.Age*PRS	-0.02	-0.12	0.09	0.79	0.00	-0.11	0.11	0.97
25 years	Rel.Age	-0.01	-0.13	0.11	0.86	0.00	-0.12	0.12	0.98
	PRS	0.11	0.04	0.19	<0.01	0.09	0.02	0.17	0.01
	Rel.Age*PRS	-0.02	-0.15	0.10	0.70	-0.01	-0.13	0.12	0.93
PRS p<0.10		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.09	-0.01	0.19	0.06	0.10	0.01	0.20	0.03
	PRS	0.10	0.04	0.16	<0.01	0.08	0.02	0.14	0.01
	Rel.Age*PRS	-0.05	-0.14	0.05	0.32	-0.03	-0.13	0.06	0.49
8years	Rel.Age	0.14	0.04	0.24	<0.01	0.14	0.05	0.24	<0.01
	PRS	0.13	0.07	0.20	<0.01	0.12	0.06	0.18	<0.01
	Rel.Age*PRS	-0.10	-0.19	0.00	0.05	-0.08	-0.18	0.01	0.09
9 years	Rel.Age	0.12	0.03	0.22	0.01	0.14	0.04	0.23	0.01

	PRS	0.11	0.05	0.18	<0.01	0.10	0.04	0.16	<0.01
	Rel.Age*PRS	-0.07	-0.16	0.03	0.17	-0.05	-0.15	0.04	0.26
11 years	Rel.Age	0.20	0.10	0.29	<0.01	0.21	0.11	0.30	<0.01
	PRS	0.12	0.06	0.18	<0.01	0.10	0.04	0.16	<0.01
	Rel.Age*PRS	-0.04	-0.14	0.06	0.41	-0.03	-0.12	0.07	0.59
13 years	Rel.Age	0.13	0.03	0.23	0.01	0.14	0.04	0.23	0.01
	PRS	0.14	0.08	0.21	<0.01	0.13	0.07	0.19	<0.01
	Rel.Age*PRS	-0.09	-0.19	0.01	0.07	-0.08	-0.17	0.02	0.10
16 years	Rel.Age	0.08	-0.03	0.19	0.14	0.09	-0.02	0.20	0.09
	PRS	0.13	0.06	0.20	<0.01	0.12	0.05	0.19	<0.01
	Rel.Age*PRS	-0.05	-0.15	0.06	0.40	-0.03	-0.14	0.07	0.54
25 years	Rel.Age	-0.01	-0.13	0.11	0.86	0.00	-0.12	0.12	0.98
	PRS	0.12	0.05	0.20	<0.01	0.11	0.04	0.18	<0.01
	Rel.Age*PRS	-0.06	-0.18	0.06	0.33	-0.04	-0.16	0.08	0.47
PRS p<0.5		Coef.	[95% Conf.	Interval]	p	Coef.	[95% Conf.	Interval]	p
7 years	Rel.Age	0.09	0.00	0.19	0.06	0.10	0.01	0.20	0.03
	PRS	0.11	0.05	0.17	<0.01	0.09	0.03	0.15	<0.01
	Rel.Age*PRS	-0.05	-0.14	0.05	0.32	-0.03	-0.13	0.06	0.49
8years	Rel.Age	0.14	0.05	0.24	<0.01	0.14	0.05	0.24	<0.01
	PRS	0.12	0.06	0.18	<0.01	0.10	0.04	0.16	<0.01
	Rel.Age*PRS	-0.05	-0.15	0.04	0.27	-0.04	-0.13	0.06	0.42
9 years	Rel.Age	0.13	0.03	0.22	0.01	0.14	0.04	0.23	<0.01
	PRS	0.09	0.03	0.15	<0.01	0.07	0.01	0.14	0.02
	Rel.Age*PRS	-0.02	-0.12	0.07	0.65	-0.01	-0.11	0.08	0.79
11 years	Rel.Age	0.20	0.10	0.30	<0.01	0.21	0.12	0.31	<0.01
	PRS	0.10	0.04	0.16	<0.01	0.08	0.02	0.14	0.01
	Rel.Age*PRS	-0.01	-0.10	0.09	0.88	0.01	-0.09	0.10	0.89
13 years	Rel.Age	0.13	0.03	0.23	0.01	0.14	0.04	0.23	0.01
	PRS	0.14	0.08	0.20	<0.01	0.12	0.06	0.18	<0.01
	Rel.Age*PRS	-0.09	-0.18	0.01	0.09	-0.08	-0.17	0.02	0.13
16 years	Rel.Age	0.08	-0.03	0.19	0.14	0.09	-0.01	0.20	0.09
	PRS	0.09	0.02	0.17	0.01	0.08	0.00	0.15	0.04
	Rel.Age*PRS	-0.02	-0.13	0.09	0.77	0.00	-0.11	0.11	0.94

25 years	Rel.Age	-0.01	-0.13	0.10	0.81	-0.01	-0.12	0.11	0.93
	PRS	0.12	0.05	0.20	<0.01	0.10	0.03	0.18	0.01
	Rel.Age*PRS	-0.06	-0.19	0.06	0.32	-0.05	-0.17	0.07	0.43

N=2561. Coef. represents mean change in standardised parent-report SDQ total difficulties score per 1 year difference in relative age (Rel.Age), or mean change in standardised parent-report SDQ total difficulties score per 1 SD unit change in PRS (PRS). Unadjusted Model" = Age within School Year entered in the regression + principal components. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression.

Table A4.10: Regression results for SDQ total difficulties by relative age, stratified by ADHD symptoms at age 4 years. Complete case analysis.

Continuous	Unadjusted model					Adjusted model			
7 years (n=7486)	Coef.	[95% Conf.	Interval]	p	7 years (n=6679)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.18	0.11	0.26	<0.01	Rel.Age	0.18	0.10	0.26	<0.01
Borderline	0.65	0.52	0.78	<0.01	Borderline	0.56	0.42	0.70	<0.01
High	1.01	0.89	1.12	<0.01	High	0.90	0.78	1.02	<0.01
Rel.Age*Borderline	-0.05	-0.27	0.18	0.68	Rel.Age*Borderline	-0.01	-0.25	0.22	0.90
Rel.Age*High	-0.03	-0.23	0.17	0.79	Rel.Age*High	-0.04	-0.25	0.17	0.70
8 years (n=6729)	Coef.	[95% Conf.	Interval]	p	8 years (n=6030)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.22	0.14	0.30	<0.01	Rel.Age	0.22	0.13	0.30	<0.01
Borderline	0.57	0.43	0.71	<0.01	Borderline	0.52	0.37	0.67	<0.01
High	1.08	0.96	1.20	<0.01	High	0.97	0.84	1.10	<0.01
Rel.Age*Borderline	-0.03	-0.27	0.22	0.83	Rel.Age*Borderline	-0.04	-0.29	0.21	0.75
Rel.Age*High	-0.20	-0.42	0.01	0.06	Rel.Age*High	-0.19	-0.41	0.03	0.09
9 years (n=6760)	Coef.	[95% Conf.	Interval]	p	9 years (n=6058)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.15	0.07	0.23	<0.01	Rel.Age	0.16	0.08	0.24	<0.01
Borderline	0.44	0.30	0.58	<0.01	Borderline	0.36	0.21	0.50	<0.01
High	0.96	0.83	1.08	<0.01	High	0.91	0.78	1.04	<0.01
Rel.Age*Borderline	0.11	-0.13	0.34	0.38	Rel.Age*Borderline	0.16	-0.09	0.40	0.21
Rel.Age*High	-0.06	-0.27	0.15	0.57	Rel.Age*High	-0.14	-0.36	0.08	0.21
11 years (n=6228)	Coef.	[95% Conf.	Interval]	p	11 years (n=5608)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.21	0.13	0.30	<0.01	Rel.Age	0.21	0.12	0.30	<0.01
Borderline	0.39	0.24	0.54	<0.01	Borderline	0.33	0.17	0.49	<0.01
High	0.85	0.72	0.99	<0.01	High	0.74	0.61	0.88	<0.01
Rel.Age*Borderline	0.16	-0.10	0.42	0.22	Rel.Age*Borderline	0.14	-0.13	0.41	0.31
Rel.Age*High	-0.08	-0.32	0.15	0.48	Rel.Age*High	-0.07	-0.31	0.17	0.55
13 years (n=5969)	Coef.	[95% Conf.	Interval]	p	13 years (n=5378)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.14	0.05	0.23	<0.01	Rel.Age	0.13	0.04	0.22	<0.01
Borderline	0.35	0.20	0.50	<0.01	Borderline	0.32	0.16	0.48	<0.01
High	0.82	0.68	0.96	<0.01	High	0.74	0.60	0.89	<0.01
Rel.Age*Borderline	0.13	-0.14	0.39	0.35	Rel.Age*Borderline	0.07	-0.20	0.35	0.61
Rel.Age*High	-0.11	-0.35	0.13	0.36	Rel.Age*High	-0.11	-0.36	0.14	0.37

16 years (n=4864)	Coef.	[95% Conf.	Interval]	p	16 years (n=4417)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.13	0.03	0.23	0.01	Rel.Age	0.12	0.02	0.22	0.02
Borderline	0.33	0.16	0.51	<0.01	Borderline	0.29	0.11	0.48	<0.01
High	0.70	0.54	0.86	<0.01	High	0.66	0.49	0.82	<0.01
Rel.Age*Borderline	0.04	-0.26	0.34	0.80	Rel.Age*Borderline	-0.01	-0.32	0.30	0.95
Rel.Age*High	-0.20	-0.48	0.07	0.15	Rel.Age*High	-0.24	-0.52	0.04	0.10
25 years (n=3607)	Coef.	[95% Conf.	Interval]	p	25 years (n=3262)	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.10	-0.21	0.02	0.10	Rel.Age	-0.10	-0.21	0.02	0.11
Borderline	0.13	-0.07	0.33	0.21	Borderline	0.07	-0.14	0.28	0.51
High	0.52	0.33	0.71	<0.01	High	0.54	0.34	0.73	<0.01
Rel.Age*Borderline	0.47	0.13	0.82	0.01	Rel.Age*Borderline	0.45	0.09	0.80	0.02
Rel.Age*High	0.15	-0.18	0.47	0.38	Rel.Age*High	0.07	-0.26	0.40	0.68

4 weeks									
7 years (n=1376)	Coef.	[95% Conf.	Interval]	p	7 years (n=1222)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.18	0.06	0.30	<0.01	Rel.Age	0.21	0.09	0.34	<0.01
Borderline	0.57	0.34	0.81	<0.01	Borderline	0.51	0.25	0.76	<0.01
High	0.96	0.75	1.18	<0.01	High	0.95	0.71	1.18	<0.01
Rel.Age*Borderline	0.09	-0.27	0.45	0.62	Rel.Age*Borderline	0.03	-0.35	0.41	0.87
Rel.Age*High	-0.15	-0.47	0.18	0.38	Rel.Age*High	-0.26	-0.60	0.08	0.14
8 years (n=1186)	Coef.	[95% Conf.	Interval]	p	8 years (n=1058)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.28	0.15	0.41	<0.01	Rel.Age	0.28	0.15	0.42	<0.01
Borderline	0.41	0.15	0.68	<0.01	Borderline	0.34	0.05	0.63	0.02
High	1.18	0.96	1.41	<0.01	High	1.10	0.85	1.34	<0.01
Rel.Age*Borderline	0.14	-0.25	0.53	0.47	Rel.Age*Borderline	0.12	-0.30	0.54	0.58
Rel.Age*High	-0.49	-0.84	-0.14	0.01	Rel.Age*High	-0.47	-0.84	-0.11	0.01
9 years (n=1218)	Coef.	[95% Conf.	Interval]	p	9 years (n= 1081)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.11	-0.01	0.24	0.08	Rel.Age	0.18	0.05	0.31	0.01
Borderline	0.40	0.15	0.64	<0.01	Borderline	0.25	-0.02	0.52	0.07
High	1.11	0.89	1.34	<0.01	High	1.05	0.80	1.30	<0.01
Rel.Age*Borderline	0.29	-0.09	0.67	0.13	Rel.Age*Borderline	0.36	-0.04	0.76	0.08
Rel.Age*High	-0.40	-0.73	-0.06	0.02	Rel.Age*High	-0.46	-0.81	-0.10	0.01
11 years (n=1102)	Coef.	[95% Conf.	Interval]	p	11 years (n=990)	Coef.	[95% Conf.	Interval]	p

Rel.Age	0.16	0.02	0.30	0.02	Rel.Age	0.21	0.07	0.36	<0.01
Borderline	0.19	-0.09	0.46	0.19	Borderline	0.11	-0.18	0.40	0.46
High	0.93	0.68	1.17	<0.01	High	0.87	0.61	1.13	<0.01
Rel.Age*Borderline	0.42	0.00	0.84	0.05	Rel.Age*Borderline	0.34	-0.10	0.77	0.13
Rel.Age*High	-0.31	-0.69	0.06	0.10	Rel.Age*High	-0.39	-0.78	-0.01	0.04
13 years (n=1055)	Coef.	[95% Conf.	Interval]	p	13 years (n=948)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.12	-0.03	0.26	0.11	Rel.Age	0.14	-0.01	0.29	0.06
Borderline	0.19	-0.10	0.48	0.20	Borderline	0.10	-0.22	0.41	0.55
High	0.80	0.54	1.05	<0.01	High	0.66	0.38	0.94	<0.01
Rel.Age*Borderline	0.32	-0.13	0.77	0.16	Rel.Age*Borderline	0.30	-0.17	0.78	0.21
Rel.Age*High	-0.31	-0.70	0.08	0.12	Rel.Age*High	-0.29	-0.70	0.11	0.16
16 years (n=875)	Coef.	[95% Conf.	Interval]	p	16 years (n=787)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.14	-0.02	0.30	0.08	Rel.Age	0.19	0.02	0.35	0.02
Borderline	0.35	0.05	0.65	0.02	Borderline	0.24	-0.07	0.55	0.13
High	0.67	0.37	0.97	<0.01	High	0.57	0.26	0.88	<0.01
Rel.Age*Borderline	-0.06	-0.53	0.41	0.80	Rel.Age*Borderline	-0.17	-0.65	0.32	0.50
Rel.Age*High	-0.21	-0.65	0.23	0.35	Rel.Age*High	-0.18	-0.63	0.26	0.42
25 years (n=652)	Coef.	[95% Conf.	Interval]	p	25 years (n=585)	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.05	-0.22	0.11	0.54	Rel.Age	-0.01	-0.19	0.16	0.89
Borderline	0.09	-0.24	0.43	0.58	Borderline	0.11	-0.28	0.49	0.59
High	0.40	0.07	0.73	0.02	High	0.53	0.18	0.89	<0.01
Rel.Age*Borderline	0.27	-0.26	0.81	0.31	Rel.Age*Borderline	0.20	-0.37	0.77	0.48
Rel.Age*High	0.00	-0.49	0.49	1.00	Rel.Age*High	-0.20	-0.71	0.32	0.46

8 weeks									
7 years	Coef.	[95% Conf.	Interval]	p	7 years (n=2421)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.20	0.11	0.29	<0.01	Rel.Age	0.18	0.09	0.28	<0.01
Borderline	0.70	0.53	0.88	<0.01	Borderline	0.62	0.43	0.80	<0.01
High	0.98	0.83	1.14	<0.01	High	0.88	0.72	1.05	<0.01
Rel.Age*Borderline	-0.06	-0.33	0.21	0.65	Rel.Age*Borderline	-0.06	-0.34	0.22	0.67
Rel.Age*High	-0.18	-0.43	0.07	0.15	Rel.Age*High	-0.20	-0.46	0.06	0.13
8 years (n=2378)	Coef.	[95% Conf.	Interval]	p	8 years (n=2119)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.27	0.17	0.37	<0.01	Rel.Age	0.26	0.16	0.36	<0.01

Borderline	0.57	0.38	0.76	<0.01	Borderline	0.48	0.27	0.69	<0.01
High	1.07	0.91	1.23	<0.01	High	0.95	0.78	1.12	<0.01
Rel.Age*Borderline	-0.07	-0.37	0.22	0.62	Rel.Age*Borderline	-0.08	-0.39	0.23	0.62
Rel.Age*High	-0.33	-0.59	-0.07	0.01	Rel.Age*High	-0.29	-0.57	-0.02	0.03
9 years (n=2470)	Coef.	[95% Conf.	Interval]	p	9 years (n=2190)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.15	0.05	0.25	<0.01	Rel.Age	0.16	0.06	0.27	<0.01
Borderline	0.47	0.29	0.65	<0.01	Borderline	0.36	0.16	0.56	<0.01
High	0.93	0.77	1.09	<0.01	High	0.88	0.70	1.05	<0.01
Rel.Age*Borderline	0.11	-0.18	0.40	0.47	Rel.Age*Borderline	0.17	-0.14	0.47	0.28
Rel.Age*High	-0.15	-0.42	0.11	0.25	Rel.Age*High	-0.20	-0.47	0.08	0.16
11 years (n=2237)	Coef.	[95% Conf.	Interval]	p	11 years (n=1997)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.21	0.10	0.31	<0.01	Rel.Age	0.20	0.09	0.30	<0.01
Borderline	0.37	0.18	0.57	<0.01	Borderline	0.28	0.08	0.49	0.01
High	0.78	0.61	0.96	<0.01	High	0.68	0.49	0.86	<0.01
Rel.Age*Borderline	0.16	-0.15	0.47	0.32	Rel.Age*Borderline	0.10	-0.22	0.42	0.55
Rel.Age*High	-0.16	-0.44	0.12	0.26	Rel.Age*High	-0.15	-0.44	0.14	0.32
13 years (n=2131)	Coef.	[95% Conf.	Interval]	p	13 years (n=1907)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.17	0.06	0.28	<0.01	Rel.Age	0.14	0.03	0.25	0.01
Borderline	0.31	0.11	0.51	<0.01	Borderline	0.26	0.05	0.47	0.02
High	0.73	0.54	0.91	<0.01	High	0.56	0.37	0.76	<0.01
Rel.Age*Borderline	0.08	-0.24	0.41	0.61	Rel.Age*Borderline	0.02	-0.31	0.36	0.91
Rel.Age*High	-0.21	-0.50	0.09	0.17	Rel.Age*High	-0.10	-0.40	0.21	0.52
16 years (n=1769)	Coef.	[95% Conf.	Interval]	p	16 years(n=1589)	Coef.	[95% Conf.	Interval]	p
Rel.Age	0.16	0.04	0.28	0.01	Rel.Age	0.15	0.03	0.27	0.02
Borderline	0.36	0.14	0.58	<0.01	Borderline	0.26	0.03	0.49	0.03
High	0.65	0.44	0.86	<0.01	High	0.62	0.40	0.84	<0.01
Rel.Age*Borderline	-0.04	-0.40	0.31	0.81	Rel.Age*Borderline	-0.08	-0.44	0.29	0.69
Rel.Age*High	-0.29	-0.63	0.04	0.08	Rel.Age*High	-0.29	-0.64	0.05	0.09
25 years (n=1313)	Coef.	[95% Conf.	Interval]	p	25 years (n=1175)	Coef.	[95% Conf.	Interval]	p
Rel.Age	-0.09	-0.22	0.04	0.17	Rel.Age	-0.10	-0.23	0.04	0.17
Borderline	0.08	-0.17	0.33	0.53	Borderline	0.05	-0.23	0.32	0.75
High	0.40	0.16	0.64	<0.01	High	0.47	0.22	0.73	<0.01
Rel.Age*Borderline	0.42	0.02	0.82	0.04	Rel.Age*Borderline	0.45	0.03	0.87	0.04

Rel.Age*High	0.16	-0.22	0.54	0.41	Rel.Age*High	0.07	-0.33	0.46	0.74

"Continuous" = All individuals included. "4 week" = Restricted to individuals born up to 4 weeks either side of the September 1st cut-off; 8 weeks = Restricted to individuals born up to 8 weeks either side of the September 1st cut-off. Coefficient (Coef.) represents mean change in standardised parent-report SDQ score per 1 year difference in relative age (Rel.Age), or mean change in standardised parent-report SDQ score compared to low-risk ADHD group (borderline vs low; high vs low). "Unadjusted Model" = Age within School Year entered in the regression alone. "Adjusted" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. Borderline = SDQ hyperactivity scores at 4 years of age = 6. High = SDQ hyperactivity scores at 4 years of age >=7.

Table A4.11: Regression results for SDQ subscales by relative age and PRS scores for ADHD, threshold level p<0.05 ("PRS p<0.05"). Complete case analysis

Continuous											
Unadjusted model		Coef.	[95% Conf.	Interval]	p	Adjusted model		Coef.	[95% Conf.	Interval]	p
7 y	Rel.Age	0.11	0.03	0.19	0.01	7 y	Rel.Age	0.12	0.04	0.20	0.01
n=5492	PRS	0.11	0.06	0.15	<0.01	n=4922	PRS	0.07	0.02	0.12	0.01
	Rel.Age*PRS	-0.06	-0.14	0.03	0.18		Rel.Age*PRS	-0.03	-0.11	0.06	0.50
8y	Rel.Age	0.13	0.05	0.22	<0.01	8y	Rel.Age	0.15	0.06	0.24	<0.01
n=5262	PRS	0.13	0.08	0.18	<0.01	n=4582	PRS	0.09	0.04	0.14	<0.01
	Rel.Age*PRS	-0.06	-0.15	0.03	0.17		Rel.Age*PRS	-0.03	-0.12	0.06	0.51
9 y	Rel.Age	0.14	0.05	0.22	<0.01	9 y	Rel.Age	0.14	0.06	0.23	<0.01
n=5500	PRS	0.11	0.06	0.16	<0.01	n=4683	PRS	0.10	0.04	0.15	<0.01
	Rel.Age*PRS	-0.07	-0.15	0.02	0.12		Rel.Age*PRS	-0.07	-0.15	0.02	0.13
11 y	Rel.Age	0.22	0.13	0.31	<0.01	11 y	Rel.Age	0.23	0.14	0.32	<0.01
n=5113	PRS	0.11	0.06	0.16	<0.01	n=4380	PRS	0.07	0.02	0.12	0.01
	Rel.Age*PRS	-0.03	-0.12	0.05	0.44		Rel.Age*PRS	0.00	-0.09	0.09	0.98
13 y	Rel.Age	0.16	0.07	0.24	<0.01	13 y	Rel.Age	0.12	0.03	0.21	0.01
n=4911	PRS	0.10	0.05	0.15	<0.01	n=4213	PRS	0.09	0.04	0.14	<0.01
	Rel.Age*PRS	-0.01	-0.10	0.07	0.74		Rel.Age*PRS	-0.04	-0.13	0.06	0.46
16 y	Rel.Age	0.06	-0.04	0.16	0.26	16 y	Rel.Age	0.06	-0.04	0.17	0.23
n=4044	PRS	0.04	-0.02	0.10	0.16	n=3519	PRS	0.00	-0.06	0.06	0.90
	Rel.Age*PRS	0.05	-0.05	0.15	0.35		Rel.Age*PRS	0.09	-0.01	0.19	0.09
25 y	Rel.Age	-0.06	-0.17	0.06	0.33	25 y	Rel.Age	-0.04	-0.16	0.08	0.54
n=2996	PRS	0.07	0.01	0.14	0.03	n=2614	PRS	0.04	-0.03	0.10	0.31
4 Weeks											
7 y	Rel.Age	0.09	-0.04	0.22	0.18	7 y	Rel.Age	0.12	-0.01	0.26	0.07
n=1022	PRS	0.10	0.01	0.19	0.03	n=916	PRS	0.05	-0.04	0.15	0.25
	Rel.Age*PRS	-0.05	-0.18	0.07	0.40		Rel.Age*PRS	-0.01	-0.14	0.12	0.89
8 y	Rel.Age	0.12	-0.02	0.26	0.08	8 y	Rel.Age	0.18	0.03	0.32	0.02
n=938	PRS	0.11	0.02	0.21	0.02	n=826	PRS	0.07	-0.03	0.17	0.16
	Rel.Age*PRS	-0.02	-0.16	0.11	0.73		Rel.Age*PRS	0.02	-0.12	0.16	0.81
9 y	Rel.Age	0.10	-0.04	0.23	0.16	9 y	Rel.Age	0.16	0.02	0.30	0.03
n=981	PRS	0.10	0.01	0.19	0.03	n=847	PRS	0.11	0.01	0.21	0.03

	Rel.Age*PRS	-0.04	-0.17	0.10	0.60		Rel.Age*PRS	-0.07	-0.22	0.07	0.30
11 y	Rel.Age	0.13	-0.01	0.27	0.06	11 y	Rel.Age	0.18	0.03	0.32	0.02
n=897	PRS	0.14	0.05	0.23	<0.01	n=772	PRS	0.10	0.00	0.20	0.06
	Rel.Age*PRS	-0.07	-0.21	0.07	0.32		Rel.Age*PRS	-0.01	-0.16	0.13	0.85
13 y	Rel.Age	0.14	-0.01	0.28	0.06	13 y	Rel.Age	0.15	0.00	0.30	0.05
n=862	PRS	0.10	0.00	0.19	0.05	n=762	PRS	0.08	-0.02	0.19	0.11
	Rel.Age*PRS	0.00	-0.14	0.14	0.99		Rel.Age*PRS	0.00	-0.15	0.15	0.98
16 y	Rel.Age	0.05	-0.11	0.22	0.51	16 y	Rel.Age	0.10	-0.07	0.27	0.24
n=728	PRS	0.11	0.00	0.22	0.05	n=637	PRS	0.05	-0.06	0.17	0.37
	Rel.Age*PRS	-0.08	-0.24	0.08	0.34		Rel.Age*PRS	-0.02	-0.19	0.15	0.79
25 y	Rel.Age	-0.04	-0.20	0.12	0.60	25 y	Rel.Age	-0.02	-0.19	0.16	0.84
n=540	PRS	0.06	-0.04	0.16	0.25	n=480	PRS	0.06	-0.06	0.17	0.33
	Rel.Age*PRS	0.03	-0.13	0.19	0.73		Rel.Age*PRS	0.03	-0.14	0.21	0.70
8 weeks											
	Rel.Age	0.07	-0.03	0.17	0.15		Rel.Age	0.07	-0.03	0.17	0.16
7 y	PRS	0.11	0.05	0.17	<0.01	7 y	PRS	0.08	0.02	0.15	0.01
n=2046	Rel.Age*PRS	-0.06	-0.16	0.04	0.23	n=1829	Rel.Age*PRS	-0.03	-0.13	0.07	0.59
	Rel.Age	0.13	0.02	0.23	0.02		Rel.Age	0.14	0.04	0.25	0.01
8 y	PRS	0.12	0.06	0.19	<0.01	8 y	PRS	0.10	0.03	0.17	0.01
n=1885	Rel.Age*PRS	-0.06	-0.16	0.04	0.25	n=1656	Rel.Age*PRS	-0.03	-0.14	0.08	0.58
	Rel.Age	0.12	0.02	0.22	0.02		Rel.Age	0.14	0.03	0.24	0.01
9 y	PRS	0.10	0.04	0.17	<0.01	9 y	PRS	0.13	0.06	0.20	<0.01
n=2004	Rel.Age*PRS	-0.07	-0.17	0.03	0.16	n=1723	Rel.Age*PRS	-0.10	-0.21	0.00	0.06
	Rel.Age	0.20	0.10	0.30	<0.01		Rel.Age	0.20	0.10	0.31	<0.01
11 y	PRS	0.11	0.04	0.17	<0.01	11 y	PRS	0.09	0.02	0.16	0.01
n=1848	Rel.Age*PRS	-0.03	-0.14	0.07	0.53	n=1584	Rel.Age*PRS	-0.02	-0.13	0.09	0.74
	Rel.Age	0.16	0.06	0.27	<0.01		Rel.Age	0.12	0.01	0.23	0.04
13 y	PRS	0.11	0.05	0.18	<0.01	13 y	PRS	0.12	0.05	0.19	<0.01
n=1772	Rel.Age*PRS	-0.04	-0.14	0.06	0.45	n=1542	Rel.Age*PRS	-0.07	-0.18	0.04	0.22
	Rel.Age	0.07	-0.05	0.19	0.26		Rel.Age	0.08	-0.04	0.20	0.21
16 y	PRS	0.07	0.00	0.15	0.06	16 y	PRS	0.02	-0.06	0.10	0.64
n=1490	Rel.Age*PRS	0.00	-0.12	0.11	0.94	n=1306	Rel.Age*PRS	0.05	-0.07	0.18	0.41
25 y	Rel.Age	-0.04	-0.17	0.08	0.50	25 y	Rel.Age	-0.02	-0.16	0.11	0.71
n=1094	PRS	0.08	0.00	0.16	0.05	n=967	PRS	0.06	-0.03	0.14	0.19

	Rel.Age*PRS	0.00	-0.13	0.13	0.98		Rel.Age*PRS	0.05	-0.08	0.18	0.44

"Continuous" = All individuals included. "4 week" = Restricted to individuals born up to 4 weeks either side of the September 1st cut-off. 8 weeks = Restricted to individuals born up to 8 weeks either side of the September 1st cut-off Imputed data. Coefficient (Coef.) represents mean change in standardised parent-report SDQ score per 1 year difference in relative age (Rel.Age) or mean change in standardised parent-report SDQ score per 1 SD unit change in PRS (PRS) "Unadjusted Model" = Age within School Year entered in the regression + principal components. "Adjusted Model" = Model after adjustments for maternal age at birth, sex, age at completion, and maternal depression. Rel.Age = Relative age. PRS p<0.05 = PRS scores for ADHD, threshold level p<0.05

Table A4.12: Generalized estimating equation (GEE) results for parent-rated SDQ total difficulties

SDQ Total Difficulties	Coef.	[95% Conf.	Interval]	p
Rel.Age				
7 years	0.14	0.07	0.20	<0.01
8 years	0.15	0.09	0.22	<0.01
9 years	0.13	0.06	0.20	<0.01
11 years	0.20	0.12	0.27	<0.01
13 years	0.12	0.04	0.20	<0.01
16 years	0.09	0.00	0.18	0.04
25 years	-0.02	-0.12	0.08	0.70
ADHD Risk				
Borderline	0.70	0.62	0.79	<0.01
High	1.19	1.10	1.27	<0.01
ADHD Risk*Rel.Age				
Borderline	0.01	-0.14	0.17	0.86
High	-0.07	-0.23	0.08	0.35
ADHD Risk*Rel.Age				
Borderline	0.01	-0.02	0.05	0.51
High	0.00	-0.05	0.05	0.90
ADHD Risk*Rel.Age*Age at completion of SDQ				
Borderline	-0.06	-0.13	0.02	0.15
High	-0.04	-0.12	0.04	0.33
N	9149			

(N=9172). Coefficient (Coef.) represents mean change in standardised parent-report SDQ score per 1 year difference in relative age (Rel.Age), or mean change in standardised parent-report SDQ score compared to low-risk ADHD group (borderline vs low; high vs low). Rel.Age = Relative age in school year. Borderline = SDQ hyperactivity at 4 years = 6. High = SDQ hyperactivity at 4 years >=7.

Table A4.13: Generalised estimating equation (GEE) results for parent-rated SDQ total difficulties and PRS

SDQ Total Difficulties	Coef.	[95% Conf.	Interval]	p
Rel.Age				
7 years	0.08	0.00	0.16	0.05
8 years	0.10	0.02	0.18	0.02
9 years	0.09	0.02	0.17	0.02
11 years	0.16	0.08	0.24	<0.01
13 years	0.08	0.00	0.16	0.06
16 years	0.00	-0.08	0.09	0.96
25 years	-0.08	-0.18	0.01	0.08
PRS p<0.05	0.12	0.08	0.15	<0.01
Rel.Age*PRS p<0.05	-0.04	-0.11	0.02	0.18
Rel.age*Age	0.01	-0.02	0.03	0.64
PRS p<0.05*Age	0.01	-0.01	0.02	0.35
Rel.Age*PRS p<0.05*Age at completion SDQ	-0.01	-0.04	0.01	0.36
N	6927			

(N=6933). Coefficient (Coef.) represents mean change in standardised parent-report SDQ score per 1 year difference in relative age. (Rel.Age) or mean change in standardised parent-report SDQ score per 1 SD unit change in PRS (PRS) Rel.Age = Relative age in school year.

Appendix: Chapter 5

Table A5.1: Main effect of age within school year, stratified by group.

ADHD controls (N=22624)	RR	CI	p	ADHD cases (N=7556)	RR	CI	p	ASD controls (n=14690)	RR	CI	p	ASD Cases N=4912)	RR	CI	p
Anx/Dep	1.09	0.93, 1.28	0.28	Anx/Dep	1.06	0.83, 1.34	0.66	Anx/Dep	1.13	0.91, 1.41	0.28	Anx/Dep	1.08	0.77, 1.53	0.66
Self-Harm	1.29	0.95, 1.74	0.10	Self-Harm	1.02	0.77, 1.35	0.90	Self-Harm	1.31	0.91, 1.89	0.15	Self-Harm	1.14	0.71, 1.83	0.59
Drug misuse	1.18	0.80, 1.73	0.40	Drug misuse	1.36	0.98, 1.88	0.07	Drug misuse	1.35	0.77, 2.38	0.29	Drug misuse	1.36	0.68, 2.72	0.39
Alcohol misuse	1.25	0.89, 1.77	0.20	Alcohol misuse	0.89	0.62, 1.27	0.52	Alcohol misuse	2.24	1.46, 3.44	<0.01	Alcohol misuse	0.69	0.33, 1.44	0.32
A&E services use	1.14	1.03, 1.25	0.01	A&E services use	1.06	0.88, 1.26	0.57	A&E services use	1.16	1.01, 1.34	0.03	A&E services use	1.20	0.91, 1.57	0.20

RR = Risk ratio of an outcome over the follow-up period for a one-year difference in relative age, ADHD cases and controls (left), ASD cases and controls (right). All months entered.

Table A5.2: Effect of relative age in school year (Rel.age) on outcomes, August/September only.

ADHD Controls (N=3760)	RR	CI	p	ADHD Cases (N=1256)	RR	CI	p	ASD Controls (N=2434)	RR	CI	p	ASD Cases (N=814)	RR	CI	p
Anx/Dep	1.05	0.82, 1.36	0.69	Anx/Dep	1.04	0.73, 1.49	0.83	Anx/Dep	1.14	0.82, 1.58	0.44	Anx/Dep	1.31	0.77, 2.23	0.32
Self-Harm	1.55	0.92, 2.62	0.10	Self-Harm	1.36	0.84, 2.18	0.21	Self-Harm	1.33	0.73, 2.42	0.35	Self-Harm	1.08	0.50, 2.33	0.85
Drug misuse	1.89	0.99, 3.61	0.05	Drug misuse	1.63	0.93, 2.87	0.09	Drug misuse	1.32	0.57, 3.05	0.52	Drug misuse	1.99	0.53, 7.44	0.31
Alcohol misuse	1.17	0.68, 2.02	0.57	Alcohol misuse	0.82	0.47, 1.43	0.49	Alcohol misuse	2.14	1.06, 4.31	0.03	Alcohol misuse	0.68	0.18, 2.55	0.56
A&E services use	1.13	0.98, 1.31	0.10	A&E services use	1.01	0.77, 1.34	0.93	A&E services use	1.40	1.14, 1.73	<0.01	A&E services use	1.44	0.96, 2.15	0.08

RR = risk ratios of an outcome per one-year decrease in relative age (Rel.age), assuming a linear association. ADHD cases and controls (left), ASD cases and controls (right).

Table A5.3: effects of relative age in the school year and neurodevelopmental disorder on outcomes, and interactions between relative age and neurodevelopmental disorder on outcomes. August/September only.

ADHD Case/Controls (N=5016)	Effect	RR	CI	p	ASD Case/Controls (N=3248)	Effect	RR	CI	p
Anx/Dep	Rel.age	1.04	0.81, 1.34	0.76	**Anx/Dep**	Rel.age	1.14	0.82, 1.58	0.44
	ADHD	2.34	1.07, 3.20	<0.01		ASD	1.81	1.19, 2.73	0.01
	Interaction	1.02	0.66, 1.57	0.93		Interaction	1.15	0.62, 2.14	0.65
Self-Harm	Rel.age	1.48	0.88, 2.49	0.14	**Self-Harm**	Rel.age	1.33	0.73, 2.41	0.35
	ADHD	5.61	3.30, 9.55	<0.01		ASD	2.75	1.45, 5.20	<0.01
	Interaction	0.94	0.48, 1.87	0.87		Interaction	0.81	0.31, 2.15	0.68
Drug misuse	Rel.age	1.88	1.00, 3.54	0.05	**Drug misuse**	Rel.age	1.31	0.57, 3.03	0.53
	ADHD	5.41	2.79, 10.47	<0.01		ASD	1.18	0.38, 3.64	0.78
	Interaction	0.87	0.38, 2.01	0.87		Interaction	1.53	0.32, 7.72	0.60
Alcohol misuse	Rel.age	1.17	0.68, 2.00	0.57	**Alcohol misuse**	Rel.age	2.14	1.07, 4.30	0.03
	ADHD	4.49	2.64, 7.64	<0.01		ASD	1.99	0.80, 4.97	0.14
	Interaction	0.70	0.33, 1.50	0.36		Interaction	0.32	0.07, 1.41	0.13
A&E services use	Rel.age	1.12	0.97, 1.30	0.13	**A&E services use**	Rel.age	1.40	1.14, 1.79	<0.01
	ADHD	1.51	1.20, 1.90	<0.01		ASD	1.24	0.88, 1.75	0.22
	Interaction	0.93	0.68, 1.27	0.63		Interaction	1.03	0.65, 1.62	0.91

Rel.age = Relative age. RR = risk ratio of an outcome per one-year decrease in relative age (Rel.age), or risk ratio of an outcome by presence of a neurodevelopmental disorder (ADHD/ASD) diagnosis (diagnosis vs no diagnosis), assuming a linear association; interaction = Interaction between Rel.age and ADHD/ASD (ADHD/ASD = 1 if diagnosis present). ADHD cases and controls (left), ASD cases and controls (right).