

Patterns, Influences and Genetic Underpinnings of the Development of ADHD

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Declaration

I, Chaoyu K. Liu, hereby confirm that, except where explicit attribution from other sources is made, the work presented in this thesis is entirely my own.

Signed:

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Abstract

Background

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterised by age-inappropriate, disruptive and pervasive manifestations of inattention and/or hyperactivity/impulsivity. ADHD symptoms typically emerge in childhood and persist into later stages of life. ADHD also frequently co-occurs with a number of psychiatric disorders and medical conditions, thereby bringing a tremendous burden to affected individuals as well as society. In addition to symptom severity and chronicity, the development of ADHD also plays a determinant role in disease outcomes. However, few studies have systematically investigated different predictive factors and underlying aetiologies associated with the development of ADHD.

Aims

This thesis aims to examine patterns, influences and genetic underpinnings of the development of ADHD from childhood to adolescence. The first study investigates childhood factors that differentiate late-onset ADHD from childhood-onset ADHD and differences in adolescent outcomes. The second study examines genetic and environmental contributions underlying the effects of the development of inattention on academic performance. The third and the fourth studies investigate the developmental relationships between ADHD and BMI through triangulation of evidence from longitudinal statistical analyses and genetically informed causal inference approaches.

Methods

All of the studies adopt a development-sensitive design using data from the “Twin Early Development Study” (TEDS), a longitudinal cohort in the UK. A pluralistic statistical

approach is employed for different study objectives. To strengthen causal inference, this thesis compares and contrasts findings from longitudinal statistical approaches and different genetically informed methods under a triangulation framework.

Results

Findings of this thesis suggest that 1) late-onset ADHD is more likely to be found in males and children who exhibit increased conduct problems and experience more childhood family adversity. Moreover, low socioeconomic status specifically predicts de novo late-onset ADHD, while additional factors predict subthreshold late-onset ADHD; 2) both the baseline level and the developmental course of inattention influence academic performance. Genetic contributions to the development of inattention also affect academic performance; 3) longitudinal statistical analyses identify unidirectional effects from ADHD symptoms to subsequent BMI, while genetic methods suggest a bidirectional causal relationship. Triangulation of evidence shows that multiple sources of confounding are involved in the relationships between ADHD and BMI, including unmeasured confounding and dynastic effects.

Conclusions

This thesis identifies specific childhood risk factors and genetic underpinnings associated with different developmental patterns of ADHD. Influences of the developmental course of ADHD on psychological and functional outcomes can be attributable to direct causal relationships, genetic and environmental confounding, or a combination of both. Altogether, these findings contribute to a more complete and systematic understanding of different developmental aspects of ADHD. To disentangle aetiological pathways between the

development of ADHD and associated conditions, a pluralistic statistical approach to triangulate evidence regarding causal mechanisms is necessary.

Impact statement

ADHD affects 5-10% school-age children around the world. ADHD symptoms are associated with a wide range of behavioural and psychosocial problems, which lead to poor mental and physical wellbeing. Current evidence suggests that the development of ADHD is as important as symptom severity in relation to individual outcomes. Therefore, better understanding towards why some children develop persistent or increasing ADHD symptoms while other children remit is important to the management of ADHD. Studies that investigate predicting factors and underlying mechanisms of different ADHD development and influences of developmental trends on long-term prognosis can provide us with better insights.

This thesis employs longitudinal analyses and genetically informed methods to systematically examine the development of ADHD symptoms across childhood and adolescence, including different developmental patterns, associated conditions, outcomes and genetic and environmental underpinnings. Findings suggest that family adversity and childhood conduct problems can predict an increase in ADHD symptoms beyond the childhood years. However, time-varying risk factors may as well have a determinant role. In addition, the developmental patterns of inattentive symptoms have independent influences on academic performance and shared genetic aetiology explains a large part of such influences. Finally, the frequent co-occurrence of ADHD and obesity may result from bidirectional causal relationships, while multiple genetic and environmental confounding is also at play.

The development of ADHD is a multifactorial process that involves a dynamic interaction between genetic and environmental influences. Such a developmental pattern matters as it is linked to differential outcomes across psychological, functional and physical domains. Findings of this thesis have important clinical implications as they demonstrate potential areas for intervention. For example, remediation of adverse family environment in early childhood may curb deterioration of ADHD symptoms and to improve behavioural and

functional outcomes of individuals with ADHD. Furthermore, the pluralistic approach in this thesis provides future study with a good example of triangulation efforts when dissecting aetiological pathways to the development of ADHD.

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1 Chapter 1: General introduction

1.1 What is ADHD and why is it important?

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common mental health condition that affects 5-8% of school-age children and adolescents (Polanczyk *et al.*, 2007). ADHD is conceptualised as a neurodevelopmental disorder and characterised by combinations of age-inappropriate, pronounced and debilitating inattention, hyperactivity and impulsivity symptoms, which typically emerge in early childhood (American Psychiatric and American Psychiatric Association, 2013).

ADHD is associated with increased risks of various negative outcomes through the life course, such as depression and anxiety, low academic achievement, and impairment in social and occupational functioning (Gau *et al.*, 2005, Polderman *et al.*, 2010). In general, a child with more severe ADHD symptoms faces a worse prognosis (Cheung *et al.*, 2015). However, other factors such as cognitive ability, family environment, parental psychopathology and treatment history also act interactively and cumulatively to influence ADHD outcomes (Kaiser *et al.*, 2011, Murray *et al.*, 2008). It is noteworthy that the impact of ADHD is not confined to mental wellbeing and social/occupational functioning. Research has indicated that ADHD is linked strongly to multiple somatic diseases such as obesity, sleep disorders and asthma, and thus leads to increased healthcare service utilisation that brings a substantial burden to the public health system (Instanes *et al.*, 2018, Sciberras *et al.*, 2017a). Furthermore, individuals with persistent ADHD symptoms have higher medical expenditures compared with non-ADHD controls and individuals with childhood-limited ADHD (Du Rietz *et al.*, 2020). The negative and enduring impact of ADHD across a wide range of domains

highlights the importance of early intervention to curb disease progression and to prevent the development of multimorbidity.

1.2 The developmental aspects of ADHD

ADHD is a chronic condition: 44% to 85% of children with ADHD continue to have symptoms or experience functional impairments during adolescence and adulthood (Biederman *et al.*, 2010) (Bussing *et al.*, 2010). Research suggests that ADHD symptom dimensions follow different developmental pathways: hyperactivity and impulsivity tend to subside with age, while inattention is more likely to persist (Biederman *et al.*, 2000, Molina *et al.*, 2009, Pingault *et al.*, 2015b). The persistence of ADHD symptoms is an important indicator for poorer outcomes. Children with ADHD symptoms persisting into adolescence have been found to be more aggressive, and present higher levels of antisocial behaviour, criminal offenses, and social maladjustment than those with childhood-confined symptoms (Sasser *et al.*, 2016). Risk of early school drop-out, low occupational achievement and dependence on government support are also markedly higher in adults with persistent ADHD symptoms (Hechtman *et al.*, 2016). These detrimental effects underscore the need to monitor how ADHD symptoms develop throughout the life course.

Although in general ADHD denotes a childhood-onset condition with a chronic disease course, some individuals may experience varying symptom development throughout the life course (Faraone *et al.*, 2015, Larsson *et al.*, 2011). More specifically, individual differences in the age of symptom onset and how ADHD symptoms decrease or increase across different developmental stages can be observed in the population (Agnew-Blais *et al.*, 2016, Pingault *et al.*, 2015b). Evidence further indicates that variations in systematic change in symptom severity and age of onset are associated with diverse clinical and functional outcomes. For example, a systematic increase in inattentive symptoms from childhood to adolescence

predicts premature school failure in young adulthood (Pingault *et al.*, 2014). Individuals with ADHD symptoms that emerge in adolescence and adulthood present higher levels of mood symptoms and problematic substance use than those with childhood-onset ADHD symptoms (Agnew-Blais *et al.*, 2016) (Moffitt *et al.*, 2015). However, most studies in the current literature still adopt the conventional approach that defines ADHD according to childhood presentations, focusing on consequences associated with symptom persistence; whereas, the aforementioned findings highlight the dynamic and diverse nature of the development of ADHD, stressing the need for developmental sensitive approaches in related research.

1.3 Genetic and environmental underpinnings of ADHD development

ADHD is a multifactorial disorder that involves complex aetiological pathways (Luo *et al.*, 2019). Great epidemiological efforts have identified a range of genetic and environmental factors associated with increased risks of ADHD. The genetic influences on ADHD are evidenced by its moderate to high heritability (0.6 to 0.9) reported across twin studies and family aggregation analyses (Todd, 2000). Genome Wide Association Studies (GWAS) have recently identified common genetic variants explaining population variation in ADHD diagnosis (Demontis *et al.*, 2019) and ADHD symptom severity (Middeldorp *et al.*, 2016). Equally important, a number of environmental factors (both prenatal and postnatal) have also been linked to ADHD (Cherkasova *et al.*, 2013, Sciberras *et al.*, 2017b). For example, maternal smoking, pregnancy complications, low socioeconomic status and high parental conflicts may predict ADHD diagnosis in offspring (Galera *et al.*, 2011, Larsson *et al.*, 2011). However, to what extent such environmental factors are directly causal to ADHD

development remains undetermined, as some evidence indicates that unmeasured confounding may bias the association (Ginsberg *et al.*, 2019, Obel *et al.*, 2016).

Similar to the incidence of ADHD, the developmental course of ADHD also arises from a web of biological and environmental determinants. An abundance of research has documented factors associated with the persistence of ADHD symptoms across childhood and adolescence. Those factors can be roughly categorised as genetic predisposition, clinical characteristics and environmental influences. Genetic studies have suggested that higher polygenic scores for ADHD are associated with more severe clinical manifestations and symptom persistence (Martin *et al.*, 2014, Riglin *et al.*, 2016). Individuals with clinical characteristics such as higher levels of ADHD symptoms or comorbid conduct and mood problems in the childhood years are more likely to remain symptomatic in adolescence and adulthood (Holbrook *et al.*, 2016). Finally, it was found that prenatal and perinatal insults, low family socioeconomic status and parental psychopathology also predict enduring ADHD courses (Galera *et al.*, 2011, Larsson *et al.*, 2011).

Compared to symptom persistence, relatively few studies have investigated mechanisms underlying developmental courses and age of onset of ADHD and how they relate to different outcomes. Available evidence has suggested that a balance of genetic and environmental influences may explain individual differences in the developmental course. For example, the study by Larsson *et al.* (Larsson *et al.*, 2011) found that different developmental trajectories of inattention and hyperactivity/impulsivity were largely determined by genetic influences and modestly by non-shared environmental effects. Pingault, Viding, *et al.* (Pingault *et al.*, 2015b) further uncovered that the strong genetic influences underlying the systematic change in ADHD symptoms are partly independent from those that explained the baseline symptom levels. Similarly, late-onset ADHD symptoms are predicted by environmental adversity such as perinatal complications and

childhood maltreatment (Agnew-Blais *et al.*, 2016) and differential genetic predisposition (Riglin *et al.*, 2016). However, it remains unknown whether genetic and environmental influences on the developmental courses of ADHD also relate to developmental outcomes. Research in this area can advance our understanding of the diverse components and dynamic nature of ADHD. Furthermore, it also can inform clinicians and public health organisations in planning the deployment of prevention and intervention initiatives to tackle different developmental needs.

1.4 Outstanding Research questions and study designs

Increasing evidence suggests that the development of ADHD symptoms across childhood and adolescence has a critical influence on individual functioning and a wide range of outcomes. However, current research is lacking on the developmental features of ADHD. This thesis aims to systematically examine several aspects of the development of ADHD, including different ages of onset, systematic change in symptom severity and the developmental influences of ADHD symptoms. Studies comprised in the thesis also investigate genetic and environmental factors contributing to different developmental patterns of ADHD, and whether and how those patterns differentially relate to functional outcomes. The multifactorial nature of ADHD and its complex relationships with other conditions prompt the need for different approaches for different research objectives. Therefore, I employ multiple statistical methods throughout this thesis for research questions in each study. The overview of the methods applied can be found in Table 1.1. The majority of the analyses are based on data collected from a population-based twin cohort in the United Kingdom, the “Twins Early Development Study” (TEDS).

Table 1.1 Overview of the methods applied in the thesis

Strategy	Data type	Summary of the strategy	Key assumptions	Limitations
Classical twin design: variance component decomposition	Data collected from a sample with monozygotic (MZ) and dizygotic (DZ) twins.	<ul style="list-style-type: none"> • Univariate approach: partitioning variance of a trait into additive genetic (A), dominant genetic (D), shared environmental (C) and non-shared environmental (E) components. • Multivariate analysis: decompose genetic-environmental basis of the correlation between multiple traits. 	<ul style="list-style-type: none"> • MZ twins share 100% and DZ twins share 50% of segregated genetic material. • Heritability represents “narrow sense heritability”, where all genetic effects are additive (i.e. no dominant genetic effects). • Equal environment assumption: C components are equal in magnitude between MZ and DZ twins. • Random mating in the population. 	<ul style="list-style-type: none"> • If equal environment assumption is violated, then it will lead to inflation of genetic effects/heritability. • Non-additive genetic effects, including G-E correlation, gene-gene interaction and G x E interaction cannot be further quantified.
Cross-lagged panel model (CLPM)	Longitudinal observation data of different constructs assessed at least for two occasions.	<ul style="list-style-type: none"> • The reciprocal relationships between two variables across time are described by cross-lagged effects. • The autoregressive effects assess the stability within each variable across time. 	<ul style="list-style-type: none"> • Measurements of different constructs occur at the same time. • Measurements are without errors. • The influence of one construct on another construct correspond to the measurement time lag. • All possible confounding has been controlled for. 	<ul style="list-style-type: none"> • Model is based on common group mean and thus ignores individual differences in how variables change over time. • Conflate within-individual and between-individual effects in the estimates may yield false interpretations of the results. • Cannot capture effects beyond measurement time lag.
Autoregressive latent trajectory with structured residuals (ALT-SR)	Longitudinal observation of different variables with at least four waves of data collection	<ul style="list-style-type: none"> • A model combines a latent growth curve with the CLPM components. • The latent growth curve captures group-level/between-individual differences in the initial level and the systematic change in each construct. 	<ul style="list-style-type: none"> • Share the general assumptions as the CLPM. • The developmental trend of the variables can be correctly modelled by the latent growth curve. 	<ul style="list-style-type: none"> • The model cannot be applied to categorical or ordinal data, where structuring time-specific residuals is not possible.

Strategy	Data type	Summary of the strategy	Key assumptions	Limitations
		<ul style="list-style-type: none"> The cross-lagged relationships between two constructs are estimated between the residuals from the underlying growth trajectory, and thus are time- and person-specific. 	<ul style="list-style-type: none"> Residuals from the underlying trajectory do not include measurement errors. 	<ul style="list-style-type: none"> Precise estimation of the model relies on appropriate spacing and sufficient number of the observation. Findings provide direct examination of reciprocal effects but are difficult to translate into magnitude of the influences.
Cross-lagged twin-differences analysis	Longitudinal data collected from a twin sample. This model can be constructed with data from MZ and DZ twins.	<ul style="list-style-type: none"> This approach capitalises on twins' characteristics to control for potential genetic and shared environmental confounding. MZ twins provides a more stringent control for confounding. Findings can inform whether the effects are due to non-shared environment and direct influence between traits. 	<ul style="list-style-type: none"> MZ twins share 100% genetic material. No unobserved non-shared environmental confounding. Plausible nonshared environmental confounder can be adjusted in the model. 	<ul style="list-style-type: none"> Factors such as de novo mutation, epigenetic changes, stochastic gene expression and intrauterine growth environment may lead to discordance in MZ twins, which are difficult to adjust for in the model. Because of the stringent control of confounding, MZ twin differences analysis usually yields smaller effect sizes so that it may limit the relevance of the results.
Polygenic score analysis	A polygenic score (PS) for a specific trait per individual is calculated from the sum of the trait-associated alleles weighted by their relative	<p>Between- and within-family PS association in DZ twins</p> <ul style="list-style-type: none"> PS associations provide an initial indication of a possible causal relationship. Within-family PS association shows genetic effects independent of dynastic effects, population stratification and assortative mating. 	<ul style="list-style-type: none"> A PS indexes an individual's genetic liability to a particular trait, thus can be used as a proxy (i.e. the instrumental variable) of one trait in cross-trait analyses. Exclusion restriction assumption (genetic instruments only work through the risk factor): for the use of PS association in the context of causal 	<ul style="list-style-type: none"> PS derived from many genetic variants are more likely to correlate with confounders and violate exclusion restriction assumption.

Strategy	Data type	Summary of the strategy	Key assumptions	Limitations
	<p>effect sizes as reported in the genome-wide association summary statistics (i.e. the discovery GWAS).</p> <p>The discovery GWAS and the study sample should be independent.</p>		<p>inference is the absence of pleiotropy or dynastic effects.</p> <ul style="list-style-type: none"> • A within-family PS analysis on DZ twins controls for confounding shared between siblings. 	
Mendelian randomisation (MR)	<p>MR analysis builds on Mendel's Laws of Inheritance, and utilises genetic variants associated with an exposure (e.g. SNPs associated with a trait) as instrumental variables to examine causal effects of the study variable on the outcome.</p>	<ul style="list-style-type: none"> • A bidirectional MR evaluates reciprocal relationships between two variables. • Different MR estimators are available to investigate potential violations to basic MR assumptions. • Estimators used in the current study include: the IVW regression, MR-Egger regression, Weighted-median method, weighted-mode method, robust adjusted profile score, and multivariable MR. 	<ul style="list-style-type: none"> • Three core instrumental assumptions regarding the IV should be met for all the MR analyses: <ul style="list-style-type: none"> ○ Relevance assumption: the genetic variants are associated with the exposure. ○ Exchangeability assumption: association between the genetic variants and the outcome is not confounded by unmeasured factors. ○ Exclusion restriction: genetic variants only affect the outcome through their effects on the exposure. 	<ul style="list-style-type: none"> • MR analysis can still be biased by population stratification, assortative mating and dynastic effects. • MR IVW regression has better statistical power, but it cannot control for unbalanced horizontal pleiotropy. • MR Egger regression and weighted mode method can be used when most of the instrumental variables are invalid, but they are less powerful.

1.4.1 What childhood factors may drive an increase in ADHD symptom development and predict late-onset ADHD?

Findings from several large population-based cohorts suggest ADHD symptoms can first emerge in adolescence and beyond. In addition, late-onset ADHD may be divided into subgroups that display heterogeneous developmental patterns, for example, subthreshold late-onset ADHD that refers to individuals with 3-5 childhood ADHD symptoms and de novo late-onset ADHD that represents those with 0-2 childhood ADHD symptoms (Agnew-Blais *et al.*, 2016) (Cooper *et al.*, 2018, Manfro *et al.*, 2018). However, debates remain regarding the definition of late-onset ADHD and whether it is distinct from childhood-onset ADHD. By contrasting early childhood characteristics and adolescent outcomes between non-ADHD control, de novo late-onset ADHD, subthreshold late-onset ADHD and childhood-onset persistent ADHD, Study 1 aims to better characterise late-onset ADHD. I use parent-reported ADHD symptoms from age 8 to age 16 years, data on childhood risk factors and a range of adolescent outcomes collected from the TEDS cohort. I employ multinomial logistic regression analysis to identify childhood risk factors that differentiate ADHD categories. Results can help to clarify the debate surrounding late-onset definition and advance our understanding of risk factors associated with the increase in ADHD symptom beyond the childhood years.

1.4.2 Whether and how the development of inattentive symptoms from childhood to adolescence influences adolescent academic performance?

Previous studies have documented that the developmental course of ADHD can influence outcomes. It was shown that a high and increasing inattention trajectory in

childhood was associated with early school dropout in young adulthood (Pingault *et al.*, 2011). Genetic studies have further indicated that individual variation in the developmental course of ADHD symptoms can be explained largely by genetic factors (Pingault *et al.*, 2015b). Therefore, the aim of Study 2 is to examine to what extent the developmental course of inattention across childhood and adolescence influences adolescent academic performance. If so, whether the genetic and environmental influences on inattention development explain its effects on academic performance. I employ a latent growth curve model to estimate the systematic change in inattention symptoms across ages 8 to 16 years. I also used twin modelling to separate aetiological contributions into additive genetic and non-shared environmental effects. Uncovering aetiological pathways underlying the influence of inattention can help to devise targeted interventions to ameliorate associated academic impairment.

1.4.3 Does the co-occurrence of ADHD and obesity in epidemiologic studies involve causal relationships? Making causal inferences from longitudinal observational data.

ADHD is associated with a range of biopsychosocial problems across the life span. Although most studies have focused on behavioural and psychiatric impairments associated with ADHD, increasing evidence suggests that individuals with ADHD also are at higher risks of somatic disorders (Instanes *et al.*, 2018). Medical multimorbidity and high health expenditure are found to be troublesome issues associated with persistent ADHD symptoms (Du Rietz *et al.*, 2020). Systematic reviews and meta-analytic evidence have outlined a positive association between ADHD and overweight/obesity (Cortese and Tessari, 2017, Nigg *et al.*, 2016). Despite the well-established link, evidence from longitudinal observational studies still cannot conclude whether the relationship between ADHD and

obesity is causal or confounded (Cortese, 2019). Furthermore, the incremental comorbid rates between ADHD and overweight/obesity during the transition from childhood to early adulthood implies potential developmentally sensitive associations (Cortese and Tessari, 2017). Therefore, the objective of Study 3 is to investigate the nature of the relationship between ADHD and overweight/obesity across the critical period from childhood to late adolescence. I use continuous measures for ADHD symptoms and body mass index (BMI) as study variables rather than binary categories due to sample characteristics. The dimensional approach also helped to capture more phenotypic variation in population samples. I employ a cross-lagged panel model to examine bidirectional relationships between ADHD and BMI at different developmental time points. Furthermore, I performed an autoregressive latent trajectory model on the structured residuals as a complementary analysis to examine whether the relationships between ADHD and BMI involve unmeasured confounding. The approaches with the cross-lagged panel model and the autoregressive latent trajectory model on the structured residuals provide clear time ordering to minimise potential bias due to reverse causality.

1.4.4 Does the co-occurrence of ADHD and obesity in epidemiologic studies involve causal relationships? Making causal inferences from genetically informed approaches.

Study 3 investigates prospective reciprocal relationships between ADHD and BMI with longitudinal statistical methods. Recent advances in causal inference research has demonstrated genetically informed methods as powerful tools to study causality. Genetically informed causal inference methods capitalise on the knowledge that genetic materials are determined randomly at conception and hence are more robust to environmental confounding

and reverse causality. Despite such advantages, evidence suggests that genetically informed methods still may be subject to confounding such as horizontal pleiotropy, population stratification, assortative mating and dynastic effects (Davies *et al.*, 2018, Duncan *et al.*, 2019, Sohail *et al.*, 2019). Therefore, Study 4 aims to triangulate findings from different genetically causal inference approaches to acquire evidence approving or disapproving causal relationships. Methods applied in the current study include cross-lagged twin-differences analysis, within-family polygenic score analysis and Mendelian randomization. Triangulating findings can provide a better understanding of the nature of the relationship and identify potential sources of bias.

Findings from Study 3 and Study 4 help to advance understanding of the co-occurrence between ADHD and obesity. This knowledge can be applied to devise management strategies for individuals struggling with both conditions.

2 Chapter 2: Early predictors of late-onset ADHD symptoms

As set out in the general introduction of this thesis, new evidence from large-scale population-based studies indicates that ADHD symptoms can first emerge in the adolescent years and beyond for some individuals. However, little is known whether individuals with late-onset ADHD symptoms can be distinguished from those with childhood-onset symptoms in terms of childhood presentations and adolescent outcomes. In addition, which childhood characteristics can predict late-onset ADHD symptoms also needs further investigation. In this chapter I compared and contrasted childhood characteristics and adolescent outcomes between individuals with late-onset ADHD, non-ADHD controls and those with childhood-onset persistent ADHD. I divided late-onset ADHD into de novo late-onset ADHD and subthreshold late-onset ADHD according to the levels of childhood ADHD symptoms in order to better characterise late-onset symptomatology.

This chapter is adapted from a manuscript published in the *Journal of Attention Disorders*.

Liu, C. Y., Asherson, P., Viding, E., Greven, C. U., & Pingault, J. B. (2019). Early Predictors of De Novo and Subthreshold Late-Onset ADHD in a Child and Adolescent Cohort. Journal of Attention Disorders, 1087054719892888.

Supplementary materials for this chapter are attached in Appendix 1.

2.1 Introduction

2.1.1 ADHD is a lifelong condition

Conventionally, ADHD is conceptualized as a childhood-onset neurodevelopmental disorder with pervasive and debilitating manifestations of inattention, hyperactivity and impulsivity. However, ADHD is not confined to the childhood years. The weight of the evidence indicates that the majority of ADHD children remain functionally impaired by part, if not all, of their symptoms in adolescence and adulthood (Faraone *et al.*, 2015, Spencer *et al.*, 2014). Persistent ADHD symptoms are associated with poorer outcomes. Children with persistent ADHD from childhood to adolescence are more aggressive, and have more antisocial behaviours, higher rates of truancy, criminality, and lower socio-occupational achievement than those with childhood-limited symptoms in late adolescence and early adulthood (Sasser *et al.*, 2016).

Several factors may help to differentiate children at higher risk of developing persistent ADHD. For example, it has been found that children who suffered from prenatal and perinatal insults, including premature birth, low birth weight and tobacco exposure during pregnancy exhibited more enduring ADHD symptoms from infancy to early childhood (Galera *et al.*, 2011, Lindstrom *et al.*, 2011). The severity of ADHD symptoms in early childhood, comorbid oppositional defiant and conduct problems, and comorbid depression and anxiety have been shown to consistently predict ADHD symptom persistence into adolescence and adulthood across different studies (Caye *et al.*, 2016a, Holbrook *et al.*, 2016).

2.1.2 Should it all begin in childhood?

In current practice, displaying ADHD symptoms in early childhood is required for an ADHD diagnosis. However, the age-of-onset requirement in the DSM system has long been debated. Different lines of research concluded that shifting the age-of-onset criterion from 7 years old to 12 years old did not affect the psychometric property of the diagnostic criteria, but instead improved diagnostic accuracy for ADHD (Applegate *et al.*, 1997) (Faraone *et al.*, 2006b). Findings also indicated that individuals who met ADHD diagnosis except for the age-of-onset criterion displayed similar clinical manifestations and levels of impairment in adulthood as those with childhood-onset symptoms (Faraone *et al.*, 2006a). A number of prospective studies concurred with such findings and found a large proportion of adults with ADHD symptoms did not fulfil ADHD diagnosis in childhood (Agnew-Blais *et al.*, 2016, Caye *et al.*, 2016b).

2.1.3 Late onset ADHD

The strict age-of-onset requirement has been reconsidered and shifted from age 7 years to age 12 years in the DSM-5 (American Psychiatric and American Psychiatric Association, 2013). Nevertheless, loosening of the restriction to age 12 years still cannot reconcile evidence showing that ADHD symptoms can first emerge later in the life course (Hinshaw *et al.*, 2012, Willoughby *et al.*, 2012). In fact, adolescents and adults with late-onset ADHD symptoms were found to have prevalence rates that ranged from 3 to 13% across different population-based samples (Agnew-Blais *et al.*, 2016, Caye *et al.*, 2016b, Hinshaw *et al.*, 2012). Furthermore, individuals with late-onset ADHD experience more functional impairment than non-ADHD controls. Individuals with late-onset ADHD also present higher comorbidity with mood disorders and substance misuse in early adulthood

than childhood-onset ADHD (Agnew-Blais *et al.*, 2016). These findings suggest that more research is needed to better understand the late-onset category.

It is noteworthy that late-onset ADHD also displays heterogeneous symptom developmental courses, which results in divergent definitions and inclusion criteria in the related research. For example, some late-onset ADHD individuals already display elevated levels of ADHD symptoms in childhood (usually 3-5 inattention or hyperactivity/impulsivity symptoms). They were called “subthreshold late-onset ADHD” and were excluded from some of the studies (Cooper *et al.*, 2018, Manfro *et al.*, 2018). The main reason to exclude subthreshold late-onset ADHD was the concern that those individuals may not reflect true late-onset symptomatology but mis-categorised due to measurement limitations or scaffolded by protective factors (e.g. supportive environment or better cognitive ability) (Kosaka *et al.*, 2018, Sibley *et al.*, 2018). Therefore, some studies only included individuals with very few (usually 0-2) ADHD symptoms in childhood as “genuine” late-onset ADHD (Cooper *et al.*, 2018, Manfro *et al.*, 2018, Sibley *et al.*, 2018). Consequently, little is known about the similarities and differences between late-onset ADHD with different levels of childhood symptoms, and how they are comparable with childhood-onset ADHD.

2.1.4 Study aims

Although late-onset ADHD has been identified and discussed in several population-based studies, there are insufficient data to fully characterise late-onset ADHD symptomatology. To this end, the definition of late-onset ADHD is still actively debated. To clarify whether late-onset ADHD forms a different category from childhood-onset ADHD, investigation on early factors differentiating these conditions is necessary.

In the current study, I aimed to better characterise late-onset ADHD by examining early childhood characteristics and adolescent outcomes associated with late-onset ADHD and childhood-onset ADHD. I divided late-onset ADHD into “de novo late-onset ADHD” if there were 0-2 inattention or hyperactivity/impulsivity symptoms in childhood, and “subthreshold late-onset ADHD” if there were 3-5 inattention or hyperactivity/impulsivity symptoms in childhood. I then investigated what early childhood factors predicted an increase in ADHD symptom development in the late-onset ADHD groups. The final analysis contrasted similarity and differences among three mutually exclusive developmental categories of ADHD (de novo late-onset ADHD, subthreshold late-onset ADHD and childhood-onset persistent ADHD) and non-ADHD controls.

2.2 Material and methods

2.2.1 Study Sample

This study used data from the Twins Early Development Study (TEDS), a UK population representative cohort of twins. 13,694 families were recruited between 1994 and 1996 in England and Wales and receive multiple waves of assessments from birth (Haworth *et al.*, 2013). The current study used data collected from birth to age 16 years. After excluding participants with extreme pre-/perinatal conditions, missing at ADHD ratings in childhood (age 8 or age 12) and adolescence (age 14 or age 16), the final study sample comprised a total of 9,875 individuals. ADHD symptoms were lower in the study sample compared with the initial sample, but the effect sizes of the differences were close to zero (Cohen’s d 0.02-0.07). The selected sample in this study was fairly representative of the UK population (Appendix 1.1).

All procedures involving human subjects were approved by the Institute of Psychiatry, Psychology and Neurosciences Ethics Committee at King's College London Psychology and Neuroscience Department. Written informed consent was acquired from parents prior to data collection.

2.2.2 Measures

2.2.2.1 ADHD symptoms

ADHD symptoms were assessed using the ADHD subscale of the Revised Edition of Conners' Parent Rating Scale (CPRS-R) (Conners *et al.*, 1998). The CPRS-R is a screening instrument derived from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for childhood behavioural problems (Conners, 1997). The ADHD index was calculated from 18 items (9 items for inattention and 9 items for hyperactivity/impulsivity) from the CPRS-R to provide a comprehensive assessment of ADHD-related behaviours. Each item was evaluated by the twins' parents on a 4-point Likert scale based on the frequency of question behaviours, with 0 as "not at all" to 3 as "very much true". The CPRS-R has been proved to effectively discriminate ADHD children from no-ADHD controls in different studies (Chang *et al.*, 2016, Gau *et al.*, 2006). Parent-reported ADHD symptoms were also shown to have better concordance with youth-reported ADHD symptoms than teachers' reports (Kaner, 2011). The internal consistency of the scales was assessed separately in this study at each age (approximate 8, 12, 14 and 16 years) and for each symptom domain using standardised Cronbach alphas, which ranged between 0.88 and 0.91 for inattention and 0.81 and 0.84 for hyperactivity/impulsivity.

2.2.2.2 Early childhood characteristics

Early childhood characteristics that have been reported to associate with late-onset ADHD were selected, including sex, general cognitive performance, childhood behavioural problems and family socioeconomic status (Agnew-Blais *et al.*, 2016, Caye *et al.*, 2016b) (Moffitt *et al.*, 2015). I also included factors associated with childhood-onset persistent ADHD in the current study to contrast the similarity and difference between late-onset ADHD and childhood-onset ADHD. These factors included perinatal adversity, parental psychopathology and harsh parenting (Larsson *et al.*, 2011, Richards *et al.*, 2014, Sagiv *et al.*, 2013).

Overall, childhood characteristics in the current study can be categorised into 1) prenatal and perinatal factors, 2) family environmental factors and 3) emotional and behavioural characteristics.

2.2.2.3 Prenatal and perinatal factors

Prenatal and perinatal factors included birth weight and a composite score reflecting maternal medical problems during pregnancy and childbirth. The maternal health risk composite score comprised the following measures: alcohol and tobacco use during pregnancy, pregnancy-related medical complications, psychological distress during pregnancy, whether there was a fertility treatment before pregnancy and slow growth of the baby. A higher score suggested higher maternal health risk related to pregnancy and childbirth.

2.2.2.4 Family environmental factors

I used family socioeconomic status, maternal depression and harsh parenting to reflect family environmental risks. Family socioeconomic status (SES) was the standardised

composite score derived from the sum of parents' highest educational qualifications and parents' occupational classification collected at the initial contact.

Maternal depression was evaluated using the 10-item Edinburgh Postnatal Depression Scale (Cox *et al.*, 1987). The questionnaire evaluates how the mother felt during the previous one week before assessment. Each item is scored on a 0 to 3 Likert scale, with a total score higher than 12 indicating possible maternal depression. The current study used the standardised average of the scores collected when the study participants were 3 and 4 years old.

Harsh parenting was assessed via parents' responses on an adapted questionnaire tapping the frequency (1: rarely or never; 5: usually) of parental disciplinary strategies ('smacking and slapping' and 'telling off and shouting') when the child misbehaved (Deater-Deckard *et al.*, 1998). The final scores were derived from the standardised average of the reports across age 3, 4 and 7.

2.2.2.5 *Emotional and behavioural characteristics*

This category included general cognitive performance, behavioural and emotional problems of the study participants.

General cognitive performance in early childhood was the standardised average of parent-based MacArthur Communicative Development Inventory (MCDI: UK short form) for verbal performance (Fenson *et al.*, 2000) and the Parent Report of Children's Abilities (PARCA) (Saudino *et al.*, 1998) for non-verbal performance assessed at ages 2, 3 and 4 years.

Behavioural and emotional problems were derived from the parent-reported Strengths and Difficulties Questionnaires (SDQ) (Goodman, 2001). The SDQ is a brief behavioural screening measure to assess different psychological adjustment of children and adolescents

aged 4 to 16 years old. The SDQ can be divided into five subscales: conduct problems, hyperactivity/inattention, emotional symptoms/anxiety, peer problems, and prosocial behaviours with 5 items for each subscale. Each item is rated on a 3-point Likert scale (0 for Not true, 1 for Somewhat True and 2 for Certainly True) (Goodman, 1999). We used the average parent-reported SDQ scores collected at ages 4 and 7 years to index emotional and behavioural problems in early childhood. The final analysis did not include ratings of the hyperactivity/inattention subscale because of its overlapping construct with the CPRS-R.

2.2.2.6 Adolescent outcomes

Adolescent outcomes were assessed at age 16 years, which included 1) general cognitive performance, 2) academic performance and 3) co-occurring emotional and behavioural problems.

2.2.2.7 *General cognitive performance*

General cognitive performance was the standardised average scores of Raven's Progressive Matrices test (Raven, 1938, Van der Elst *et al.*, 2013) for non-verbal IQ and the WISC-III-PI vocabulary test (Kaplan, 1999) for verbal IQ.

2.2.2.8 *Academic performance*

Academic performance was assessed using the standardised scores of the General Certificate of Secondary Education (GCSE), a standardised examination in the UK taken by students at the end of compulsory education. The current study used the average score of GCSE on three compulsory core subjects: English, mathematics and science. The GCSE scores were obtained by questionnaires sent via mail and by telephone interviews of parents and study participants.

The GCSE grades (G to A*) were converted to grade coding (4 to 11, with G corresponding to 4 and A* to 11) in the TEDS sample to unify all the pass grades from different qualification types (e.g. NVQ, Functional Skills etc.). More details can be found at <http://www.teds.ac.uk>. Self-reported GCSE scores of the TEDS participants showed high reliability, with a correlation of 0.98 for English and 0.99 for mathematics with data obtained from a subsample of the National Pupil Database (NPD: <https://www.gov.uk/government/collections/national-pupil-database>).

2.2.2.9 *Co-occurring emotional and behavioural problems*

I used parent-reported SDQ for conduct problems, peer relational problems and emotional/anxiety problems at age 16 years to reflect emotional and behavioural problems in adolescence. In addition, I included the short-version Mood and Feeling Questionnaire (MFQ) (Angold *et al.*, 1996) collected from parents and youth participants to assess depressive symptoms, and the Anxiety-Related Behaviours Questionnaire (ARBQ) (Eley *et al.*, 2003) from parents to assess anxiety-related behaviours of the youth participants.

The MFQ consists of 13 questions tapping core depressive symptoms in the past two weeks. Each item is rated on a 3-point Likert scale, with 0 for “not true”, 1 for “sometimes true” and 2 for “true”. Higher scores on the MFQ suggest more severe depressive symptoms. The ARBQ is comprised of 19 items with a total score ranging 0 to 38. Previous analysis showed a five-factor structure of the ARBQ reflecting symptoms of anxiety disorders and anxiety temperament: negative cognition, negative affect, fear, social anxiety and obsessive-compulsive behaviour (Hallett *et al.*, 2009).

2.2.3 Statistical Analysis

2.2.3.1 ADHD categories

The study categorised participants according to their ADHD symptom ratings on the CPRS-R in childhood (age 8 and 12) and adolescence (age 14 and 16).

First, I recoded the CPRS-R ratings to relate to symptom counting in the DSM system: endorsement of 0 or 1 on the CPRS-R was recoded as 0 (not indicative of symptom presence), while endorsement of 2 or 3 was recoded as 1 (indicative of symptom presence) (Conners, 1997).

Second, I obtained separate sum scores for inattention and hyperactivity/impulsivity domains. If more than four out of nine items in either domain (inattention or hyperactivity/impulsivity) were unanswered, the sum score of that domain was recoded as missing. Sum score of the recoded items takes a value ranging from 0 to 9 for inattention and hyperactivity/impulsivity respectively.

Third, sum scores were divided into three levels according to the suggestive threshold in the literature (Takeda *et al.*, 2015): 6 and more as clinically significant, 3 to 5 as subthreshold and 0 to 2 as low. For the objectives of this study, I selected the following four groups for further analysis (7084 out of 9875 eligible participants):

- Non-ADHD controls: participants with low ADHD symptom level (sum score 0-2) across childhood and adolescence.
- De novo late-onset ADHD: individuals with a low level of ADHD symptoms (sum scores 0-2) across childhood (age 8 and age 12) who developed significant ADHD symptoms (6 and more) in adolescence (by age 14 or age 16).
- Subthreshold late-onset ADHD: individuals with a subthreshold level (sum score 3-5) of ADHD symptoms in childhood (by age 8 or age 12) who developed significant ADHD symptoms (sum score 6 and more) in adolescence (by age 14 or age 16).

- Childhood-onset persistent ADHD: individuals with a significant level of ADHD symptoms (sum score 6 and more) in both childhood (age 8 or age 12) and adolescence (age 14 or age 16).

The number of participants with other combinations of the recoded CPRS-R scores can be found in Appendix 1.2.

2.2.3.2 Data analysis

Analyses were performed with R Software Version 3.4.0 (Team, 2017). I fitted multinomial regression models with ADHD categories as the dependent variable using the package ‘multgee’ (Generalised estimating equations (GEE) solver for correlated nominal or ordinal multinomial responses, version 1.5.0) (Touloumis, 2014). Because the two twins from the same family were treated as independent individuals in this study, I used GEE modelling to account for the non-independence within twin pairs by setting the covariance structure to ‘exchangeable’ (i.e. no specific order within the pair) so that comparison between each twin and its co-twin is less biased. In addition, I computed robust standard errors to account for correlated residuals due to non-independence of the twin data.

The analyses were performed in three steps: 1) pairwise comparison between de novo late-onset ADHD, subthreshold late-onset ADHD, childhood-onset persistent ADHD and non-ADHD controls in terms of childhood characteristics and adolescent outcomes, 2) multinomial logistic regression to examine early childhood characteristics predictive of de novo late-onset ADHD and subthreshold late-onset ADHD, with non-ADHD controls as the reference group, 3) multinomial logistic regression between three ADHD groups using childhood-onset persistent ADHD as the reference group to contrast similarity and differences in early childhood characteristics between childhood-onset and late-onset ADHD.

2.3 Results

2.3.1 Descriptive statistics and pairwise comparison of early childhood characteristics and adolescent outcomes

Demographics and descriptive statistics of the early childhood characteristics for non-ADHD controls and the three mutually exclusive ADHD groups (de novo late-onset, subthreshold late-onset and childhood-onset persistent ADHD) are summarised in Table 2.1. Among a total of 9875 study participants 65.9% ($n=6,509/9,875$) did not meet ADHD symptom threshold from childhood to adolescence, 1.2% ($n=123/9,875$) were de novo ADHD, 1.7% ($n=164/9,875$) were subthreshold late-onset ADHD, and 2.9% ($n=288/9,875$) were childhood-onset persistent ADHD.

Table 2.1 also shows pairwise comparison of childhood characteristics between the study groups. The pairwise comparison between the three ADHD groups and non-ADHD controls showed a congruent pattern. First, the proportion of males was significantly higher in the three ADHD groups. Second, more family environmental adversity (lower SES, more disciplinary parenting and higher parental psychopathology) was found in individuals with ADHD. Finally, individuals with ADHD regardless of the age-of-onset presented poorer cognitive performance and elevated emotional and behavioural problems in childhood than non-ADHD controls.

The pairwise comparison among the three ADHD groups were heterogeneous and more informative. First, more differences can be found between de novo late-onset ADHD vs. childhood-onset persistent ADHD than between subthreshold late-onset ADHD vs. childhood-onset persistent ADHD. For example, male-to-female ratio was higher in childhood-onset persistent ADHD than in de novo late-onset ADHD, but the proportion was

not statistically different between subthreshold late-onset ADHD and childhood-onset persistent ADHD. Second, de novo late-onset ADHD experienced more family environmental adversity than the other two ADHD groups, in particular, family SES. Third, childhood behavioural problems were the most severe in childhood-onset persistent ADHD, followed by subthreshold late-onset ADHD and then de novo late-onset ADHD.

Adolescent outcomes with pairwise comparison of the four study categories can be found in Table 2.2. Pairwise comparison between the three ADHD groups against non-ADHD controls showed more severe emotional and behavioural problems than non-ADHD controls, similar to the patterns in childhood. On the contrary, comparison of adolescent outcomes among the three ADHD groups showed different patterns from the results in childhood. The three ADHD groups became less distinguishable in terms of emotional and behavioural problems at age 16 years. The three ADHD groups were only different in GCSE scores, where childhood-onset persistent ADHD demonstrated the worst performance.

Table 2.1 Childhood characteristics with pairwise comparison of non-ADHD controls, late-onset ADHDs and persistent ADHD

	No ADHD n=6509	Late-onset ADHD				Persistent ADHD n=288	De novo vs. Persistent effect size	Subthreshold vs. persistent effect size	De novo vs. subthreshold effect size	
		De novo n=123	effect size	Subthreshold n=164	effect size					
Pre/perinatal factors										
Male sex, No. (%)	2595(40%)	70(57%)	0.05***	110(67%)	0.09***	211(73%)	0.14***	0.16***	0.07	0.10
Birth weight (kg), mean (SD)	2.53(0.53)	2.51(0.56)	0.05	2.57(0.51)	0.06	2.48(0.56)	0.10	0.05	0.16	0.11
Maternal health risk during pregnancy mean (SD)	-0.13(0.95)	0.07(0.99)	0.21*	-0.07(0.96)	0.06	0.13(1.03)	0.27***	0.05	0.20*	0.15
Family environment										
Single parenthood, No. (%)	278(4%)	11(9%)	0.03*	13(8%)	0.03*	31(11%)	0.06***	0.03	0.05	0.02
SES, mean (SD)	0.02(0.88)	-0.37(0.87)	0.44***	-0.19(0.90)	0.24**	-0.26(0.90)	0.32***	0.12	0.08	0.20
Harsh parenting, mean (SD)	-0.15(0.73)	0.09(0.81)	0.33***	0.41(0.85)	0.77***	0.42(0.79)	0.77***	0.41***	0.002	0.39**
Maternal depression, mean (SD)	6.65(4.14)	8.18(4.44)	0.37***	9.11(4.72)	0.65***	9.36(4.79)	0.59***	0.25*	0.05	0.20
Clinical characteristics										
General cognitive performance, mean (SD)	0.14(0.85)	-0.17(0.84)	0.37***	-0.16(0.94)	0.36***	-0.25(0.98)	0.46***	0.08	0.09	0.02

	No ADHD n=6509	Late-onset ADHD				Persistent ADHD n=288	De novo vs. Persistent effect size	Subthreshold vs. persistent effect size	De novo vs. subthreshold effect size	
		De novo n=123	effect size	Subthreshold n=164	effect size					
Childhood SDQ, mean (SD)										
Conduct problems	1.42(1.15)	2.16(1.26)	0.64***	2.63(1.54)	1.03***	3.13(1.78)	1.45***	0.59***	0.30**	0.33*
Emotional/ Anxiety	1.58(1.32)	2.03(1.30)	0.34**	2.13(1.59)	0.41**	2.28(1.75)	0.52***	0.15	0.09	0.07
Peer problems	0.98(1.08)	1.37(1.30)	0.36**	1.41(1.26)	0.39***	1.87(1.51)	0.81***	0.34**	0.32**	0.03
Prosocial behaviours	7.96(1.52)	7.53(1.68)	0.28**	7.26(1.76)	0.46***	7.20(1.73)	0.50***	0.19	0.03	0.16

Note. This table presents results from the comparison with non-ADHD controls. SES, socioeconomic status. SDQ, Strengths and Difficulties Questionnaire. De novo late-onset ADHD, between 0 and 2 inattention and hyperactivity symptom at age 8 and age 12. Subthreshold late-onset ADHD, 3-5 inattention and hyperactivity symptoms at age 8 and/or 12. Effect size (Cohen's d) was calculated for continuous variables and Cramer's phi was calculated for categorical variables, *p<0.05, **p<0.01, ***p<0.001.

Table 2.2 Adolescent outcomes with pairwise comparison of non-ADHD controls, late-onset ADHD and childhood-onset persistent ADHD

	No ADHD n=6509	Late-onset ADHD				Persistent ADHD n=288	De novo vs. Persistent effect size	Subthreshold vs. persistent effect size	De novo vs. subthreshold effect size	
		De novo n=123	effect size	Subthreshold n=164	effect size					
General cognitive performance, mean (SD)	0.13(0.97)	-0.33(0.94)	0.48**	-0.38(0.92)	0.53***	-0.31(1.05)	0.46***	0.02	0.07	0.05
GCSE scores, mean (SD)	9.21(1.13)	8.28(1.16)	0.82***	8.32(1.22)	0.79***	7.94(1.31)	1.12***	0.27*	0.30**	0.03
SDQ, mean (SD)										
Conduct problems	0.88(1.08)	2.80(2.01)	1.75***	2.70(1.83)	1.65***	2.92(2.19)	1.78***	0.05	0.11	0.06
Emotional/Anxiety	2.70(2.21)	3.38(2.37)	0.30**	3.15(2.49)	0.20	3.05(2.49)	0.16	0.13	0.04	0.09
Peer problems	1.38(1.37)	2.00(1.77)	0.45***	2.05(1.87)	0.48***	2.23(1.90)	0.61***	0.12	0.10	0.02
Prosocial behaviours	8.53(1.76)	7.47(2.25)	0.60***	6.70(2.36)	1.03***	6.82(2.43)	0.95***	0.27	0.05	0.33
Self-report MFQ, mean (SD)	3.42(4.27)	4.98(5.41)	0.36**	5.10(5.58)	0.39***	5.07(5.46)	0.38***	0.02	0.005	0.02
Parent-report MFQ, mean (SD)	0.64(1.79)	2.77(3.96)	1.15***	2.71(3.13)	1.13***	3.31(3.98)	1.38***	0.14	0.16	0.02
Parent report ARBQ, mean (SD)	2.87(3.46)	6.16(4.72)	0.94***	5.52(5.39)	0.75***	6.46(6.63)	0.99***	0.05	0.15	0.13

Note. This table presents results from the comparison with non-ADHD controls. SES, socioeconomic status. SDQ, Strengths and Difficulties Questionnaire. De novo late-onset ADHD, between 0 and 2 inattention and hyperactivity symptom at age 8 and age 12. Subthreshold late-onset ADHD, 3-5 inattention and hyperactivity symptoms at age 8 and/or 12. Effect size (Cohen's d) was calculated for continuous variables and Cramer's phi was calculated for categorical variables, *p<0.05, **p<0.01, ***p<0.001.

2.3.2 Childhood characteristics predicting late-onset ADHD

Early childhood predictors for de novo late-onset ADHD, subthreshold late-onset ADHD, and childhood-onset persistent ADHD from non-ADHD controls are shown in Table 2.3. Male sex and higher childhood conduct problems were common predictors for the three ADHD groups. And for each ADHD group, lower family SES (OR 0.70, 95%CI 0.54-0.90, $p=0.006$) differentiated de novo late-onset ADHD from non-ADHD controls, while harsh parenting (OR 1.81, 95%CI 1.37-2.39, $p<0.001$) and higher maternal depression (OR 1.07, 95%CI 1.03-1.11, $p=0.001$) predicted subthreshold late-onset ADHD. More factors differentiated childhood-onset persistent ADHD from non-ADHD controls, including lower birth weight (OR 0.74, 95%CI 0.55-0.99, $p=0.043$), single parenthood (OR 1.93, 95%CI 1.10-3.36, $p=0.021$), harsh parenting (OR 1.51, 95%CI 1.23-1.85, $p<0.001$), higher maternal depression (OR 1.06, 95%CI 1.02-1.10, $p=0.002$) and peer problems (OR 1.31, 95%CI 1.19-1.46, $p<0.001$).

Table 2.3 Early childhood predictors for late-onset ADHD and persistent ADHD

	De novo late-onset ADHD			Subthreshold late-onset ADHD			Persistent ADHD		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
Perinatal factors									
Male sex, No. (%)	2.13	1.41-3.21	<0.001	2.67	1.85-3.85	<0.001	4.47	3.24-6.17	<0.001
Birth weight, mean (SD)	0.90	0.58-1.39	0.623	1.06	0.74-1.52	0.736	0.74	0.55-0.99	0.043
Maternal health risk during pregnancy	1.07	0.83-1.37	0.614	0.99	0.82-1.2	0.923	1.12	0.94-1.32	0.198
Family environment									
Single parenthood, No. (%)	1.59	0.74-3.39	0.231	1.04	0.48-2.26	0.918	1.93	1.10-3.36	0.021
SES, mean (SD)	0.70	0.54-0.90	0.006	1.03	0.84-1.27	0.775	1.10	0.93-1.3	0.288
Harsh parenting, mean (SD)	1.21	0.90-1.63	0.214	1.81	1.37-2.39	<0.001	1.51	1.23-1.85	<0.001
Maternal depression, mean (SD)	1.04	0.99-1.09	0.146	1.07	1.03-1.11	0.001	1.06	1.02-1.10	0.002
Clinical characteristics									
General cognitive performance, mean (SD)	0.86	0.68-1.08	0.190	0.91	0.73-1.12	0.368	0.84	0.70-1.00	0.050
Childhood SDQ, mean (SD)									
Conduct problems	1.22	1.06-1.40	0.004	1.46	1.28-1.67	<0.001	1.74	1.55-1.95	<0.001

	De novo late-onset ADHD			Subthreshold late-onset ADHD			Persistent ADHD		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
Emotional/ Anxiety	1.13	0.98-1.30	0.082	1.11	0.98-1.25	0.101	1.10	0.99-1.23	0.077
Peer problems	1.10	0.93-1.30	0.247	1.02	0.88-1.18	0.815	1.31	1.19-1.46	<0.001
Prosocial behaviours	0.97	0.85-1.11	0.668	0.90	0.81-1.01	0.069	1.00	0.91-1.09	0.929

Note. This model presents estimates of the multinomial regression with non-ADHD controls as the reference group. SES, socioeconomic status. SDQ, Strengths and Difficulties Questionnaire. De novo late-onset ADHD, less than 3 inattention and hyperactivity symptom at age 8 and age 12. Subthreshold late-onset ADHD, 3-5 inattention and hyperactivity symptoms at age 8 and/or 12.

2.3.3 Similarity and differences between late-onset ADHD and childhood-onset persistent ADHD

Childhood characteristics differentiating late-onset ADHD from childhood-onset persistent ADHD are shown in Table 2.4. Compared with persistent ADHD, de novo late-onset ADHD was less likely to be found in males (OR 0.48, 95%CI 0.29-0.79, $p=0.004$) and can be predicted by lower family SES (OR 0.64, 95%CI 0.47-0.86, $p=0.003$) and fewer childhood conduct problems (OR 0.70, 95%CI 0.59-0.83, $p<0.001$). Factors differentiating subthreshold late-onset ADHD from persistent ADHD included male sex (OR 0.6, 95%CI 0.37-0.95, $p=0.030$), childhood conduct problems (OR 0.84, 95%CI 0.71-0.99, $p=0.036$) and peer problems (OR 0.77, 95%CI 0.66-0.91, $p=0.002$).

Table 2.4 Early childhood predictors differentiating late-onset from persistent ADHD

Childhood characteristics	De novo late-onset ADHD ^a vs. Persistent ADHD			Subthreshold late-onset ADHD ^b vs. persistent ADHD		
	OR ^c	95%CI	P value	OR	95%CI	P value
Perinatal factors						
Male sex, No. (%)	0.48	0.29-0.79	0.004	0.6	0.37-0.95	0.030
Birth weight, mean (SD)	1.21	0.73-2	0.460	1.43	0.93-2.22	0.106
Maternal health risk during pregnancy	0.96	0.71-1.28	0.764	0.89	0.7-1.12	0.318
Family environment						
Single parenthood, No. (%)	0.83	0.34-2.02	0.67	0.54	0.23-1.28	0.163
SES, mean (SD)	0.64	0.47-0.86	0.003	0.94	0.73-1.21	0.629
Harsh parenting, mean (SD)	0.8	0.56-1.15	0.226	1.2	0.87-1.66	0.265
Maternal depression, mean (SD)	0.98	0.93-1.03	0.435	1.01	0.96-1.06	0.690
Clinical characteristics						
General cognitive performance, mean (SD)	1.03	0.77-1.36	0.860	1.08	0.83-1.41	0.560
Childhood SDQ, mean (SD)						
Conduct problems	0.7	0.59-0.83	<0.001	0.84	0.71-0.99	0.036
Emotional/Anxiety	1.02	0.87-1.21	0.777	1	0.86-1.17	0.958
Peer problems	0.84	0.7-1.01	0.061	0.77	0.66-0.91	0.002
Prosocial behaviours	0.97	0.83-1.14	0.747	0.91	0.8-1.04	0.150

Note. This model presents estimates of the multinomial regression with childhood-onset persistent ADHD as the reference group. SES, socioeconomic status. SDQ, Strengths and Difficulties Questionnaire. De novo late-onset ADHD, less than 3 inattention and hyperactivity symptom at age 8 and age 12. Subthreshold late-onset ADHD, 3-5 inattention and hyperactivity symptoms at age 8 and/or 12.

2.4 Discussion

This study aimed to better characterise late-onset ADHD through contrasting early childhood characteristics and adolescent outcomes between de novo late-onset ADHD, subthreshold late-onset ADHD, childhood-onset persistent ADHD and non-ADHD controls. Using multinomial logistic regression, this study further investigated which early childhood factor predicted an increase in ADHD symptoms across the development. The results showed that de novo late-onset ADHD and subthreshold late-onset ADHD were more likely to be found as male, as well as in children with increased childhood conduct problems and adverse family environment compared to non-ADHD controls. Although de novo late-onset ADHD and subthreshold late-onset ADHD showed fewer behavioural problems in early childhood compared to childhood-onset persistent ADHD, the three ADHD groups presented similar levels of behavioural and emotional problems in adolescence. Among early childhood predictors, low family socioeconomic status was specific to de novo late-onset ADHD, while harsh parenting and maternal depression were specific to subthreshold late-onset ADHD. Additional childhood predictors were identified for childhood-onset persistent ADHD.

2.4.1 Early childhood characteristics and adolescent outcomes of late-onset ADHD

Findings of this study support that ADHD symptoms can first emerge in the adolescent years. Furthermore, this study found childhood factors differentiating late-onset ADHD from childhood-onset ADHD and late-onset ADHD with different levels of childhood symptoms. It is noteworthy that even with very few childhood ADHD symptoms, de novo late-onset ADHD can already be differentiated from non-ADHD controls by showing higher levels of behavioural and emotional problems in early childhood.

Interestingly, the level of co-occurring childhood behavioural problems were related to the level of childhood ADHD symptoms: childhood-onset persistent ADHD had the highest ratings of conduct and peer problems, followed by subthreshold late-onset ADHD, and then de novo late-onset ADHD. These findings correspond to previous research showing that childhood ADHD symptoms and related psychosocial impairment are dimensionally distributed in the population (Noren Selinus *et al.*, 2016). However, findings were different in terms of adolescent outcomes. Unlike the presentations in childhood, de novo late-onset ADHD, subthreshold late-onset ADHD and childhood-onset persistent ADHD exhibited similar levels of conduct problems, peer problems, depression and anxiety psychopathology at age 16 years. This suggests that the increase in ADHD symptoms was in concert with the increase in comorbid emotional and behavioural problems. The finding that late-onset ADHD experienced impairment as severe as childhood-onset persistent ADHD in adolescence carries an important message: early identification and intervention for children at risk of an increasing ADHD symptom development is needed to prevent undesirable outcomes. Furthermore, the co-development of ADHD symptoms and other psychopathology warrants further investigation into risk factors underlying a common psychopathological liability or a feedback network formed by dimension of symptoms to explain psychiatric comorbidity developing over time (Borsboom, 2017) (Caspi *et al.*, 2014).

2.4.2 Childhood factors predicting late-onset ADHD

In addition to male sex and increased childhood conduct problems, I found other childhood characteristics predicting de novo late-onset ADHD and subthreshold late-onset ADHD from non-ADHD controls. Interestingly, the number of independent early childhood predictors was related to the levels of childhood ADHD symptoms: more predictors were

found for individuals with childhood-onset persistent ADHD, followed by subthreshold late-onset ADHD, and finally de novo late-onset ADHD, who exhibited very few childhood ADHD symptoms. However, the fact that there were fewer predictors for the late-onset ADHD categories compared to childhood-onset persistent ADHD implies that early childhood risk factors may not be sufficient to predict late-onset symptoms. As age-specific genetic and environmental influences also contribute to ADHD symptom development (Pingault *et al.*, 2015a), it is possible that late-onset ADHD symptoms are in part attributable to time-varying risk factors across the development, whether environmental (e.g. school transitions) (Langberg *et al.*, 2008) or biological (e.g. genetic) (Greven *et al.*, 2011), as reflected in developmental changes at the neurobiological level (Shaw *et al.*, 2013). As such, research which incorporates time-varying covariates (Brammer *et al.*, 2016) with a developmentally sensitive design is warranted to better understand the developmental processes of late-onset ADHD. Moreover, the finding that environmental risk factors for de novo late-onset ADHD did not completely overlap those for subthreshold late-onset ADHD suggest potentially distinct aetiological pathways involved in the two conditions. Together with the finding that different polygenic risk scores for ADHD are associated with different ADHD phenotypes, investigation on unique genetic and environmental contribution to late-onset ADHD symptomatology may advance our understanding towards aetiology (Riglin *et al.*, 2016, Vuijk *et al.*, 2019).

2.4.3 The role of low socioeconomic status on the development of late-onset ADHD

Previous studies showed that SES was strongly related to the onset of psychiatric disorders in childhood and adolescence and that parental education was predictive of the

severity of psychiatric disorder in offspring (McLaughlin *et al.*, 2011). Neurobiological studies also indicated that low family income and low parental education may pose enduring impacts on neurodevelopment in offspring (Noble *et al.*, 2012) (Noble *et al.*, 2015). Findings of this study are in support of the aforementioned reports. More importantly, this study suggests that the negative impact of low SES in early childhood may linger and lead to deterioration of attention and impulse control to a significant level later in life. However, other potential explanations should also be considered. It is possible that the negative influences of low SES on neurodevelopment were small and thereby unidentified in early childhood until the individuals failed to cope with increased cognitive and environmental demands in adolescence. Alternatively, children with low SES and high ADHD symptoms early in life were inadequately represented in the current study, so that the findings only reflect bias of sample selection. To arbitrate between these alternative explanations, further research and replication studies are needed.

It is noteworthy that findings of the current study are at odds with the argument that late-onset ADHD simply uncovers 'masked' childhood-onset cases. Such argument stipulates that a protective family environment or better cognitive ability can help ADHD children to compensate better in childhood and make early diagnosis more difficult (Kosaka *et al.*, 2018). In contrast, this study found that de novo late-onset ADHD had lower SES than non-ADHD controls. The role of SES in creating a challenging early environment is well documented and SES has been linked to increased health-related adversity and a range of mental health problems including ADHD (Hagan *et al.*, 2016) (Luby *et al.*, 2017). In addition, the finding that harsh parenting and maternal depression also linked to subthreshold late-onset ADHD further supports the role of adverse parental influences in the development of ADHD symptoms in their offspring (Tung *et al.*, 2015, Wolford *et al.*, 2017). Altogether, these findings add to the accumulating evidence showing that exposure to family

environmental adversity in the early stage of life may increase the risks of long-term mental health problems (Sharp *et al.*, 2019) and that interventions targeting low socioeconomic status may have an impact on curbing the development of mental health problems, including late-onset ADHD.

Nevertheless, some caution needs to be taken when interpreting the prediction effects of low SES on de novo late-onset ADHD symptoms. Previous research has documented associations between low socioeconomic status, poorer parental involvement in education and lower level of parent-child connectedness (Chen *et al.*, 2018b). It is therefore possible that parents from a lower socioeconomic background are inadequately involved and thus under-report ADHD symptoms of their children. As such, the finding that low SES predicting de novo late-onset ADHD can be attributable to systematic bias in the reporting rather than actual impact of low SES on the development of late-onset ADHD symptoms. However, evidence also indicates that parents with lower income perceived more severe behavioural problems of their school aged children than teachers (Stone *et al.*, 2013) and that low SES is associated with higher levels of other mental health problems in childhood (Reiss, 2013). Hence, the link between low SES and late-onset ADHD is unlikely only due to lack of awareness or under-reporting of the parents. Combining observation from school teachers and the use of multidimensional assessments can help to delineate to what extent low SES conferring to a higher risk of late-onset ADHD and how inequality associated with low SES affects parents' reports.

2.5 Limitations

Several limitations should be considered when interpreting the results. First, participants were categorised into different ADHD groups based on parent-rated CPRS-R in childhood and adolescence. The sole reliance on parent reports may affect the reliability of ADHD diagnosis, especially in retrospective studies and in adult samples (Angold *et al.*, 1996). However, parental ratings on the CPRS-R have been demonstrated to differentiate ADHD cases and non-cases with moderate to high accuracy among children and adolescents (Chang *et al.*, 2016). Using parental reports across the follow-up also has the benefit of informant consistency. Second, ADHD diagnosis was based on questionnaires that did not include other criteria such as functional impairment and situational pervasiveness, which may result in false positive or negative diagnosis (Parker and Corkum, 2016). We categorised subthreshold ADHD based on symptom levels with cut-off thresholds of 3 to 5 symptoms in either inattention or hyperactivity/impulsivity domain. Although these cut-off values have been widely used in previous studies, they remain, to some extent, arbitrary. Therefore, replications using full diagnostic criteria in larger cohorts are needed. Third, analyses were conducted using a population-based twin birth cohort of predominantly white Caucasian individuals in the UK. Consequently, the study results may not generalise to other populations or samples of singletons.

2.6 Conclusion

The finding that divergent childhood characteristics predicted de novo late-onset ADHD, subthreshold late-onset ADHD and childhood-onset persistent ADHD suggests diverse mechanisms underlying the developmental course of ADHD. Although de novo and subthreshold late-onset ADHD differ substantially from childhood-onset persistent ADHD on

a range of co-occurring behavioural problems and cognitive characteristics in childhood, these differences dissipated in adolescence. Distinct childhood risk factors for late-onset ADHD symptomatology inform remediation programmes potential targets to curb the development of ADHD symptoms. Future research into time-varying genetic and environmental factors contributing to the development of ADHD is necessary to better understand the aetiology of late-onset ADHD.

3 Chapter 3: Genetic contributions to the development of inattentive symptoms and its influences on adolescent academic performance

ADHD is a debilitating disorder that brings negative impact across different aspects of affected individuals' lives. One of the common functional impairment associated with ADHD is poor academic performance (Arnold *et al.*, 2020). Current evidence suggests that inattentive symptoms are more specifically associated with poor academic performance, while hyperactive/impulsive symptoms are better predictors of classroom disruption (Garner *et al.*, 2013). There are studies further showing that the developmental patterns of inattention can differentially influence academic performance (Breslau *et al.*, 2010) (Pingault *et al.*, 2014). However, mechanisms explaining the developmental effects of inattention on academic performance remain unclear. This chapter set out to investigate independent influences of the developmental course of inattention from childhood to adolescence on GCSE performance at age 16 years. In addition, this chapter also investigated genetic and environmental underpinnings of the effects of inattention development on academic performance.

This chapter is adapted from a manuscript published in the *Journal of European Child & Adolescent Psychiatry*. This chapter is a collaboration with Ms. Yan Li and the analysis was performed with the syntax modified from Ms. Li's work.

Liu, C. Y., Li, Y., Viding, E., Asherson, P., & Pingault, J. B. (2019). The developmental course of inattention symptoms predicts academic achievement due to shared genetic

aetiology: a longitudinal twin study. European Child & Adolescent Psychiatry, 28(3), 367-375.

Supplementary materials for this chapter are attached in Appendix 2

3.1 Introduction

3.1.1 Academic outcomes of ADHD

Attention-Deficit Hyperactivity Disorder (ADHD) has been associated with a wide range of functional impairment in affected individuals. Among all, poor academic outcome is a common difficulty experienced by youth with ADHD (Biederman *et al.*, 1996) (Loe and Feldman, 2007). Children with ADHD show lower reading and writing performance in standardised tests, higher rates of grade retention and increased utilisation of remedial educational services (Ek *et al.*, 2011, Loe and Feldman, 2007). The level of impairment was positively predicted by the levels of ADHD symptoms (Rennie *et al.*, 2014). More importantly, even when children had outgrown their ADHD symptoms, they may still experience academic difficulties and poor overall school functioning (Wu and Gau, 2013).

It is noteworthy that not all ADHD symptoms exert similar degree of influence on academic outcomes. Current literature suggests a domain-specific relationship between ADHD symptoms and academic outcomes, whereby inattention is more closely linked to cognitive performance (e.g. working memory) and academic performance (e.g. school grades, learning ability), while hyperactivity/impulsivity is associated with externalising behaviours, classroom disruption and peer relational problems at school (Daley and Birchwood, 2010, Garner *et al.*, 2013).

3.1.2 The development of inattention and academic outcomes

In addition to symptom severity, prior studies also examined effects of the development of inattention on academic performance. Breslau *et al.* (Breslau *et al.*, 2010) investigated whether changes in teachers' ratings of inattention between ages 6 and 11 years

predicted changes in math and reading performance between ages 11 and 17 years. Their findings showed that an increase in inattentive symptoms was associated with a decrease in test performance. The study by Pingault et al. (Pingault *et al.*, 2014) examined the associations between the developmental trajectories of inattentive symptom from age 6 to age 12 years and graduation failure at age 22 years. It was shown that individuals with a rising inattention trajectory were at a higher risk of graduation failure (OR 1.76) than those with a stable symptom trajectory. Despite different approaches, both studies converged on the finding that the development of inattentive symptoms contributed greatly to academic impairment. However, neither study investigated mechanisms underlying the developmental effects of inattention on academic performance.

3.1.3 Genetic contributions to the development of inattention and academic performance

Recent advances in genetic analysis have revealed the genetic basis of different disorders and phenotypes. A large proportion of the variance in ADHD and academic performance can be explained by genetic factors, with estimated heritability around 70% to 90 % (Larsson *et al.*, 2014, Nikolas and Burt, 2010) and 65 to 70% (Krapohl *et al.*, 2014) respectively. Genetic factors also contribute greatly to the systematic change in ADHD symptoms, explaining 54% and 81% of the total variance in the developmental course of inattention and hyperactivity/impulsivity respectively (Pingault *et al.*, 2015b). Genetic correlation studies further help to unravel the genetic relationships between different conditions. Evidence of genetic correlations may arise from shared biological pathways or direct causal relationships underlying the phenotypic relationship (van Rheenen *et al.*, 2019). For example, a previous study showed that the phenotypic ($r_p = -0.26$) and genetic

correlations ($r_a = -0.41$) between inattention and math ability were significantly larger than the relationships between hyperactivity/impulsivity and math ability ($r_p = -0.18$, $r_a = -0.22$) (Greven *et al.*, 2014). More importantly, shared genetic risks may explain the stronger associations between inattention and academic performance observed in phenotypic analyses (Polderman *et al.*, 2010). However, whether the unique influence of the development of inattention on academic performance can be attributable to shared genetic contributions has not been investigated.

3.1.4 Study aims

The current study aimed to advance understanding towards the effects of inattention on academic performance. First, this study examined to what extent the developmental course of inattention from childhood to adolescence independently predicts academic performance at age 16 years. Here, the developmental course of inattention referred to the systematic change in symptom levels from childhood to adolescence. Second, this study investigated genetic and environmental contributions to the effects of the developmental course of inattention on academic performance.

3.2 Material and methods

3.2.1 Study Sample

This study used data from the “Twins Early Development Study” (TEDS), a UK population representative cohort of twins. Details of the TEDS cohort can be found in the previous chapter and elsewhere (Haworth *et al.*, 2013). The current study included twin pairs with General Certificate of Secondary Education (GCSE) scores provided for both twins at the end

of compulsory schooling and at least one ADHD symptom assessment at ages 8, 12, 14 and 16 years. Twins with pre- or perinatal complications, severe congenital anomalies, autistic disorder, chromosomal disorders, and those who failed to provide zygosity information were excluded. A total of 5,634 twin pairs were included in the final analysis, of which 36.5% (2057 pairs) were monozygotic (MZ) twins. 46.7% (n=5986) of the total study participants were male, including 912 pairs of male MZ twins and 830 pairs of same-sex male DZ twins. This study also included 966 pairs of same-sex female DZ twins and 1781 pairs of opposite-sex DZ twins (hence 3577 pairs of DZ twins in total).

The study sample was adequately representative of the UK population as compared with the UK census data from the general household survey (Appendix 2.1). Approval was obtained from the Institute of Psychiatry, Psychology and Neurosciences Ethics Committee at King's College London Psychology and Neuroscience Department. Written informed consent was acquired from parents prior to data collection.

3.2.2 Measures

3.2.2.1 Inattentive symptoms

Inattentive symptoms were assessed with the Conners' Parent Rating Scales-Revised (CPRS-R) at ages 8, 12, 14 or 16 years. The CPRS-R comprises 18 items tapping ADHD-related behaviours of the child based on the DSM-IV criteria (Conners *et al.*, 1998). Each item was rated on a 0-3 Likert scale. This study used the sum of the inattention subscale of the CPRS-R, which contains 9 items that describe ADHD-related inattentive symptoms. A higher sum score indicated greater inattention severity. The standardised Cronbach alphas for inattentive symptom ratings across the four assessment time points ranged between 0.87 and 0.90.

3.2.2.2 Academic performance

Academic performance was assessed using scores from the General Certificate of Secondary Education (GCSE) at age 16 years. Data were collected by telephone interviews and mail sent to the twins and their parents. The GCSE grades (G to A*) were converted to grade coding (4 to 11, with G corresponding to 4 and A* to 11) in the TEDS sample to unify all the pass grades from different qualification types (e.g. NVQ, Functional Skills etc.). More details can be found at <http://www.teds.ac.uk>. The self-reported GCSE results were highly correlated with data from the National Pupil database (correlation of 0.98 for English, 0.99 for mathematics, and 0.96 for all sciences) (Rimfeld *et al.*, 2015). This study used the mean score of the three core subjects of the GCSE: mathematics, English and science. Missing GCSE scores can be due to sample attrition, missing from family who chose not to report GCSE results, twins with special educational arrangements or school dropouts. The mean level of inattentive symptoms was higher in twin pairs without GCSE scores, although only to a small degree (Cohen *d* 0.24 to 0.38) (Appendix 2.2).

3.2.3 Data analysis

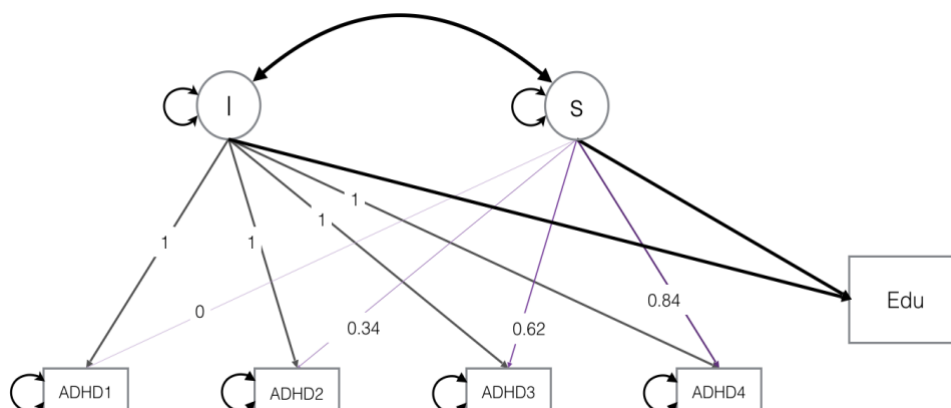
All analyses were performed with R software (Version 3.2.3) (Team, 2014) and the built-in package “Lavaan” (version 0.5-20) (Rosseel, 2012). I applied structured equation modelling (SEM) for the following analyses. Missing data were considered to be missing at random and estimates were computed via full information maximum likelihood (FIML). The goodness-of-fit of the constructed models were assessed using the chi-square (χ^2), comparative fit index (CFI), root mean square error of approximation (RMSEA) and the standardised root mean square residual (SRMR). A model was considered as an adequate fit when $CFI \geq 0.90$, $RMSEA \leq 0.06$ and $SRMR \leq 0.08$ (Bentler, 1990, Hu and Bentler, 1998).

3.2.3.1 Latent growth curve model for the developmental course of inattention

A latent growth curve (LGC) model was built to capture the development of inattentive symptoms. This model estimated the baseline level (latent intercept) and the developmental course (latent slope) of inattentive symptoms across childhood and adolescence (Figure 3.1). Loadings on the latent intercept were fixed to 1 across the four time points (ages 8, 12, 14 and 16), while loadings on the latent slope were fixed at 0, 0.34, 0.62, 0.84 to reflect unequal time spacing so that the value of the latent slope can be interpreted as the average symptom change per decade.

Once the unconditional model was established, it was expanded to include regression parameters to investigate the relationship between the latent intercept and the latent slope with GCSE scores respectively. To account for non-independence of the twin data, relevant parameter constraints were imposed in the model following the procedure described in Olsen and Kenny for exchangeable dyads (Olsen and Kenny, 2006).

Figure 3.1 Latent growth curve model for the development of inattentive symptoms



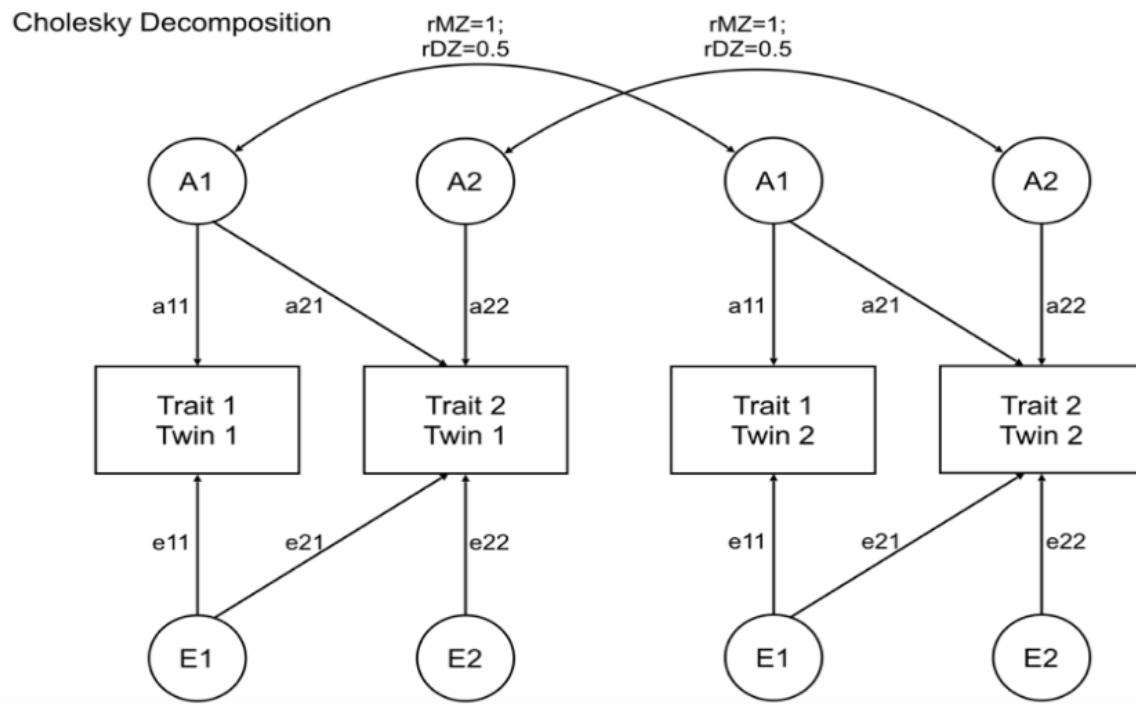
Note. Rectangle variables represent the observed measures in the study: “ADHD 1-4” represent the repeated measures of inattentive symptoms at four time points; “Edu” is the mean GCSE scores. Round variables represent latent factors estimated by the model: “I” represents the intercept; “S” represents the linear slope.

3.2.3.2 Multivariate genetic modelling for genetic and environmental contributions

This part of the analysis was built on the LGC models constructed earlier. I expanded the LGC models into multivariate genetic models to examine genetic and environmental contributions to the relationship of the latent intercept and the latent slope with GCSE scores. Multivariate genetic models can specify the relative contributions of additive genetic (A), dominant genetic (D, part of non-additive genetic effects), shared environmental (C, environmental factors that make the twins similar) and non-shared environmental (E, environmental factors that make the twins different) effects by parsing the phenotypic variance of the observed variables. Basic model specifications also include: 1) genetic (A) correlation for monozygotic (MZ) twins is set to 1 and to 0.5 for dizygotic (DZ) twins; 2) shared environmental (C) correlation is set to 1 for both MZ and DZ twins.

I used the standard Cholesky decomposition (Figure 3.2) (Neale and Cardon, 1992) for the multivariate genetic model. The Cholesky decomposition investigates contributions of genetic continuity (stable genetic contributions) and genetic innovation (new genetic contributions emerging at different ages) to the target phenotypes in longitudinal settings. The multivariate genetic model can (i) separately examine genetic and environmental influences on the latent intercept and the latent slope of inattention, and (ii) determine how much of the variance in GCSE scores was attributable to the genetic and environmental components underlying the developmental course of inattention.

Figure 3.2 Bivariate genetic model with Cholesky decomposition



Note. r_{MZ} is the cross-twin correlation of MZ pairs; r_{DZ} is the cross-twin correlation of DZ pairs. A1 and A2 are genetic contributions; E1 and E2 are non-shared environmental contributions. In Cholesky decomposition, the first set of latent aetiological factors (A1 and E1) can affect all traits, but the second set (A2 and E2) can only affect the second trait. Therefore, the Cholesky decomposition is useful for longitudinal study, when there is specific ordering in aetiological factors.

Because previous studies found the best-fitted genetic model for inattentive symptoms was an ADE model for the current study sample (Pingault *et al.*, 2015b), where dominant genetic effects (D) explained 55% and 35% of the variance in the intercept and the slope of inattentive symptoms. However an ACE model fitted best for GCSE scores, with shared-environmental factors (C) explaining 26% of the variance in GCSE (Krapohl *et al.*, 2014). Given the difference in best-fitting models for inattention and GCSE and the need to model

them simultaneously, this study adopted an AE model to estimate the relationship between inattention symptoms and GCSE.

3.3 Results

3.3.1 Descriptive statistics and phenotypic relationships

A total of 5,634 twin pairs were included in the current analysis (2,057 pairs MZ twins, 3,577 pairs of DZ twins). The descriptive statistics and age-to-age within-twin/cross-twin phenotypic correlations between inattentive symptoms and the GCSE score are presented in Table 3.1 for MZ twins and Table 3.2 for DZ twins. As shown in the tables, the age-to-age correlations of inattention were high for both MZ and DZ twins, indicating a moderate stability for inattention from childhood to adolescence. However, the correlations of inattention at the same age between twins were two times higher in MZ twins than in DZ twins, suggesting that genetic factors contributed considerably to inattentive symptoms. Negative correlations between inattention and GCSE scores were found for both MZ and DZ twins. The cross-twin correlations between GCSE scores and inattention were more negative in MZ twins (-0.31 to -0.20) than DZ twins (-0.11 to -0.06), indicating that higher levels of inattention of one twin at all ages were associated with lower GCSE scores of the co-twin. The cross-twin cross-trait correlation also suggested possible shared genetic contributions between inattention and the GCSE score.

Table 3.1 Phenotypic correlation of inattention and GCSE for MZ twins

MZ	Twin 1					Twin 2				
	8 years	11 years	14 years	16 years	GCSE	8 years	11 years	14 years	16 years	GCSE
Twin 1										
8 years	-	-	-	-	-	-	-	-	-	-
11 years	0.60^a	-	-	-	-	-	-	-	-	-
14 years	0.47	0.67	-	-	-	-	-	-	-	-
16 years	0.42	0.55	0.68	-	-	-	-	-	-	-
GCSE	-0.23	-0.27	-0.31	-0.35	-	-	-	-	-	-
Twin 2										
8 years	<u>0.76^b</u>	0.52	0.43	0.37	<i>-0.20</i>	-	-	-	-	-
11 years	0.52	<u>0.73^b</u>	0.58	0.46	<i>-0.22</i>	0.66^a	-	-	-	-
14 years	0.41	0.54	<u>0.78</u>	0.54	<i>-0.25</i>	0.52	0.70	-	-	-
16 years	0.37	0.43	0.54	<u>0.72</u>	<i>-0.29^c</i>	0.44	0.56	0.70	-	-
GCSE	<i>-0.20^c</i>	<i>-0.22</i>	<i>-0.28</i>	<i>-0.31</i>	0.84	-0.24	-0.25	-0.30	-0.38	-
Mean (MZ)	4.76	5.04	4.55	3.31	8.95	4.86	5.14	4.88	4.08	8.97
SD(MZ)	4.5	4.59	4.66	4.04	1.2	4.73	4.8	5.13	4.76	1.2

Note. MZ: monozygotic twins; GCSE: General Certificate of Secondary Education. Below the diagonal are the MZ twin correlations. The top left and bottom right show the within-individual correlations of inattention for MZ (in bold, for example, correlation between age 8 and age 11 of twin 1 is 0.60 and 0.66 for twin 2, see ^a). The cross-twin correlations of inattention are presented in the diagonal (underlined, for example, correlation between twin 1 and twin 2 is 0.76 at age 8 and 0.73 at age 11, see ^b). The cross-twin correlation between inattention and GCSE is shown in the bottom left matrix (in italics, for example, correlation of inattention of twin 1 at age 8 and GCSE of twin 2 is -0.20; correlation between inattention of twin 2 at age 16 and GCSE of twin 1 is -0.29, see ^c). The results suggested that higher levels of inattention of one twin at all ages were significantly associated with lower GCSE scores of the co-twin. In all cases correlations were significant at $p < .001$.

Table 3.2 Phenotypic correlation of inattention and GCSE for DZ twins

DZ	Twin 1					Twin 2					Mean (DZ)	SD (DZ)	
	8 years	11 years	14 years	16 years	GCSE	8 years	11 years	14 years	16 years	GCSE			
Twin 1	8 years	-	0.63^a	0.55	0.44	-0.27	<u>0.32^b</u>	0.21	0.20	0.16	<i>-0.10^c</i>	4.78	4.46
	11 years	-	-	0.66	0.57	-0.29	0.19	<u>0.32^b</u>	0.22	0.19	<i>-0.08</i>	5.16	4.62
	14 years	-	-	-	0.69	-0.32	0.18	0.22	<u>0.33</u>	0.24	<i>-0.09</i>	4.5	4.49
	16 years	-	-	-	-	-0.32	0.15	0.21	0.21	<u>0.34</u>	<i>-0.08</i>	3.5	4.2
	GCSE	-	-	-	-	-	<i>-0.06</i>	<i>-0.08</i>	<i>-0.08</i>	<i>-0.11^c</i>	0.54	8.9	1.21
Twin 2	8 years	-	-	-	-	-	-	0.65^a	0.58	0.50	-0.27	5.15	4.97
	11 years	-	-	-	-	-	-	-	0.70	0.60	-0.29	5.43	5.1
	14 years	-	-	-	-	-	-	-	-	0.70	-0.32	5.13	5.16
	16 years	-	-	-	-	-	-	-	-	-	-0.34	4.24	4.83
	GCSE	-	-	-	-	-	-	-	-	-	-	8.95	1.22

Note. DZ: dizygotic twins; GCSE: General Certificate of Secondary Education. Above the diagonal are the DZ twin correlations. The top left and bottom right parts show the within-individual correlations of inattention for DZ twins (in bold, for example, correlation between age 8 and age 11 of twin 1 is 0.63 and 0.65 for twin 2, see ^a). The cross-twin correlations of inattention are presented in the diagonal (underlined, for example, correlation between twin 1 and twin 2 is 0.32 at age 8 and 0.32 at age 11, see ^b). The cross-twin correlation between inattention and GCSE is shown in the top right matrix (in italics, for example correlation between inattention of twin 1 at age 8 and GCSE of twin 2 is -0.10; correlation between inattention of twin 2 at age 16 and GCSE of twin 1 is -0.11, see ^c). In all cases correlations were significant at $p < .001$. Cross-twin phenotypic correlation between inattention and GCSE ranged from -0.11 to -0.06 in DZ twins. The results suggested that higher levels of inattention of twin 1 at all ages significantly associated with lower GCSE scores of the co-twin. Compared with Table 3.1, correlations between inattention and GCSE were about twice higher in MZ than in DZ twins, indicating significant genetic overlap between inattention and GCSE scores.

3.3.2 The developmental course of inattention

The estimated initial level (latent intercept) of inattention was 5.26 (95% CI 5.14, 5.38), and the estimated developmental course of inattention (latent slope) was -1.12 (95% CI -1.28, -0.95). Because the loadings to the latent growth slope were scaled to per decade, the negative slope corresponded to a systematic decrease of 1.12 point in the inattention ratings per 10 years, leading to a predicted score of 4.31 at the end of the follow-up (mean age difference between the start and the end of the follow-up was 8.4 years).

3.3.3 The relationship between the development of inattention and GCSE scores

Table 3.3 displays the predictive effects of the intercept and the slope of inattention on GCSE scores. The contributions of both the intercept ($B=-0.13$, 95% CI -0.14, -0.12) and the slope ($B=-0.08$, 95% CI -0.09, -0.07) of inattention to GCSE scores were significant. The findings suggest that a 1-point higher initial level of inattentive symptoms was associated with 0.13-point decrease in GCSE scores. Similarly, a steeper decline in inattentive symptoms across childhood to adolescence (a more negative slope) was associated with higher GCSE scores.

Table 3.3 The prediction of GCSE scores by the development of inattentive symptoms

	B	95% CI	<i>p</i>
Inattention			
Intercept	-0.13	-0.14, -0.12	<0.001
Slope	-0.08	-0.09, -0.07	<0.001

Note. B represents non-standardised regression coefficient; the 95% CIs were obtained by bootstrapping with 5000 replicate draws.

3.3.4 Multivariate genetic models for inattentive symptoms at different ages across childhood to adolescence

A standard AE Cholesky decomposition model was fitted for inattention. Fit indices indicated a well-fit model: $\chi^2(64)=144.54$, $p<0.001$; CFI=0.99; RMSEA=0.021; SRMR=0.077. The standardised genetic and environmental contributions to inattention symptoms in the AE Cholesky model can be found in Table 3.4. The finding of the Cholesky model showed that inattention at different ages was influenced by stable genetic effects as well genetic innovation at each age. The non-shared environmental contributions accounted for 20% to 25% of the total variance of inattentive symptoms (Table 3.4). However, continuity of the non-shared environmental influences from earlier time points were small, ranging from only 1% to 5%.

Table 3.4 AE Cholesky decomposition for inattentive symptoms

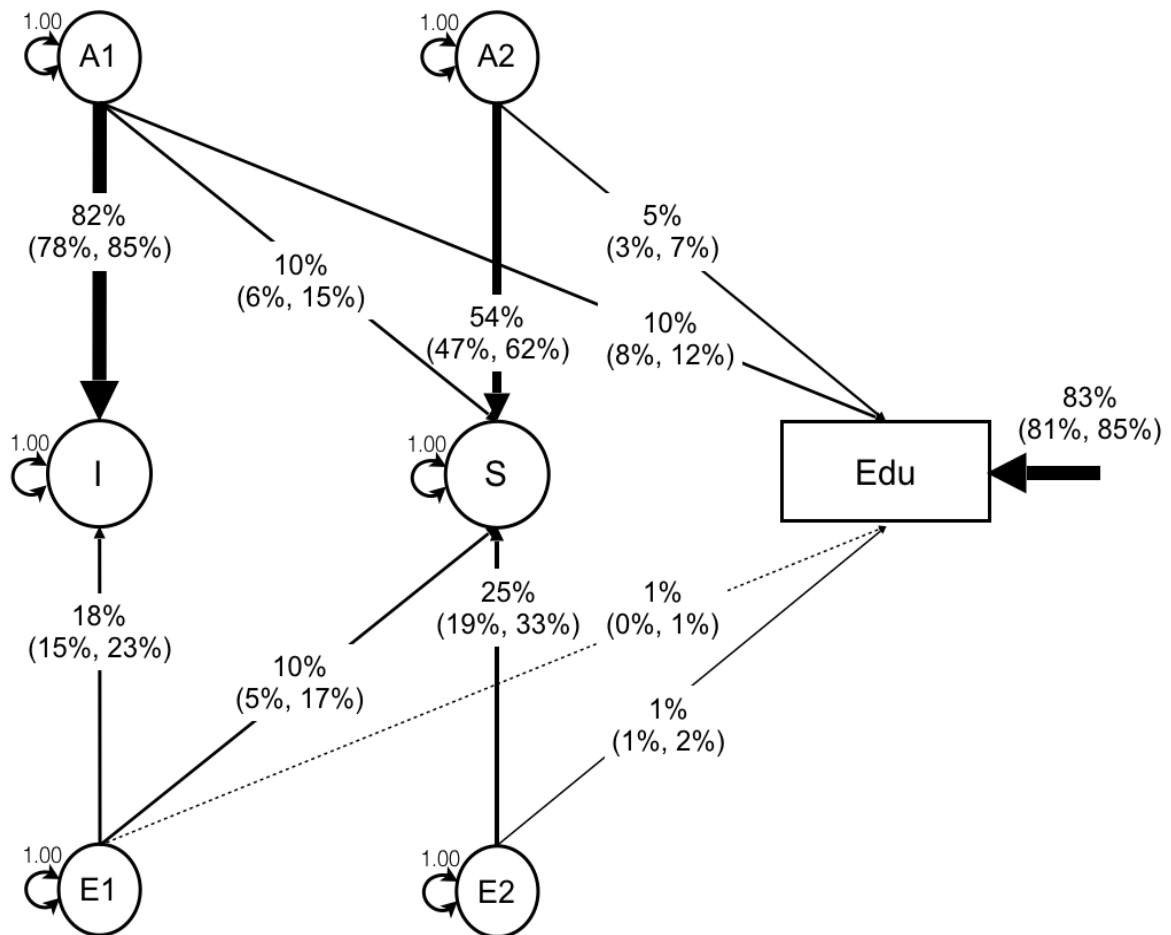
	A1	A2	A3	A4	Total a ²
8 y	0.77 (0.74, 0.81)				0.77 (0.74, 0.81)
12 y	0.39 (0.36, 0.43)	0.36 (0.33, 0.4)			0.75 (0.72, 0.79)
14 y	0.32 (0.28, 0.37)	0.15 (0.12, 0.18)	0.33 (0.29, 0.36)		0.80 (0.75, 0.84)
16 y	0.22 (0.19, 0.26)	0.12 (0.09, 0.15)	0.10 (0.07, 0.13)	0.32 (0.29, 0.36)	0.76 (0.72, 0.8)
	E1	E2	E3	E4	Total e ²
8 y	0.23 (0.19, 0.26)				0.23 (0.19, 0.26)
12 y	0.05 (0.04, 0.07)	0.20 (0.17, 0.22)			0.25 (0.21, 0.28)
14 y	0.02 (0.01, 0.04)	0.03 (0.02, 0.05)	0.15 (0.12, 0.17)		0.20 (0.16, 0.25)
16 y	0.01 (0.01, 0.03)	0.03 (0.02, 0.04)	0.05 (0.03, 0.07)	0.15 (0.13, 0.17)	0.24 (0.2, 0.28)

Note. These values are standardised components of total variance of inattentive symptoms. The total a² corresponds to sum of genetic factors coming from each age, and total e² corresponds to sum of non-shared environmental factors. Total a² + e² at each age equals to 1, indicating that inattentive symptom variation can be accounted by genetic or environmental factors. Each A_n loading (n=1~4) represents the genetic factors firstly identified at n_{th} assessing age, and so does every E_n loading. The 95% confidence intervals were obtained by bootstrapping with 5000 draws. All estimates were significant at p<0.001 level

3.3.5 Multivariate genetic model for the development of inattention and GCSE scores

Figure 3.3 illustrates the Cholesky's decomposition (AE decomposition) of the association between inattention development and GCSE scores. This multivariate genetic model examined effects of the genetic and environmental contributions to the development of inattention on GCSE scores. The fit indices indicated a good model fit: $\chi^2(106) = 543.73$, $p < .001$; CFI = 0.97; SRMR = 0.077; RMSEA = 0.038. As shown in Figure 3.3, the stable genetic effects (A1) explained 82% (95%CI: 78%-85%) of the variance in the baseline level (intercept) and 10% (95%CI 6%-15%) of the variance in the developmental course (slope) of inattention. Genetic innovation (A2) explained 54% of the variance in the developmental course of inattention. A1 and A2 respectively explained 10% (95%CI 8%-12%) and 5% (95%CI 3%-7%) of the variance in GCSE scores. With regard to environmental contributions, the stable environmental effect (E1) and the innovative environmental effect (E2) only accounted for a total of 2 % variance in GCSE scores. Overall, the genetic contributions underlying the intercept and the slope of inattentive symptoms explained 14.8% of the phenotypic variance of GCSE and 25.7% of the heritability of GCSE (see Note of Figure 3.3).

Figure 3.3 Effects of the genetic and environmental underpinnings of inattentive symptoms on GCSE



Note. ‘A’ represents genetic contributions, while ‘E’ represents non-shared environmental contributions; ‘Edu’ represents the mean GCSE scores; ‘I’ represents latent intercept, which is the baseline symptom level; ‘S’ represents the latent slope, which captures the developmental course (systematic changes in inattentive symptoms across ages). The arrows represent the standardised components of variance. The sum of these components in each variable equals to 1 (e.g., for GCSE variance: 5%+10%+1%+1%+83%=100%). The aetiological effects are proportional to the width of arrows. Dotted arrows mean nonsignificant. The 95% confidence intervals were obtained by bootstrapping with 5000 draws.

The model described in the figure also included the decomposition of GCSE. Genetic, non-shared environmental and shared environmental contributions to GCSE were 57.4%, 15.5% and 27.1% respectively. Among the 57.4% genetic variance in GCSE, 9.6% were explained by genetic factors coming from the intercept, 5.2% coming from the slope and 42.6% were specific to GCSE. Among the 15.5% non-shared environmental variance in GCSE, 0.9% came from the intercept, 1.1% from the slope and 13.5% were specific to GCSE. Thus, the variance specific to GCSE was 83% (42.6%+13.5%+27.1%).

3.4 Discussion

The current study examined respective influences of the baseline level and the developmental course of inattentive symptoms from childhood to adolescence on GCSE scores at age 16 years. Results indicated that a higher baseline level of inattention predicted poorer academic performance. Equally important, the developmental course of inattentive symptoms also affected academic outcomes. Using multivariate genetic modelling, this study further revealed that the effects of inattention development on GCSE scores can be attributable to shared genetic underpinnings. Genetic factors contributing to the baseline level and the developmental course of inattentive symptoms collectively explained 15% of the total variance in GCSE scores.

3.4.1 The development of inattention and academic performance

The first aim of this study was to investigate to what extent the developmental course of inattentive symptoms influenced GCSE performance. Corresponding to one previous report that showed the increase in attentional problems predicted worsening academic ability, this study found a negative association between the systematic change in inattention level and GCSE scores (Breslau *et al.*, 2010). This study was also in line with the finding that a rising inattention trajectory in childhood predicted poorer educational attainment in young adulthood (Pingault *et al.*, 2014). More importantly, the current study demonstrated that the developmental course of inattentive symptoms had independent influences on GCSE from the baseline symptom level. These findings highlight the importance of close monitoring the development of inattentive symptoms and its influences on academic performance.

3.4.2 Genetic and environmental contributions to the relationship between inattention development and academic performance

Genetic relationships between ADHD and academic performance have been documented in previous studies (Stergiakouli *et al.*, 2017). The second aim of this study was to investigate whether the association between the development of inattention and GCSE score can be explained by genetic contributions. The multivariate genetic model showed that genetic contributions to the baseline inattention level influenced GCSE score. Furthermore, unique genetic contributions to the developmental course of inattention also influenced GCSE. Collectively, genetic effects underlying the development of inattentive symptoms across childhood and adolescence explained 15% of the phenotypic variance in GCSE score.

The genetic overlap between the development of inattentive symptoms and GCSE scores have the following implications: First, inattention had a direct causal effect on academic performance via genetic mechanisms. Namely, an increasing level of inattentive symptoms from childhood to adolescence due to genetic influences leads to poorer GCSE performance in adolescence. Second, the overlapping genetic contributions may suggest shared biological pathways between inattention and academic performance. It is possible that the same sets of genes independently influence neurobiological underpinnings of the developmental course of inattention and academic performance. Supporting evidence can be found in studies showing that individuals with persistent ADHD symptoms exhibited rapid thinning in frontal brain area (Shaw *et al.*, 2009, Shaw *et al.*, 2013), which is the same brain region supporting the development of working memory and other cognitive ability (Darki and Klingberg, 2015). To distinguish between causal relationship and confounding, we need to implement methods that can better account for pleiotropy and unmeasured confounding. Potential approaches include Mendelian randomization, which exploits genotyping data of unrelated individuals to provide causal estimates unbiased by horizontal pleiotropy (Davey

Smith and Hemani, 2014). Equally, a fixed-effect design that disaggregate within- and the between-individual effects can also help to unfold direct relationship between inattention and academic performance (Gunasekara *et al.*, 2014, Mund and Nestler, 2019).

Compared with genetic overlap, this study found that non-shared environmental factors played a negligible role in explaining the relationship between the development of inattention and GCSE scores. Such findings corroborate with studies showing that non-shared environmental factors mainly exerted age- and occasion-specific influences on cognitive ability and inattentive symptoms (Hoekstra *et al.*, 2007, Kan *et al.*, 2013). This is expected because children are constantly under transition from schools, teachers, peers, curricula and so forth. Hence, such environmental influences can be more time specific by nature and less explanatory to the relationships between inattention development and academic performance (Pingault *et al.*, 2015b).

3.4.3 Implications for clinical practice and educational system

It is noteworthy that despite an overlapping genetic underpinning between inattention and GCSE scores, the majority (herein 85%) of the variance in GCSE score was accounted by other factors. This may explain why interventions solely targeting at ADHD symptom reduction brought unsatisfactory improvement to educational outcomes (Powers *et al.*, 2008). Therefore, one of the important messages in the findings is the need for multimodal intervention to remediate poor educational outcomes associated with ADHD. Potential effects from time-specific environmental influences also suggest that it is crucial to identify age-specific risk factors that modify the effects of ADHD symptoms on academic performance.

It is noteworthy that the genetic contributions to the developmental course of inattention were partly independent from those to the baseline symptom level. This finding

suggests that genetic influences on the developmental course of inattention is driven by specific genetic liability. However, current literature is lacking on data regarding genetic variants linked to different developmental patterns of ADHD. Better understanding of the genetic basis of the development of ADHD can advance our knowledge of underlying pathophysiological mechanisms. The knowledge can significantly improve early identification, risk assessment and effective personalised treatment.

3.4.4 Limitations

Several limitations should be considered when interpreting the results. First, twin pairs with incomplete GCSE score reports were excluded from the analysis. It was found that inattention level was higher in individuals excluded due to missing GCSE scores, and thus may possibly underestimate contributions of inattentive symptoms to academic performance.

Second, inattentive symptoms were measured through parental reports in the current study. The use of parental reports across all the assessment points ensured consistent informants throughout the follow-up, which allowed us to estimate systematic change from childhood to adolescence without the effects of informant discrepancy. However, heritability estimates in quantitative genetic studies may be subject to informant-related issues (Nikolas and Burt, 2010). In particular the heritability of ADHD as derived from parental reports has been found to be higher than that from self-reports (Merwood *et al.*, 2013). Therefore, replication of the current findings using multiple informants is warranted.

Third, this study used questionnaire-based assessment for inattentive symptoms in a population-based sample. Such a dimensional approach is not equivalent to the categorical diagnosis in clinical settings and the results may not directly apply to clinical populations. However, evidence showed that polygenic risk scores for ADHD diagnosis were highly

corelated with ADHD traits dimensionally distributing in the general population (Groen-Blokhuis *et al.*, 2014) . The genome-wide association study (GWAS) on ADHD diagnosis also correlated well with the GWAS on ADHD symptoms, suggesting common genetic liability between the clinical ADHD diagnosis and ADHD-related inattentive and hyperactive/impulsive symptoms in the population (Demontis *et al.*, 2019).

Finally, twin studies may not be generalised to the rest of the population and samples of singletons. Therefore, the results of the study should be interpreted with caution.

3.5 Conclusion

The developmental course of inattention independently influences academic performance. This study highlights the importance of early detection and management for young children presenting impairing inattentive symptoms, as well as the need to monitor the change in symptom severity across the development. Overlapping genetic contributions between the developmental course of inattentive symptoms and long-term academic performance also imply some children may be innately more susceptible to a worse outcome. To curb the risk of poor academic outcomes, developmentally sensitive multimodal interventions targeting at inattention symptoms, age-specific environmental risks and co-developing cognitive deficits may be more effective.

4 Chapter 4: Causal relationship between ADHD and BMI across childhood and adolescence, evidence from longitudinal observational analysis

In Chapter 3, I investigated the associations between the developmental course of inattention from childhood to adolescence and GCSE scores at age 16 years. Findings indicated that in addition to baseline symptom levels, how inattentive symptoms changed over time predicted long-term educational outcomes. More importantly, the associations between the development of inattention and GCSE scores can be explained by their shared genetic contributions. However, as discussed elaborately in Chapter 3, shared genetic contributions cannot confer direct causal relationships between the development of inattention and academic performance. One of the reasons is that shared genetic contributions may arise from direct causal effects with genetic underpinnings, but it may also imply genetic pleiotropy, whereby common genetic factors simultaneously affect inattention and academic performance. Therefore, to disentangle causal links between the development of ADHD and associated outcomes, it is crucial to adopt statistical techniques that can rigorously evaluate potential sources of confounding.

In the current chapter, I continued investigation on the relationships between the development of ADHD and co-occurring conditions from childhood to adolescence. However, I aimed to extend the scope to understanding the nature of the association. A plethora of statistical strategies with different relative utility and strength are available to pursue the quest of causality. In the current chapter, I employed cross-lagged panel modelling with longitudinal observational data spanning from ages 8 to 16 years to evaluate the developmental relationships between ADHD and BMI. In addition, I implemented a within-

individual design in the cross-lagged analysis to better control for unmeasured confounding.

A longitudinal design warrants clear temporal ordering for observational data and is more reliable than a cross-sectional design in addressing potential causal relationship.

This chapter is adapted from a manuscript published in the *International Journal of Epidemiology*.

Liu, C., Schoeler, T., Davies, N. M., Peyre, H., Lim, K. X., Barker, E., Llewellyn, C., Dudbridge F., & Pingault, J. B. (2020). Are there causal relationships between ADHD and BMI? Evidence from multiple genetically informed designs.

Supplementary materials for this chapter are attached in Appendix 3.

4.1 Introduction

4.1.1 The association between ADHD and overweight/obesity

ADHD has high comorbidity with an array of mental health conditions. Evidence also shows that ADHD is a major predictor for impaired general physical health and medical multimorbidity such as metabolic disorders, cardiovascular diseases and neurological disorders and other chronic health issues for affected individuals across different age groups (Instanes *et al.*, 2018, Sciberras *et al.*, 2016, Stickley *et al.*, 2017). In recent years, there have been increasing reports on the association between ADHD and obesity (Akmatov *et al.*, 2019, Instanes *et al.*, 2018). Meta-analytic syntheses on clinical and epidemiological reports point to a positive association between ADHD and obesity. However, discrepancy can be found when examining individual studies, in particular findings among children (Cortese and Tessari, 2017, Nigg *et al.*, 2016). According to the meta-analysis by Cortese & Tessari (Cortese and Tessari, 2017), elevated pooled prevalence of obesity (10.3% versus 7.4%) can be found among children with ADHD. On the contrary, Nigg *et al.* (Nigg *et al.*, 2016) concluded that there was no reliable relationship between ADHD and obesity in pre-pubertal children. Nevertheless, both meta-analytic reports agreed on a positive association between ADHD and obesity that became more established in adulthood.

4.1.2 The nature of the association

Despite the established association, less is known about potential mechanisms explaining the association between ADHD and obesity. Some studies reported that poor impulse control, aberrant neurobiological reward processing and sedentary lifestyle associated with ADHD increased the risk of weight gain (Khalife *et al.*, 2014, Seymour *et al.*, 2015, Tong *et al.*,

2017). However, there is also evidence indicating that higher BMI predicts ADHD symptoms (Perez-Bonaventura *et al.*, 2015). It is possible that a bidirectional pathway is involved. Alternatively, the association may arise, partly or entirely, from confounding. Such confounding may operate through the overlapping neuropsychological characteristics of ADHD and obesity. For example, neurobiological abnormality which lead to aberrant dopaminergic function and impaired reward processing have been implicated in the development of ADHD and overweight/obesity (Patte *et al.*, 2016, Seymour *et al.*, 2015). Additionally, shared environmental factors have also been implicated in the association between ADHD and obesity. It was found that the association between ADHD and overweight/obesity significantly reduced after controlling for family socioeconomic status and lifestyle factors (Geuijen *et al.*, 2019, Wynchank *et al.*, 2018). Equally, parenting behaviours and parental education are associated with the development of ADHD as well as the risk of overweight/obesity in the offspring (Deault, 2010, Karbasi Amel *et al.*, 2018, McCrory *et al.*, 2019). To draw causal inference, it is important to differentiate between the aforementioned mechanisms.

4.1.3 Drawing causal inference between ADHD and obesity from observational data

Identifying direct causal effects and the sources of confounding has long been a heated subject in epidemiological research. In order to fully unravel the nature of the relationship between ADHD and obesity, the approach needs to address two major challenges in observational epidemiological research, namely reverse causality and unmeasured confounding. To minimise potential bias due to reverse causality, a common practice is to adopt a longitudinal design with repeated measures to construct a temporal sequence between the exposure and the outcome instead of simple association analysis.

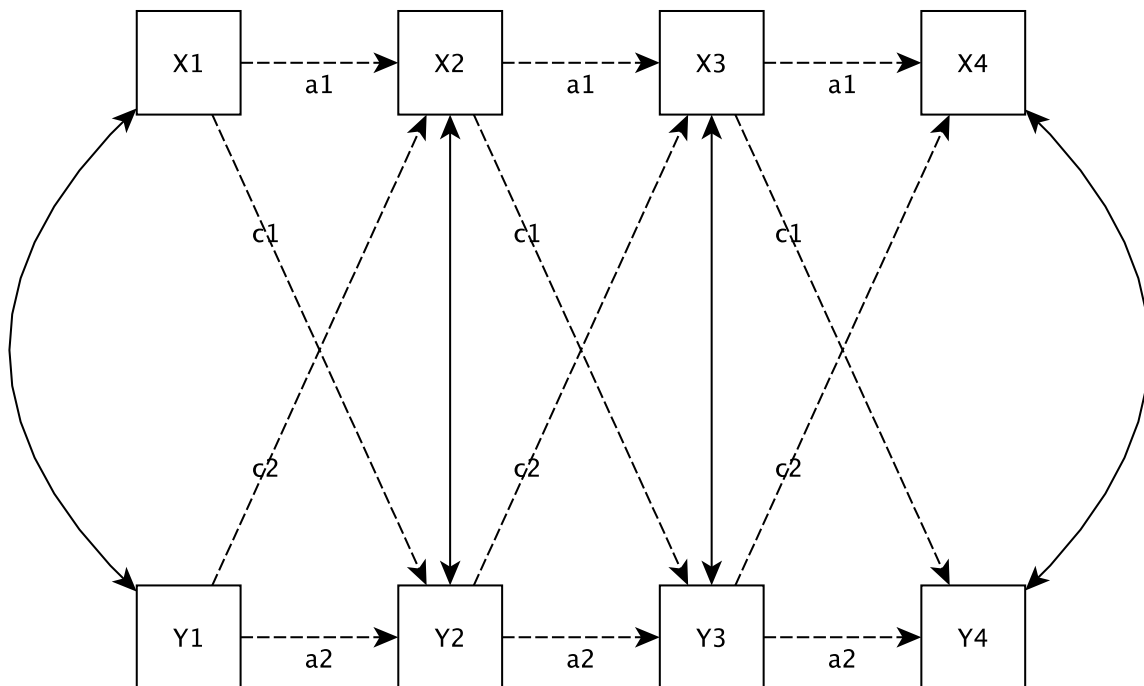
The Cross-Lagged Panel Model (CLPM) is a common approach in developmental research to examine the reciprocal relationships between repeatedly measured variables. The model examines stability (i.e. autoregression) as well as time-lagged associations (i.e. cross-lagged effect) between two longitudinally assessed constructs. However, whether estimates of the CLPM can reliably inform causality is still under debate (see detailed model description below) (Hamaker *et al.*, 2015). In recent years, a number of alternative approaches to the CLPM have been developed, including the Autoregressive Latent Trajectory Model with Structured Residuals (ALT-SR) (Curran *et al.*, 2014). The ALT-SR disaggregates the estimated relationships into between-individual and within-individual effects (see detailed model description below). Because the within-individual effect accounts for random noise and contextual bias such as unmeasured confounding and measurement errors, the within-individual estimates can better reflect direct associations between two constructs (Curran and Bauer, 2011, Robinson, 2009). Therefore, the ALT-SR can be used as a complementary analysis for the CLPM to examine whether the reciprocal relationships between two constructs are independent from systematic confounding.

4.1.4 Model characteristics: Cross-Lagged Panel Model (CLPM)

An illustration of the CLPM including estimates derived from the model can be found in Figure 4.1. The model comprises of 1) autoregressive components, which describe the stability in measurements of the same construct between two adjacent time points and 2) cross-lagged components, which describe the effect of one construct on the other construct at the subsequent time point. The CLPM has been widely used to study directional influences between longitudinally measured variables through the life course. Its findings are frequently

interpreted to suggest causality. However, some fundamental issues in the use of the CLPM need to be considered before deriving causality. First, the CLPM assumes that influence of one variable on another variable is a function of the measurement time lag. Second, the cross-lagged components are estimated on group means of the two constructs over time, hence representing the aggregation of between-individual and within-individual effects (Curran and Bauer, 2011). Therefore, it is difficult to specify whether the cross-lagged relationships are due to systematic differences between individuals (i.e. between-individual effects) or result from within-individual changes (i.e. within-individual effects). For example, a positive cross-lagged effect from A to B in the CLPM may be due to: 1) higher scores in A lead to subsequent higher scores in B (within-individual effects), or 2) individuals with higher scores in A systematically have higher scores in B due to confounding (between-individual effects). When the within-individual effects and between-individual effects are conflated, it creates much ambiguity and may increase the possibility of false causal claims (Hamaker *et al.*, 2015). In view of this, it is frequently recommended that the CLPM is performed in conjunction with other complementary approaches.

Figure 4.1 The Cross-Lagged Panel Model illustration



Note. Squares represent observed variables. Single headed arrows indicate regression; double headed arrows indicate correlations. a_1 & a_2 represent autoregressive paths, which can be fixed or freely estimated; c_1 & c_2 represent cross-lagged paths, which can also be fixed or freely estimated.

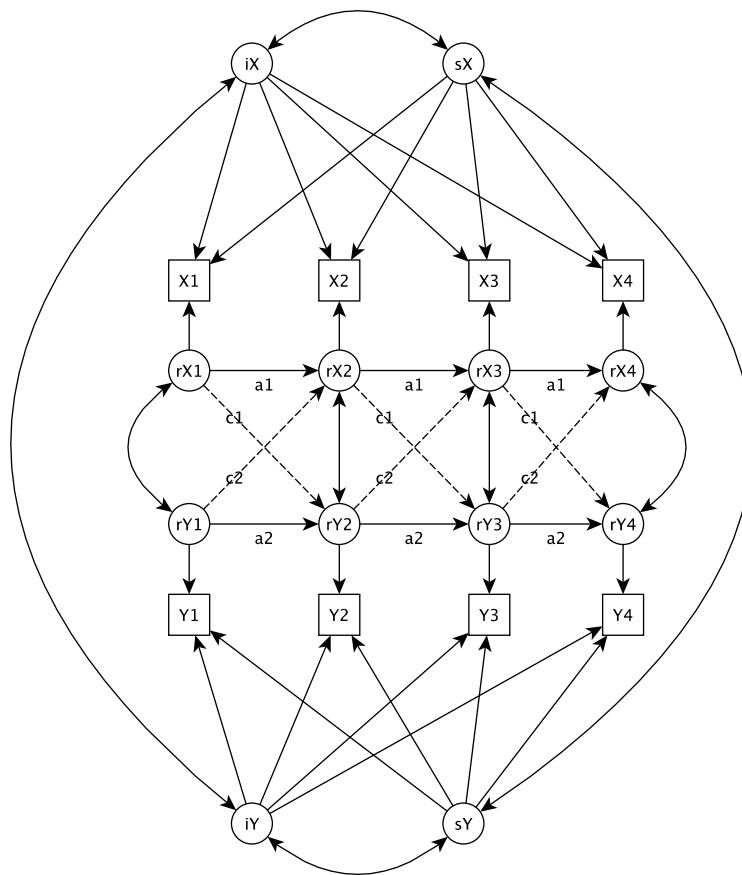
4.1.5 Model characteristics: Autoregressive Latent Trajectory Model with Structured Residuals (ALT-SR)

A number of alternative models to the CLPM have been developed aiming to better delineate the between-individual and the within-individual components in effect estimates (Mund and Nestler, 2019). One such method is the Autoregressive Latent Trajectory Model with Structured Residuals (ALT-SR) (Curran *et al.*, 2014). An illustration of the ALT-SR can be found in Figure 4.2.

The ALT-SR estimates cross-lagged relationship between two repeatedly measured constructs using the residuals of the latent growth trajectory of each construct. Because the growth trajectory contains information about the average initial level (the intercept) and the

systematic change (the slope) of the measured variable across time, residuals of the growth curve then reflect a time- and individual-specific deviation from the predicted group values. In this sense, the ALT-SR provides estimates at the individual level by modelling the reciprocal relationship between individual's specific deviations. Such estimates are valuable to inform causal inferences because, for example, we can be more confident in inferring direct relationship between two constructs and say "a person scoring higher than expected from the underlying trajectory of one variable tends to have values on the other variable that are higher/lower than could be expected from the underlying trajectory of this variable". In addition, because the within-individual estimates are independent of unmeasured attributes (Curran *et al.*, 2014, Robinson, 2009), findings can facilitate personalised intervention programmes that are more targeted and effective.

Figure 4.2 The Autoregressive Latent Trajectory Model with Structured Residuals illustration



Note. Squares represent observed variables; circles denote latent variables. Single headed arrows indicate regression; double headed arrows indicate correlations. i represents the intercept of the linear growth model; s represents the slope of the linear growth model. Loadings to the intercept were set to 1; while loadings to the slope were scaled to reflect spacing of measurement time points. rX_n & rY_n are residuals from the linear growth model that reflect deviations from the time- and person-specific estimated values. $a1$ & $a2$ represent autoregressive paths, which can be fixed or freely estimated; $c1$ & $c2$ represent cross-lagged paths, which can also be fixed or freely estimated. The autoregressive paths and cross-lagged paths are estimated between within-individual residuals of study variables.

4.1.6 Study aims

Meta-analytic data suggest a bidirectional association between ADHD and obesity, although whether the associations arise from direct causal relationship or confounding remains unresolved. In view of the high prevalence and negative psychological and physiological

impacts associated with ADHD and obesity, it is crucial to elucidate potential mechanisms and shared vulnerability behind their co-occurrence. With a focus on the directional and age-specific relationships between ADHD and obesity, this study implemented the Cross-Lagged Panel Model (CLPM) to investigate bidirectional relationships between ADHD and BMI using longitudinal observational data from childhood to adolescence. In addition, to examine potential confounding in the associations between ADHD and BMI, the Autoregressive Latent Trajectory Model with Structured Residuals was performed as a complementary analysis to the CLPM.

4.2 Material and methods

4.2.1 Study sample

Data were drawn from the Twins Early Development Study (TEDS), a cohort of 13,694 twin pairs born between 1994 and 1996 in England and Wales. The sample is representative of the UK population. Additional details of the TEDS sample can be found in previous chapters and elsewhere (Haworth *et al.*, 2013).

The present study used twins with complete information on zygosity and ratings of ADHD symptoms, weight and height at one of the four ages of 8, 12, 14 and 16 years. The final study sample included 6,655 twin pairs (48% males), with 2,386 pairs of monozygotic (MZ) twins and 4,269 dizygotic (DZ) twins. In order to account for non-independence structure of twin data, we selected one twin from each twin pair by random, yielding 6,655 unrelated individuals for final analyses.

4.2.2 Measurement for ADHD symptoms

Ratings of ADHD symptoms were derived from parents' report on the revised Conners' Parent Rating Scale (CPRS-R) at ages 8, 12, 14 and 16 years (Conners *et al.*, 1998). The CPRS-R assesses ADHD-related inattentive and hyperactive/impulsive behaviours. Each of the 18 items in the CPRS-R is rated on a 0-3 Likert scale, with 0 indicating "not at all" and 3 indicating "very much true". I used the sum score, with a minimal value 0 and a maximum of 54 for the cross-lagged analysis.

4.2.3 Measurement for the Body Mass Index (BMI)

BMI at each age was calculated from the formula:

$$BMI = \frac{weight (kg)}{Height^2 (m)}$$

Height and weight of the participants were obtained from parent reports at age 8 and self-reports at ages 12, 14 and 16 years. Parent-reported height and weight in the TEDS sample correlated well with researcher-measured heights ($r=0.90$) and weights ($r=0.83$) (Wardle *et al.*, 2008). To handle extreme values in the BMI data, I used winsorised BMI at the 1st and 99th percentiles (any value beyond the interval was set to the 1st or 99th percentile) to limit the effects due to extreme outliers (thresholds for the 1st or 99th percentile at each age can be found in Appendix 3.1) (Reifman and Keyton, 2010). I used this method to deal with extreme data so that more participants can be retained in the analysis.

4.2.4 Measurement for parental education

In addition to age and sex, parental education was entered as a covariate for ADHD and BMI in the analysis. Information of parental education level in the TEDS sample was collected at the initial contact. Parents were asked to provide their highest level of qualification ranging from 1 (no qualifications) to 8 (postgraduate qualifications). I used standardised mean scores of maternal and paternal responses to index parental education.

4.2.5 Statistical Analysis

All statistical analyses were conducted with R (version 3.5.2) (Team, 2018). The CLPM and the ALT-SR models were estimated in a Structural Equation Modelling (SEM) framework using Lavaan (R package Lavaan, (Rosseel, 2012)). I used maximum likelihood estimation with robust standard errors (MLR) to account for data non-normality and full-information maximum likelihood (FIML) to deal with missing values. Both ADHD symptoms and BMI were controlled for age, sex, birthweight and parental education (standardised composite of maternal and paternal highest education level) prior to cross-lagged analyses.

4.2.6 Model construction for the CLPM

The CLPM was constructed between ADHD symptoms and BMI across the four waves of data collection. Both the autoregressive and the cross-lagged paths were set to vary freely to investigate developmental changes. Residuals of ADHD symptoms and BMI were allowed to covary at the same time point to account for measurement errors.

4.2.7 Model construction for the ALT-SR

The ALT-SR was performed as a complementary analysis to the CLPM. For the linear growth curve of the ALT-SR, I estimated the latent intercept (the initial value) and the latent slope (the developmental course) for ADHD symptoms and BMI respectively. The intercept had factor loadings fixed to 1, while factor loadings for the latent slope were fixed at different values to reflect unbalanced spacing of assessment time. For ADHD symptoms, loadings to the slope were set at 0, 0.34, 0.62, 0.84 for ages 8, 12, 14 and 16 years, while for BMI loadings to the slope were set at 0, 0.42, 0.70, 0.93 for ages 8, 12, 14 and 16 years (loadings scaled to per 10 years for ease of interpretation). The mean and the variance of the intercept and the mean of the slope were freely estimated. The intercepts of ADHD symptoms and BMI were allowed to covary. The autoregressive and cross-lagged paths were then estimated on the time-specific residuals of the growth curve.

4.2.8 Model performance and comparison

Model performance of the CLPM and the ALT-SR was evaluated based on four indices: 1) the Sartorra-Bentler scaled χ^2 ; 2) Root Mean Square Error of Approximation (RMSEA), values < 0.06 indicate good model fit; 3) Bentler's Comparative Fit Index (CFI), values > 0.9 indicate acceptable fit; 4) Standardised Root Mean Square Residual (SRMR), values < 0.08 indicate acceptable fit (Bentler, 1990, Hu and Bentler, 1999).

4.3 Results

4.3.1 Descriptive statistics

Demographic data, ADHD ratings and winsorised BMI of the study sample are shown in Table 4.1. As shown in the table, ADHD symptoms decreased with age while BMI increased.

Table 4.1 Demographics of the study sample

	total (6655 pairs)		MZ (2386 pairs)		DZ (4269 pairs)	
	n, mean	%, sd	n, mean	%, sd	n, mean	%, sd
Male	3196	48%	1107	46%	2089	49%
Birthweight (kg)	2.50	0.56	2.43	0.56	2.54	0.55
ADHD ratings on CPRS-R						
<i>age 8</i>	10.95	9.22	11.10	9.29	10.86	9.17
<i>age 12</i>	9.75	8.55	9.68	8.47	9.79	8.60
<i>age 14</i>	8.55	8.25	8.08	7.79	8.83	8.51
<i>age 16</i>	6.49	7.13	5.93	6.76	6.82	7.32
BMI (kg/m ²)						
<i>age 8</i>	15.86	2.61	15.80	2.57	15.90	2.62
<i>age 12</i>	17.85	3.14	17.80	2.96	17.88	3.24
<i>age 14</i>	19.56	3.14	19.45	2.99	19.63	3.23
<i>age 16</i>	20.93	3.29	20.90	3.27	20.95	3.31
wBMI (kg/m ²)						
<i>age 8</i>	15.85	2.50	15.79	2.48	15.89	2.51
<i>age 12</i>	17.82	2.99	17.79	2.88	17.84	3.04
<i>age 14</i>	19.54	3.02	19.44	2.90	19.60	3.08
<i>age 16</i>	20.91	3.17	20.89	3.13	20.93	3.20

Note. MZ, monozygotic twin; DZ, dizygotic twin; CPRS-R, Conners' Parent Rating Scale Revised; BMI, body mass index; ADHD, Attention-Deficit Hyperactivity Disorder; wBMI, winsorised BMI to limit extreme values beyond the 1% and 99% percentile.

4.3.2 *The CLPM Model*

Model fit indices are presented in Table 4.2. Fit indices of the CLPM indicated good model fit: $\chi^2 = 335.484$, RMSEA=0.065, CFI=0.970, SRMR=0.036, AIC=179433.3, BIC=179650.0 (Table 4.2).

Table 4.3 presents estimates from the model. Autoregressive estimates for ADHD symptoms were Beta=0.648, 0.737 and 0.659, while autoregressive estimates for BMI were Beta=0.605, 0.736 and 0.815, indicating moderate to high measurement stability. Estimates showed that higher ADHD symptoms led to higher subsequent BMI (cross-lagged Beta=0.010, 0.015 and 0.021). The interpretation of the effects of ADHD symptoms on subsequent BMI was: a 1-point increase in ratings of ADHD symptoms at age 8 predicted a 0.01 kg/m² increase in subsequent BMI at age 12 (Table 4.3). However, little evidence supported effects of earlier BMI on subsequent ADHD symptoms (cross-lagged Beta=-0.006, 0.025 and -0.014, 95% CI all included 0).

4.3.3 *The ALT-SR Model*

The ALT-SR model showed a good fit (fit indices: $\chi^2 = 244.921$, RMSEA=0.053, CFI=0.979, SRMR=0.029, AIC=179340.7, BIC=179550.7) (Table 4.2). The latent slope of ADHD symptoms indicated a systematic decrease in symptom ratings across time (Beta=-5.123, 95% CI=-5.423, -4.822, $p < 0.001$, i.e. ADHD ratings on the CPRS-R decrease by 5.123 per 10 years). The latent slope of BMI indicated a systematic increase in BMI from age 8 to age 16 years (Beta=5.371, 95% CI=5.247, 5.494, BMI increased by 5.371 kg/m² per 10 years) (Table 4.3). The auto-regressive estimates showed moderate stability in the level of deviation from predicted trajectories of ADHD symptoms (Beta=0.382, 0.427 and 0.282 for the three

adjacent time points respectively) as well as of BMI (Beta=0.224, 0.602 and 0.706 for the three adjacent time points respectively). However, there was no evidence supporting cross-lagged relationships between ADHD symptoms and BMI in the ALT-SR (Table 4.3).

Table 4.2 Model fit indices for the CLPM and the ALT-SR

	χ^2	DF	P value	RMSEA	CFI	SRMR	AIC	BIC
CLPM	335.484	12	<0.001	0.065	0.970	0.036	179433.3	179650.0
ALT-SR	244.921	13	<0.001	0.053	0.979	0.029	179340.7	179550.7

Note. CLPM, cross-lagged panel model; ALT-SR, autoregressive latent trajectory model with structured residuals. RMSEA < 0.06, CFI values > 0.9, SRMR < 0.08 indicate good model fit.

Table 4.3 Estimates of the CLPM and ALT-SR with constrained cross-lagged paths

	CLPM			ALT-SR		
	B (95% CI)	β (95% CI)	p-value	B (95% CI)	β (95% CI)	p-value
Autoregressive path						
ADHD symptoms						
8y - 12y	0.648 (0.620,0.676)	0.699 (0.678,0.721)	<0.001	0.382 (0.325,0.439)	0.454 (0.399,0.508)	<0.001
12y - 14y	0.737 (0.702,0.771)	0.752 (0.731,0.774)	<0.001	0.427 (0.321,0.534)	0.455 (0.360,0.549)	<0.001
14y - 16y	0.659 (0.627,0.692)	0.758 (0.735,0.780)	<0.001	0.282 (0.169,0.396)	0.371 (0.229,0.512)	<0.001
BMI						
8y - 12y	0.605 (0.551,0.658)	0.509 (0.473,0.545)	<0.001	0.224 (0.031,0.417)	0.169 (0.019,0.319)	0.023
12y - 14y	0.736 (0.696,0.776)	0.722 (0.692,0.753)	<0.001	0.602 (0.535,0.669)	0.578 (0.511,0.645)	<0.001
14y - 16y	0.815 (0.764,0.866)	0.771 (0.738,0.805)	<0.001	0.706 (0.620,0.792)	0.665 (0.599,0.731)	<0.001
Cross-lagged path						
ADHD to BMI						
8y - 12y	0.010 (0.001,0.020)	0.032 (0.002,0.061)	0.037	0.013 (-0.005,0.031)	0.037 (-0.015,0.090)	0.160
12y - 14y	0.015 (0.003,0.028)	0.042 (0.008,0.076)	0.017	0.024 (-0.001,0.049)	0.057 (-0.001,0.114)	0.057
14y - 16y	0.021 (0.003,0.040)	0.055 (0.007,0.102)	0.024	0.021 (-0.021,0.064)	0.044 (-0.045,0.134)	0.330
BMI to ADHD						
8y - 12y	-0.006 (-0.092,0.080)	-0.002 (-0.028,0.024)	0.880	-0.079 (-0.249,0.091)	-0.024 (-0.077,0.028)	0.370
12y - 14y	0.025 (-0.047,0.097)	0.010 (-0.017,0.035)	0.500	-0.009 (-0.139,0.121)	-0.004 (-0.060,0.053)	0.890
14y - 16y	-0.014 (-0.082,0.054)	-0.006 (-0.035,0.023)	0.690	-0.016 (-0.141,0.109)	-0.010 (-0.084,0.064)	0.800
Within-time correlation						
8y	1.016 (0.340,1.693)	0.045 (0.015,0.075)	0.003	0.177 (-0.556,0.91)	0.014 (-0.044,0.072)	0.640
12y	0.337 (-0.191,0.865)	0.022 (-0.013,0.057)	0.210	0.144 (-0.467,0.755)	0.012 (-0.038,0.061)	0.640
14y	0.264 (-0.254,0.782)	0.024 (-0.023,0.070)	0.320	0.510 (-0.049,1.068)	0.051 (-0.005,0.106)	0.074

16y	1.016 (0.340,1.693)	-0.079,0.061	0.810	-0.201 (-1.035,0.633)	-0.026 (-0.134,0.082)	0.640
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Note. CLPM, cross-lagged panel model; ALT-SR, autoregressive latent trajectory model with structured residuals. B, unstandardised estimates; β , standardised estimates. ADHD symptoms and BMI were adjusted for age, sex, birth weight and parental education.

Intercept of the growth curve of ADHD:11.352 (95% CI 11.117,11.586); slope of the growth curve of ADHD: -5.123 (95% CI -5.423,-4.822).

Intercept of the growth curve of BMI:15.804 (95% CI 15.738,15.869); slope of the growth curve of BMI:5.371 (95% CI 5.247, 5.494).

4.4 Discussion

The current study examined the relationship between ADHD symptoms and BMI across childhood and adolescence using longitudinal observation data from a UK population representative cohort. The Cross-Lagged Panel Model (CLPM) showed that higher ADHD symptoms predicted higher BMI at a subsequent time point, while little evidence supported the reverse. Findings from the Autoregressive Latent Trajectory Model with Structured Residuals (ALT-SR) provided little support for within-individual relationships between ADHD symptoms and BMI, suggesting that the cross-lagged relationship between ADHD symptoms and BMI may be attributable to confounding.

4.4.1 The reciprocal relationship between ADHD symptoms and BMI

Findings of the CLPM correspond to previous studies showing that the liability to ADHD was linked to an increased risk of overweight and obesity (Cortese and Tessari, 2017). However, unlike what has been reported in the literature (Perez-Bonaventura *et al.*, 2015), the model did not detect cross-lagged effects from BMI to ADHD symptoms in the current study sample. This is not surprising because the associations between ADHD and overweight/obesity in children and adolescents are found to be small and mixed (Nigg *et al.*, 2016). Factors such as residual effects of birthweight on the development of ADHD symptoms and BMI in early childhood (Lim *et al.*, 2018) and differential sensitivity to hormonal effects on body composition change around puberty (Burt Solorzano and McCartney, 2010) may contribute to mixed findings in the relationships between ADHD symptoms and BMI. Arguably, different research designs and study samples may also explain our divergent findings from previous reports. It is noteworthy that Perez-Bonaventura

et al. (Perez-Bonaventura *et al.*, 2015) found that a higher BMI at age 3 years only predicted higher ADHD symptoms at age 4 years but not afterwards. Similarly, Bowling et al. (Bowling *et al.*, 2018) detected negative effects of BMI on subsequent ADHD specifically at ages 1.5 and 6 years. It is possible that the effects of BMI on ADHD occur during specific developmental periods and thus not detected at the assessment time points in the current study. Furthermore, there was a high stability in ADHD symptoms and BMI throughout the follow-up period (indexed by auto-regressive estimates around 0.7), suggesting that reciprocal effects between ADHD symptoms and BMI, if present, may be very small. Therefore, replication with a larger sample and an extended assessment period are needed to rule out small effects between ADHD symptoms and BMI and to detect age-specific associations.

4.4.2 Is the relationship causal or confounded?

The second aim of this study was to evaluate whether the cross-lagged relationship between ADHD symptoms and BMI also holds at the within-individual level. The ALT-SR model estimates cross-lagged relationship on the residuals of the growth curve to tease apart the between-individual and the within-individual effects. In contrast to the CLPM, evidence from the ALT-SR did not support cross-lagged effects of ADHD on BMI and vice versa. Findings of the ALT-SR can be interpreted as: a higher level of ADHD symptoms (BMI) than expected from the systematically predicted value (i.e. prediction from the growth curve) of a person is not linked to whether this person develops higher or lower BMI (ADHD symptoms) than expected at the adjacent time point. Because the CLPM estimates conflate the between-individual and the within-individual effects, discrepancy between the CLPM and the ALT-SR suggests that unmeasured confounding may explain the cross-lagged relationship between

ADHD symptoms and BMI. This finding corresponds to prior studies showing that variability in between-individual attributes, such as genetic composition, family environment and social experience fully explained the link between ADHD and obesity (Chen *et al.*, 2018a, Geuijen *et al.*, 2019, Wynchank *et al.*, 2018). Alternatively, it is possible that the cross-lagged associations between ADHD symptoms and BMI at the individual level, if present, are small after accounting for the developmental trajectory of each construct. The discrepancy between the CLPM and the ALT-SR implies that intervention targeting at ADHD symptom reduction may not be sufficient enough to prevent the development of obesity. To improve treatment effectiveness, it is important for future research to identify confounding contributing to the co-occurrence of ADHD and obesity.

4.4.3 Limitations

In addition to the limitations regarding the assumptions of the CLPM and the ALT-SR, the following limitations should also be considered. First, as ADHD symptoms and BMI were dimensionally measured in the current study, the results may not be readily transferred to clinical samples. Second, this study only examined the developmental relationship between ADHD symptoms and BMI from age 8 to age 16 years. It is thus difficult to arbitrate their relationships outside this age range. Since previous studies detected the influence of BMI on ADHD symptoms in early childhood (before the age of 6 years) (Bowling *et al.*, 2018), replications that span a longer developmental period are needed. Finally, the employed models may lack the statistical power to detect small cross-lagged effects between ADHD symptoms and BMI. It would be important to replicate our findings with a larger sample.

4.5 Conclusions

This study identified a positive association between earlier ADHD symptoms and subsequent BMI across childhood and adolescence. However, within-individual analyses suggested that such effects may arise from unmeasured confounding rather than direct causal effects.

Findings highlighted the importance of identifying common factors influencing the development of ADHD symptoms and BMI as targets for effective intervention.

5 Chapter 5: Causal relationship between ADHD and BMI across childhood and adolescence, evidence from genetically informed causal inference methods

Chapter 4 used longitudinal observational analyses to examine the relationships between ADHD symptoms and BMI across childhood and adolescence. Results suggested that although there were positive effects from ADHD symptoms to BMI, the effects may be largely attributable to confounding. Indeed, such confounding is frequently encountered yet difficult to control for in observational epidemiological studies, and likely to result in fallacious causal inference in the absence of real causal effects (Fewell *et al.*, 2007).

The current study continued to investigate the relationships between ADHD and BMI. However, instead of using traditional epidemiological analyses, I employed different genetically informed causal inference methods to uncover the nature of the relationship. Combining different approaches, I aimed to strengthen causal inferences under a triangulation framework and investigate to what extent the relationship results from direct causality and confounding.

This chapter is adapted from a manuscript published in the *International Journal of Epidemiology*.

Liu, C., Schoeler, T., Davies, N. M., Peyre, H., Lim, K. X., Barker, E., Llewellyn, C., Dudbridge F., & Pingault, J. B. (2020). *Are there causal relationships between ADHD and BMI? Evidence from multiple genetically informed designs.*

Supplementary materials for this chapter are attached in Appendix 4.

5.1 Introduction

5.1.1 Using different approaches to strengthen causal inferences

Observational studies with longitudinal designs have been frequently employed to infer plausible causal relationships in epidemiological research. However, despite the design providing clear temporal structuring between the exposure and the outcome, and being more reliable than associative studies, there are some limitations that require consideration. For example, longitudinal studies are best to detect causal effects within the follow-up period. Therefore, if causal effect occurs beyond the observational period or at the time that is not assessed by the study, then such effects may not be detected due to measurement limitations. In addition, the observational nature of the study cannot control for unmeasured confounding and thus may lead to biased causal estimates.

Another robust method to study causality is experimental/interventional trials (e.g. randomised control trials, RCT). Through randomly allocating participants into different conditions (e.g. treatment vs. control), the study can minimise selection bias and confounding. Similarly, although RCTs can effectively tackle reverse causality and control for confounding through careful experimental settings, challenges for RCTs include that they are unfeasible and unethical for some exposures and they are costly and time-consuming.

In view of these limitations, genetically informed methods that exploit genetic data to study causal relationship may prove to be valuable alternatives. Given the fact that our genome is randomly transmitted and fixed at conception, genetic information is less likely to be biased by reverse causality and environmental confounding (Pingault *et al.*, 2018). In addition, advances in genotyping technology have increased efficiency and lowered the cost considerably, thereby making mega-scale genotyping and phenotyping data sets increasingly

available. This advancement boosts statistical power of genetic analysis and facilitates its application across different scientific domains.

5.1.2 Genetic and environmental underpinnings of ADHD and BMI

Current evidence shows that ADHD and BMI are highly heritable. The heritability of ADHD was 70-80% (Faraone and Larsson, 2019) and that of BMI was around 70% (Elks *et al.*, 2012). ADHD and BMI also frequently co-aggregate within the same family (Chen *et al.*, 2018a, Do *et al.*, 2019). It was found that family members of ADHD probands had higher risks of obesity than those without a family history of ADHD (Chen *et al.*, 2018a). Meta-analytic data of Genome-Wide Association Studies (GWAS) also revealed correlations between the polygenic structure of ADHD and BMI (Demontis *et al.*, 2019). ADHD and obesity shared genetic correlations ranging 0.21 to 0.26 (Demontis *et al.*, 2019) and the polygenic scores for ADHD predicted 0.45% of the total variance in BMI (Du Rietz *et al.*, 2018). These findings suggest that the observed associations between ADHD and BMI may be explained by genetic underpinnings.

In light of this, the current study aimed to employ genetically informed methods to delineate the relationship between ADHD and BMI. The methods applied in this study included 1) twin differences analysis, 2) within-family polygenic score analysis and 3) bidirectional two-sample Mendelian randomization. Applying multiple methods in one study enables triangulation of evidence. If findings from different methods converge, then we can be more confident in drawing causal influence. If not, we may otherwise acquire better understanding towards the source of bias in the relationship between ADHD and BMI. Furthermore, to advance our insight into the developmental perspective of the relationship, I implemented developmental sensitive designs for each of the methods. Further details

regarding basic assumptions and limitations pertinent to each method are discussed in the Method section.

5.2 Material and methods

The current study is an extension of Chapter 4. To avoid repetition, overlapping information on the study sample and measurements will be simplified.

5.2.1 Study Sample

Data were drawn from the “Twins Early Development Study” (TEDS), a population-representative twin cohort in the UK. Additional details of the TEDS sample can be found in previous chapters and elsewhere (Haworth *et al.*, 2013).

A total of 6,655 twin pairs (48% males) were included in this study (inclusion details can be found in Chapter 4). Twin-differences analyses were performed on the selected 2,386 pairs of monozygotic twins (MZ). Within-family polygenic analyses were performed on 3,320 pairs of dizygotic twins (DZ). Finally, for Mendelian randomization, I extracted instrumental variables from the largest available Genome-Wide Association (GWA) summary statistics for ADHD and BMI respectively.

5.2.2 Phenotypic measures for ADHD symptoms and BMI

As described in Chapter 4, I used parent-reported CPRS-R as the measure for ADHD symptoms at ages 8, 12, 14 and 16 years (Conners *et al.*, 1998). BMI was calculated from parent-reported height (meter) and weight (kilogram) at age 8 and self-reported data at ages 12, 14, and 16 years. Because BMI in growing children varies significantly with age and sex, BMI data were converted to age- and sex-adjusted standardised deviation scores (BMI SDS) based on the British 1990 growth reference (Cole *et al.*, 1998, Must and Anderson, 2006). The phenotypic measures of ADHD symptoms and BMI were used in twin-differences analyses and polygenic score analyses.

5.2.3 GWAS for ADHD and BMI

The current study used summary statistics from the most recent GWA summary statistics on ADHD (N=55,374) (Demontis 2019), adult BMI (N=681,275) (Yengo *et al.*, 2018) and childhood BMI (N=35,668) (Felix *et al.*, 2016). GWAS data on ADHD and BMI were used to generate the polygenic scores and the instrumental variables for ADHD and BMI in polygenic score analyses and Mendelian randomization.

5.2.4 Polygenic score generation for the current study

Genotypic data are available in a total of 10,346 individuals in the TEDS sample (3,320 DZ twin pairs and 7,062 unrelated individuals). For the within-family polygenic score analyses, the polygenic scores (PS) for ADHD and BMI were generated on the DZ twin pairs (N=3,320) in the software LDpred (Vilhjalmsson *et al.*, 2015). PSs were calculated from the sums of the number of trait-associated alleles per individual carried and weighted for the

effect sizes from the ADHD and BMI GWAS. Using the Bayesian approach, LDpred calculates PSs based on a prior of the causal markers (i.e. the proportion of the genetic markers contributing to the trait) on the effect size and the linkage disequilibrium (LD) information in the sample. In the current study, the PSs were generated on a prior on the fraction of causal markers of 1 (i.e. assuming all the markers contribute to the trait) (details can be found in Saskia 2019). All PSs were standardised with a mean=0 and sd=1.

5.2.5 Statistical Analysis

All statistical analyses were conducted using R (Version 3.6.3) (Team, 2020).

5.2.5.1 Twin-differences analyses

Twin-differences analyses capitalise on twins' characteristics to study causal relationships. Because MZ twins share all their genetic materials and living environment, the co-twin provides a stringent matched control for shared genetic and shared environmental confounding. In this sense, twin-differences analysis in MZ twins assumes that any differences between one twin and the co-twin are the results of non-shared environment. Thereby, if one twin differs from the co-twin in the exposure also differs in the outcome, then it speaks in favour of a direct relationship that is independent from shared genetic and shared environmental confounding (Sahu and Prasuna, 2016). However, this is only valid under the condition that there is no unmeasured non-shared environmental confounding. Therefore, additional observable confounders that differ between twins should be adjusted for during the analysis.

I implemented the twin-differences analyses in MZ twins (2,386 pairs) using structural equation modelling (R package Lavaan (Rosseel, 2012)) with a cross-lagged

design. Sex, age and parental education were adjusted by design and birthweight difference was included as a covariate in the model because it has been linked to ADHD symptoms and BMI in a previous report (Lim *et al.*, 2018).

I used the model to derive the following estimates:

- Cross-lagged effects between differences in earlier measures of ADHD symptoms and subsequent measures of BMI SDS and vice versa.
- Auto-regressive effects to index stability in the twin-differences of ADHD symptoms and BMI measured across adjacent time points.

To account for data non-normality, 95% confidence intervals (CI) were obtained using bootstrapping with 10,000 repetitions.

5.2.5.2 Within-family polygenic score analysis

The PSs for a specific trait per individual are derived by computing the sum of the trait-associated alleles weighted by their relative effect sizes reported in the GWA summary statistics. The PSs index an individual's genetic liability to a specific trait and thus can be used as instrumental variables to study cross-trait associations. However, the PS association may arise from shared genetic confounding (horizontal pleiotropy) or direct causal relationships (mediated pleiotropy) (Torkamani *et al.*, 2018). Similarly, because PSs are aggregate effects of multiple genetic variants, they are less specific and more likely to be confounded. For example, it was shown that the PSs for education attainment in the offspring were also associated with parenting style and family socioeconomic status (Krapohl *et al.*, 2017). It suggests that PSs also capture effects coming from family environmental risk and protective factors that are not due to genetic transmission. The term that describes the

aforementioned confounding is “dynastic effects”, whereby parental genetic factors influence offspring through the nurturing environment created by parents. In the presence of dynastic effects, causal estimates derived from PS analysis may be inflated due to such confounding (Bates *et al.*, 2018). Other factors that may influence PS analysis include population stratification and assortative mating (van Rheenen *et al.*, 2019).

A powerful way to control for the aforementioned confounding in PS analysis is via a family-based design. Because living environment, parental factors and ancestry are identical between siblings from the same family, a family-based design can provide a good control. In the current study, I used within-family polygenic score analysis to investigate PS associations between ADHD and BMI. A total of 3,320 DZ twin pairs with valid phenotypic and genotyped data in the TEDS sample were included in the polygenic score analysis. I constructed a multilevel model using the package “lme4” (Bates *et al.*, 2014) to test the associations between the ADHD/BMI PSs and the opposite phenotype. Because twins are nested within families, the model allowed for within-family correlations and clustered standard errors. ADHD symptoms, BMI SDS, and the PSs for ADHD and BMI were adjusted for age, sex, and the first 10 principal components prior to performing the multilevel model. For each multilevel model, I estimated the associations between the polygenic scores and the opposite phenotype with:

- The family mean PS (i.e. the averaged PS across the two twins): this estimated the between family association.
- The difference between the individual PS and the family mean PS: this estimated the within-family association.

I then computed the following differences between estimates from the multilevel models:

- Differences of the within-family and the between-family estimates (the within-family minus the between-family estimates): to examine estimate change due to the bias of population stratification, assortative mating and dynastic effects.
- Differences of the within-family estimates between ages 16 and 8 years (estimate at age 16 minus estimate at age 8): to examine whether effects varied with age.

Differences were tested against the null using 95% bootstrap percentile intervals based on random sampling with replacement of DZ twin pairs (10,000 draws).

It has been shown that parental education was a potential confounder of the between-family estimates (Selzam *et al.*, 2019). To further examine the property of the between-family and the within-family estimates, I included parental education (standardised average of maternal and paternal highest educational level collected at first contact) as a covariate in the multilevel model. As above, I tested the following estimate differences:

- Differences of the within-family and the between-family estimates in the model, this time including parental education as a covariate.
- Differences of the between-family estimate before and after adjusting for parental education.

5.2.5.3 Bidirectional two-sample Mendelian Randomization (MR) analysis

MR is a causal inference method that uses genetic variants associated with the exposure (e.g. SNPs associated with BMI) as instrumental variables to probe the effect of this exposure on the outcome. Like other instrumental variable approaches, validity of MR relies on several assumptions: first, the assumption of relevance, where the instrumental variables are associated with the exposure; second, the assumption of independence, that the effects of

the instrumental variables on the outcomes are not confounded by common causes; third, the assumption of exclusion restriction, namely, instrumental variables are related to the outcome only through the exposure (Smith *et al.*, 2007). MR analysis using summarised GWAS data on two independent samples is called two-sample MR (Pierce and Burgess, 2013). This approach does not require individual genotyping data, rendering it more flexible and efficient for causal inference study (Burgess *et al.*, 2013, Pierce and Burgess, 2013). Recent development in MR analysis includes different sensitivity analyses that enable researchers to interrogate possible violations of key MR assumptions and improve robustness of the estimates (Zheng *et al.*, 2017).

The current study used SNPs selected from the GWAS of ADHD (N=55,374, (Demontis *et al.*, 2019)), childhood BMI (N=35,668, (Felix *et al.*, 2016)) and adult BMI (N=806,834, (Pulit *et al.*, 2019)) and considered ADHD and BMI in turn as exposure to evaluate bidirectional effects. The instrumental SNPs for BMI were selected at the genome-wide significance of $p < 5 \times 10^{-8}$ ($p < 5e-8$) ($N_{\text{SNPs}}=18$ for childhood BMI and $N_{\text{SNPs}}=546$ for adult BMI) and the instrumental SNPs for ADHD were selected at a suggestive p-value threshold of $p < 5e-5$ ($N_{\text{SNPs}}=190$). Clumping at the threshold of clumping r^2 cut off =0.001 and clumping window=10,000kb was performed to ensure independence between SNPs.

The analysis was performed using TwoSampleMR package (Hemani *et al.*, 2018). Effect estimates from individual SNPs were combined using random-effects inverse-variance weighted (MR-IVW) regression as the primary analysis. To assess the robustness of the IVW regression, I also performed sensitivity analyses including MR-Egger analysis, weighted median method, weighted mode method and robust adjusted profile score (MR-RAPS) analysis. Finally, considering dynastic effects in the association between the polygenic scores for educational attainment and BMI (Kong *et al.*, 2018), I performed a multivariable MR model examining confounding associated with educational attainment in the effects between

ADHD and BMI.

The following MR estimators were derived:

- IVW regression: it is the weighted regression of instrument-outcome associations on instrument-exposure associations when the intercept is constrained to zero. IVW estimators are more powerful in detecting effects compared to other MR methods and generally used as the primary analysis. However, the IVW estimator assumes there is no unbalanced pleiotropy (i.e. the average pleiotropic effect is zero), which may not always hold true (Lawlor *et al.*, 2008).
- MR-Egger regression: the MR-Egger intercept provides an estimate of unbalanced pleiotropy across instrumental variables. However, MR-Egger is less statistically powerful (Bowden *et al.*, 2015).
- Weighted median regression: it provides a valid causal estimate when over 50% of the weight in the estimates are contributed by instruments that fulfill the MR assumptions. Therefore, it provides more reliable results if instrumental variables are invalid. In addition, it is more powerful than MR-Egger regression (Bowden *et al.*, 2016).
- Weighted mode regression: it provides a valid estimate if the largest subset of instrumental variables with the same ratio of effects is formed by valid instruments. Therefore, it is robust to unbalanced pleiotropy and is not biased when the majority of the instrumental variables are invalid (Hartwig *et al.*, 2017).
- Robust adjusted profile score regression (MR-RAPS): In two-sample MR analysis, weak instruments may bias effect estimates to the null (Pierce and Burgess, 2013). MR-RAPS regression is weighted on the associative strengths of the instrumental variables, thus accounting for weak instrumental bias (Zhao *et al.*, 2018).

- Multivariable MR (MVMR) regression: it provides estimates of multiple exposures on one outcome. It controls for potential sources of pleiotropy when they are effectively captured and modelled in the model (Sanderson *et al.*, 2018). To examine whether controlling for educational attainment influences some of the reciprocal effects between ADHD and BMI, I compared the IVW MR estimator and the multivariable MR estimator using a test after adjusting for the covariance between the two estimates (Clogg *et al.*, 1995). The effects between ADHD and BMI may be confounded if findings indicate differences between the IVW and MVMR IVW estimators in any direction.

I repeated the analyses with SNPs selected at the p-value threshold of $p < 5e-8$ from the ADHD GWA summary statistics as a sensitivity analysis to examine convergence with findings at p-value threshold at $p < 5e-5$.

5.3 Results

5.3.1 Twin-differences analysis

Baseline characteristics of the study sample are presented in Table 5.1. Means and distribution of the differences in standardised ADHD ratings and BMI SDS in MZ twins at ages 8, 12, 14 and 16 are shown in Appendices 4.1 and 4.2.

Figure 5.1 shows the results of cross-lagged twin-differences analyses. The autoregressive paths for the differences in ADHD symptoms and BMI ranged from 0.472 to 0.656 and from 0.143 to 0.257 respectively, indicating stability in twin differences scores across the development. However, the model did not find evidence supporting that differences in earlier measures of ADHD symptoms were associated with subsequent

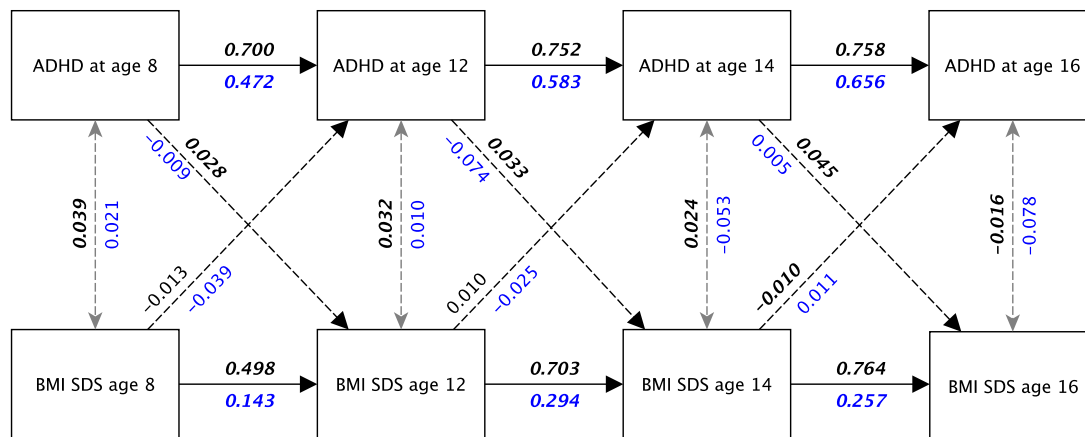
differences in BMI ($\beta=-0.009$, -0.074 and 0.005 , all 95% bootstrap CI included 0) and vice versa ($\beta=-0.039$, -0.025 and 0.011 , all 95% bootstrap CI included 0). Within-time correlations between differences in the two phenotypes were not identified, suggesting little co-development between the change in ADHD symptoms and the change in BMI.

Table 5.1 Demographics of the study sample

	total (6655 pairs)		MZ (2386 pairs)		DZ (4269 pairs)	
	n, mean	%, sd	n, mean	%, sd	n, mean	%, sd
Male	3196	48%	1107	46%	2089	49%
Birthweight (kg)	2.50	0.56	2.43	0.56	2.54	0.55
Birthweight SDS	-0.52	1.06	-0.58	1.06	-0.48	1.06
ADHD symptoms (CPRS-R)						
<i>age 8</i>	10.95	9.22	11.10	9.29	10.86	9.17
<i>age 12</i>	9.75	8.55	9.68	8.47	9.79	8.60
<i>age 14</i>	8.55	8.25	8.08	7.79	8.83	8.51
<i>age 16</i>	6.49	7.13	5.93	6.76	6.82	7.32
BMI (kg/m ²)						
<i>age 8</i>	15.86	2.61	15.80	2.57	15.90	2.62
<i>age 12</i>	17.85	3.14	17.80	2.96	17.88	3.24
<i>age 14</i>	19.56	3.14	19.45	2.99	19.63	3.23
<i>age 16</i>	20.93	3.29	20.90	3.27	20.95	3.31
BMI SDS						
<i>age 8</i>	-0.14	1.50	-0.17	1.47	-0.12	1.52
<i>age 12</i>	-0.02	1.25	-0.02	1.23	-0.02	1.26
<i>age 14</i>	0.00	1.14	-0.03	1.12	0.02	1.16
<i>age 16</i>	-0.09	1.16	-0.08	1.19	-0.09	1.15

Note. MZ, monozygotic twin; DZ, dizygotic twin; CPRS-R, Conners' Parent Rating Scale Revised; BMI, body mass index; ADHD, Attention-Deficit Hyperactivity Disorder; Birthweight SDS, birthweight converted to standardised deviation score (SDS) based on British 1990 growth reference; BMI SDS, Body Mass Index converted to standardised deviation score (SDS) based on the British 1990 growth reference.

Figure 5.1 Cross-lagged phenotypic relationships between ADHD symptoms and BMI SDS



Note. Standardised phenotypic relationships (i.e. correlations) adjusted for age, sex, birth weight and parental education are shown in black (above the lines); estimates from twin-differences analyses in MZ twins are in blue (below the lines); estimates with 95% bootstrap percentile intervals not including 0 are displayed in *italic bold*.

5.3.2 Within-family polygenic score analysis

5.3.2.1 Polygenic score for ADHD to BMI SDS

The associations between the ADHD PS and phenotypic BMI from the multilevel model are displayed in Table 5.2 and Figure 5.2. Findings indicated positive between-family associations at ages 12, 14 and 16 years (e.g. at age 12 years, $\text{Beta}=0.057$, $95\% \text{CI}=0.016, 0.098$, i.e. one SD unit increase in the ADHD PS was associated with 0.057 SD unit increase in BMI SDS). The within-family estimates provided evidence that one SD unit increase in the individual ADHD PS from the family mean was associated with a 0.128 ($95\% \text{CI}$ 0.025 to 0.228) SD unit increase in BMI SDS at age 16. There was little evidence that the ADHD PS associated with BMI within families at earlier ages. There was little evidence that the between-family and the within-family estimates differed ($\Delta=-0.041$ to 0.040, bootstrap 95% CIs all across 0) (Table 5.2). Overall, the within-family associations increased from age 8 to age 16 years ($\Delta=0.088$, 95% bootstrap CI 0.038, 0.214).

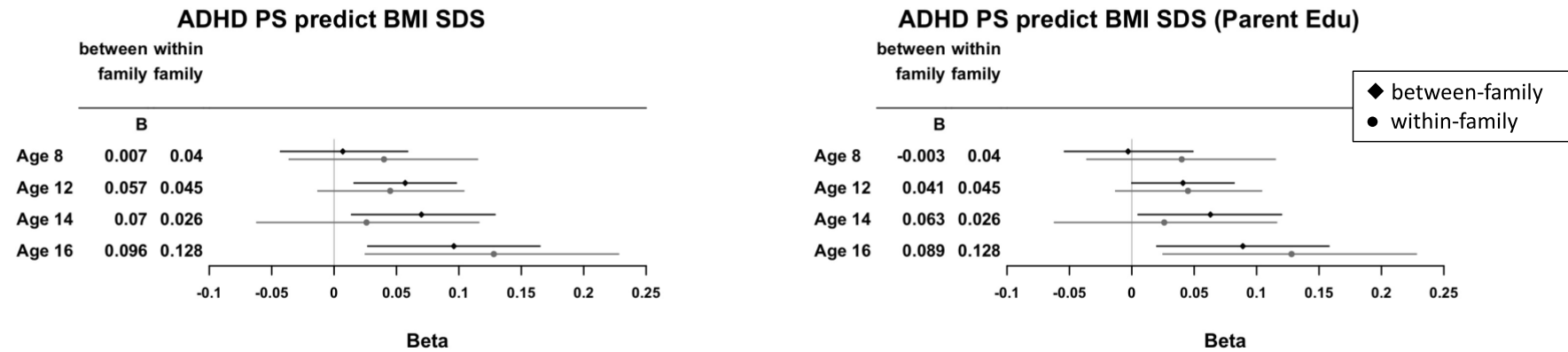
After including parental education level as a covariate, the between-family associations were attenuated at ages 8, 12 and 14 years ($\Delta=-0.010$, -0.016 and -0.009 , bootstrap 95% CIs do not include 0), while the within-family association remained unchanged. In sum, the effects of the ADHD PS on BMI SDS increased from childhood to adolescence. Parental education may be a potential confounder in the association between the ADHD PS on BMI SDS (Table 5.2 and Figure 5.2).

Table 5.2 Between- and within-family polygenic score effects of ADHD PS on BMI SDS

Phenotype	PS	Between-family			Within-family			Estimate difference (w-b)		Estimate difference (edu)	
		Beta	95% CI	β	Beta	95% CI	β	Beta	95% CI	Beta	95% CI
BMI age 8	ADHD	0.007	-0.043,0.059	0.004	0.040	-0.036,0.115	0.013	0.034	-0.057,0.124	-	-
BMI age 12	ADHD	0.057	0.016,0.098	0.041	0.045	-0.013,0.104	0.018	-0.009	-0.082,0.063	-	-
BMI age 14	ADHD	0.070	0.014,0.129	0.056	0.026	-0.062,0.116	0.011	-0.041	-0.146,0.065	-	-
BMI age 16	ADHD	0.096	0.027,0.165	0.074	0.128	0.025,0.228	0.057	0.040	-0.081,0.161	-	-
Controlling for parent educational level											
BMI age 8	ADHD	-0.003	-0.054,0.049	-0.001	0.040	-0.036,0.115	0.013	0.044	-0.048,0.135	-0.010	-0.019,-0.001
BMI age 12	ADHD	0.041	0,0.082	0.029	0.045	-0.013,0.104	0.018	0.007	-0.066,0.079	-0.016	-0.023,-0.009
BMI age 14	ADHD	0.063	0.005,0.12	0.049	0.026	-0.062,0.116	0.011	-0.032	-0.138,0.073	-0.009	-0.017,-0.002
BMI age 16	ADHD	0.089	0.02,0.158	0.069	0.128	0.025,0.228	0.057	0.047	-0.074,0.167	-0.007	-0.016,0

Note. PS, polygenic score; Beta, unstandardised regression coefficient; 95% CI, bootstrap 95% percentile intervals after 10,000 draws; β , standardised regression coefficient; Estimate difference (w-b), within-family estimate minus between-family estimate; ; Estimate difference (edu), differences in the between-family estimates after controlling for parental education.

Figure 5.2 Between- and within-family polygenic score effects of ADHD PS on BMI SDS



Note. PS, standardised polygenic score; B/Beta, unstandardised regression estimates.

5.3.2.2 Polygenic score for BMI to ADHD symptoms

The associations between the BMI PS and ADHD symptoms are shown in Table 5.3 and Figure 5.3. The BMI PS was positively associated with ADHD symptoms between-families across the four time points (e.g. at age 8 years, one SD unit increase in BMI PS was associated with 0.808-point increase in the rating of ADHD symptoms), and there was evidence of within-family associations at ages 8 and 12 and 14 years (Beta 0.628, 0.470 and 0.499 respectively). Results showed that the within-family association was smaller than the between-family association at age 16 years ($\Delta=-0.626$, bootstrap 95% CI -1.029,-0.217) (Table 5.3) but not at earlier ages. Opposite to the ADHD PS findings, the effects of the BMI PS on ADHD symptoms decreased from age 8 to age 16 years ($\Delta=-0.538$, 95% bootstrap CI -0.988,-0.094). After including parental education level as a covariate, the between-family associations were attenuated at ages 8, 12 and 16 years ($\Delta=-0.238$, -0.220 and -0.434, bootstrap 95% CIs do not cross 0) (Table 5.3).

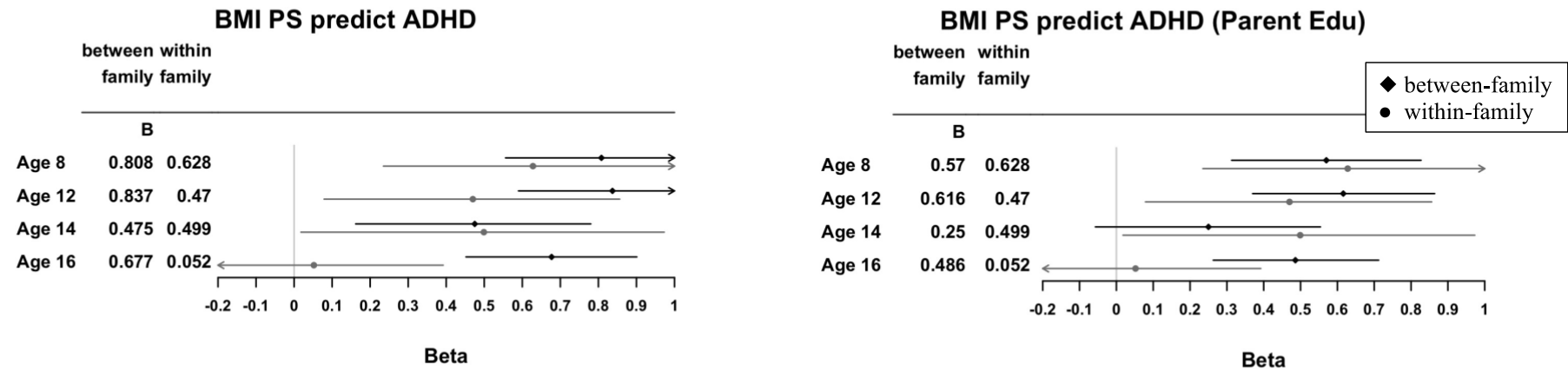
In sum, the effects of the BMI PS on ADHD symptoms decreased with age. The results also indicated that effects of the BMI PS on ADHD symptoms may be confounded by parental education.

Table 5.3 Between- and within-family polygenic score effects of BMI PS on ADHD symptoms

Phenotype	PS	Between-family			Within-family			Estimate difference (w-b)		Estimate difference (edu)	
		Beta	95% CI	β	Beta	95% CI	β	Beta	95% CI	Beta	95% CI
ADHD age 8	BMI	0.808	0.556,1.061	0.081	0.628	0.235,1.022	0.033	-0.180	-0.649,0.293	-	-
ADHD age 12	BMI	0.837	0.59,1.082	0.089	0.470	0.079,0.856	0.027	-0.365	-0.825,0.088	-	-
ADHD age 14	BMI	0.475	0.162,0.78	0.052	0.499	0.018,0.973	0.030	0.024	-0.541,0.609	-	-
ADHD age 16	BMI	0.677	0.452,0.901	0.082	0.052	-0.285,0.392	0.003	-0.626	-1.029,-0.217	-	-
Controlling for parent educational level											
ADHD age 8	BMI	0.570	0.313,0.827	0.057	0.628	0.235,1.022	0.033	0.058	-0.412,0.538	-0.238	-0.303,-0.179
ADHD age 12	BMI	0.616	0.37,0.864	0.065	0.470	0.079,0.856	0.027	-0.145	-0.606,0.308	-0.220	-0.283,-0.163
ADHD age 14	BMI	0.250	-0.057,0.554	0.028	0.499	0.018,0.973	0.030	-0.225	-0.304,-0.152	0.249	-0.314,0.824
ADHD age 16	BMI	0.486	0.263,0.712	0.059	0.052	-0.285,0.392	0.003	-0.192	-0.250,-0.139	-0.434	-0.841,-0.024

Note. PS, polygenic score; Beta, unstandardised regression coefficient; 95% CI, bootstrap 95% percentile intervals after 10,000 draws; β , standardised regression coefficient; Estimate difference (w-b), within-family estimate minus between-family estimate; ; Estimate difference (edu), differences in the between-family estimates after controlling for parental education.

Figure 5.3 Between- and within-family polygenic score effects of BMI PS on ADHD symptoms



Note. PS, standardised polygenic score; B/Beta, unstandardised regression estimates.

5.3.3 Bidirectional two-sample Mendelian Randomization (MR) analysis

5.3.3.1 Effect of the liability to ADHD on childhood BMI

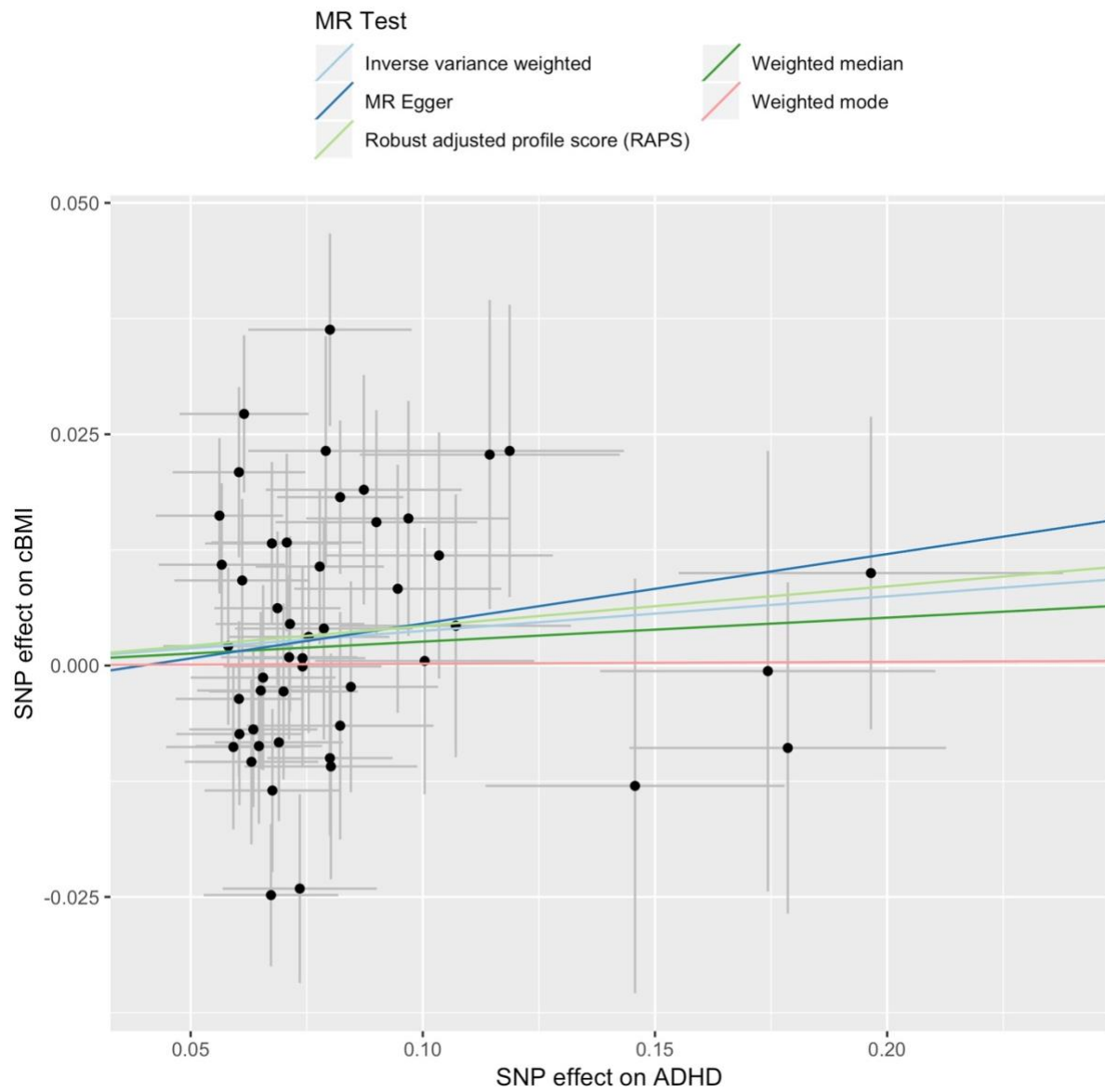
After excluding palindromic SNPs and variants that do not share the same allele pair between the exposure and the outcome, 49 of the 190 SNPs selected from the ADHD GWA summary statistics at p-value threshold of $p < 5e-5$ were used as the instrumental variables for ADHD. Table 5.4 and Figure 5.4 show the effect of the liability to ADHD on childhood BMI estimated by different MR methods. None of the MR estimators provided evidence showing an effect of the liability to ADHD on childhood BMI (β ranging 0.002 to 0.075, with 95 % CI crossing 0). The multivariable IVW estimates (multivariable MR $\beta = 0.058$, 95% CI -0.001 to 0.117, $p = 0.052$) after controlling for the effect associated with educational attainment was not different from the univariable IVW estimate ($t(45) = -1.165$, $p = 0.25$).

The sensitivity analysis using SNPs below the p-value threshold of $p < 5e-8$ for ADHD (only 4 SNPs were available as the instrumental variables) can be found in Appendix 4.3. Results provided little evidence for an effect of the liability to ADHD on childhood BMI across different MR estimators (β ranging 0.065 to 1.161, with 95% CI crossing 0).

Table 5.4 Mendelian randomization results of the effects from ADHD to childhood BMI

Exposure	Outcome	Method	Univariable MR					Multivariable MR					
			nSNP	β	Lower 95% CI	Upper 95% CI	<i>p</i> -value	nSNP	β	Lower 95% CI	Upper 95% CI	<i>p</i> - value	
ADHD	childhood BMI	IVW		0.037	-0.011	0.086	0.129		0.058	-0.001	0.117	0.052	
		MR RAPS		0.043	-0.008	0.094	0.099						
		Weighted median	49		0.026	-0.030	0.082	0.366	48				
		Weighted mode			0.002	-0.116	0.120	0.973					
		MR Egger			0.075	-0.114	0.265	0.440					
		MR Egger intercept			-0.086	-0.448	0.276	0.687					

Figure 5.4 Mendelian randomization results of the effects from ADHD to childhood BMI



5.3.3.2 Effect of the liability to ADHD on adult BMI

After harmonisation, 131 of the 190 SNPs selected for ADHD at p-value threshold of $p < 5e-5$ were used as the instrumental variables for ADHD. Table 5.5 and Figure 5.5 show the effect of the liability to ADHD on adult BMI estimated by different MR methods. The estimates suggest that a unit increase in odds of ADHD leads to 0.028 SD unit increase in BMI (IVW $\beta = 0.028$, 95% CI 0.015-0.040, $p < 0.001$). The weighted median method and MR-RAPS were consistent with the IVW findings. The weighted mode method and MR-Egger regression provided little support of an effect and were not consistent with the IVW. MR-Egger intercept did not indicate unbalanced horizontal pleiotropy (intercept = 0.002, 95% CI -0.002-0.005, $p = 0.330$).

The multivariable IVW estimates (multivariable MR $\beta = 0.019$, 95% CI 0.005-0.033, $p = 0.010$) of the effect of ADHD independent of educational attainment was smaller than the univariable IVW estimate, as found in the test of differences ($t(127) = 2.362$, $p = 0.020$).

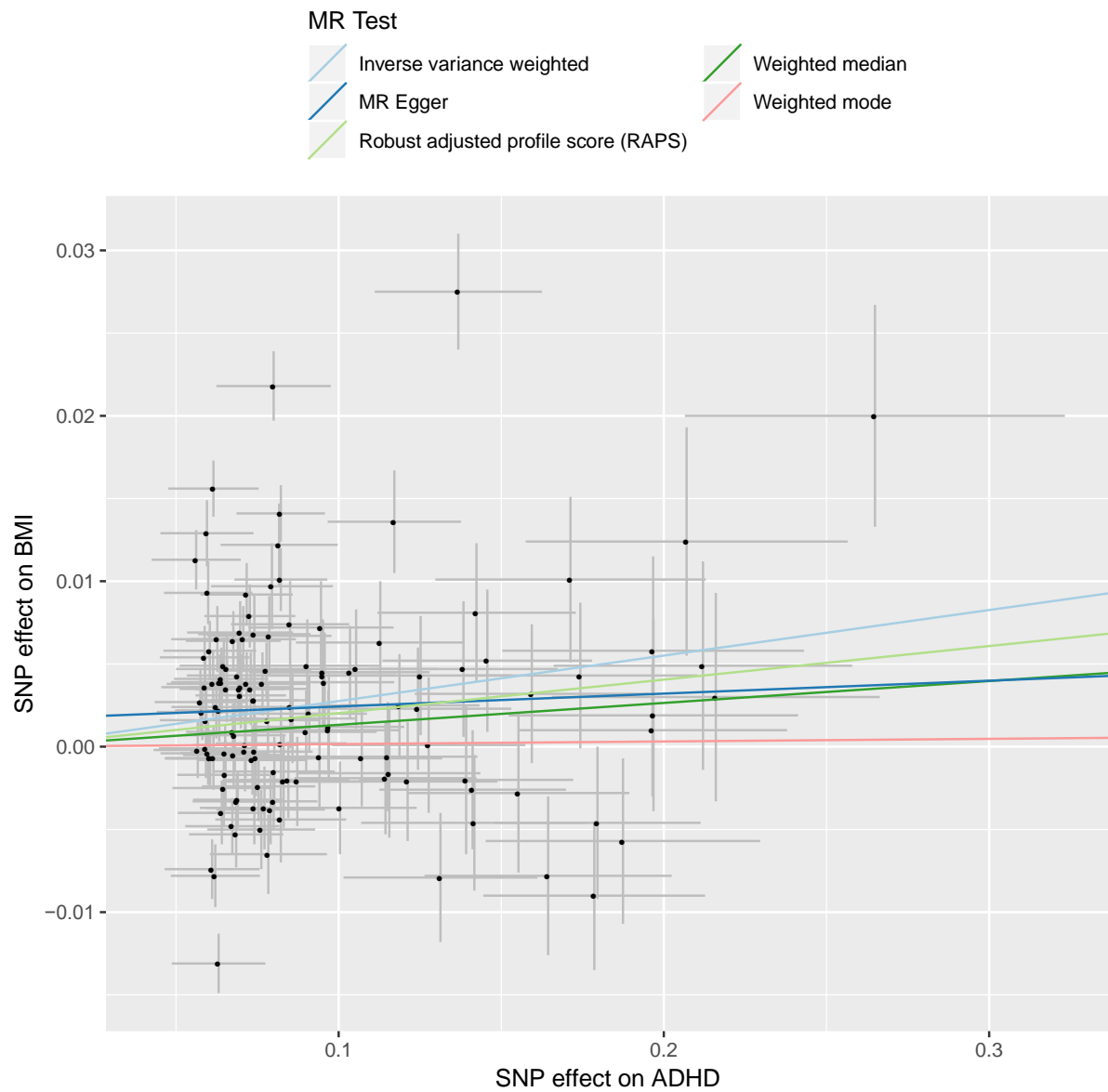
The sensitivity analysis with SNPs at $p < 5e-8$ showed that one unit increase in odds of ADHD leads to 0.064 SD unit increase in BMI (IVW $\beta = 0.064$, 95% CI 0.004-0.125, $p = 0.036$). The weighted median method was consistent with the IVW, but the weighted mode method and MR Egger regression provided little support for an effect (Appendix 4.4).

Table 5.5 Mendelian randomization results of the effects from ADHD to adult BMI

Exposure	Outcome	Method	Univariable MR					Multivariable MR					
			nSNP	β	Lower 95% CI	Upper 95% CI	<i>p</i> -value	nSNP	β	Lower 95% CI	Upper 95% CI	<i>p</i> - value	
ADHD	Adult BMI	IVW		0.028	0.015	0.040	<0.001		0.019	0.005	0.033	0.010	
		MR RAPS		0.020	0.010	0.031	<0.001						
		Weighted median	131		0.013	0.004	0.023	0.005	130				
		Weighted mode			0.002	-0.024	0.027	0.905					
		MR Egger			0.008	-0.034	0.049	0.713					
		MR Egger intercept			0.002	-0.002	0.005	0.330					

Note. β denotes odds ratio.

Figure 5.5 Mendelian randomization results of the effects from ADHD to adult BMI



5.3.3.3 Effect of childhood BMI on the liability to ADHD

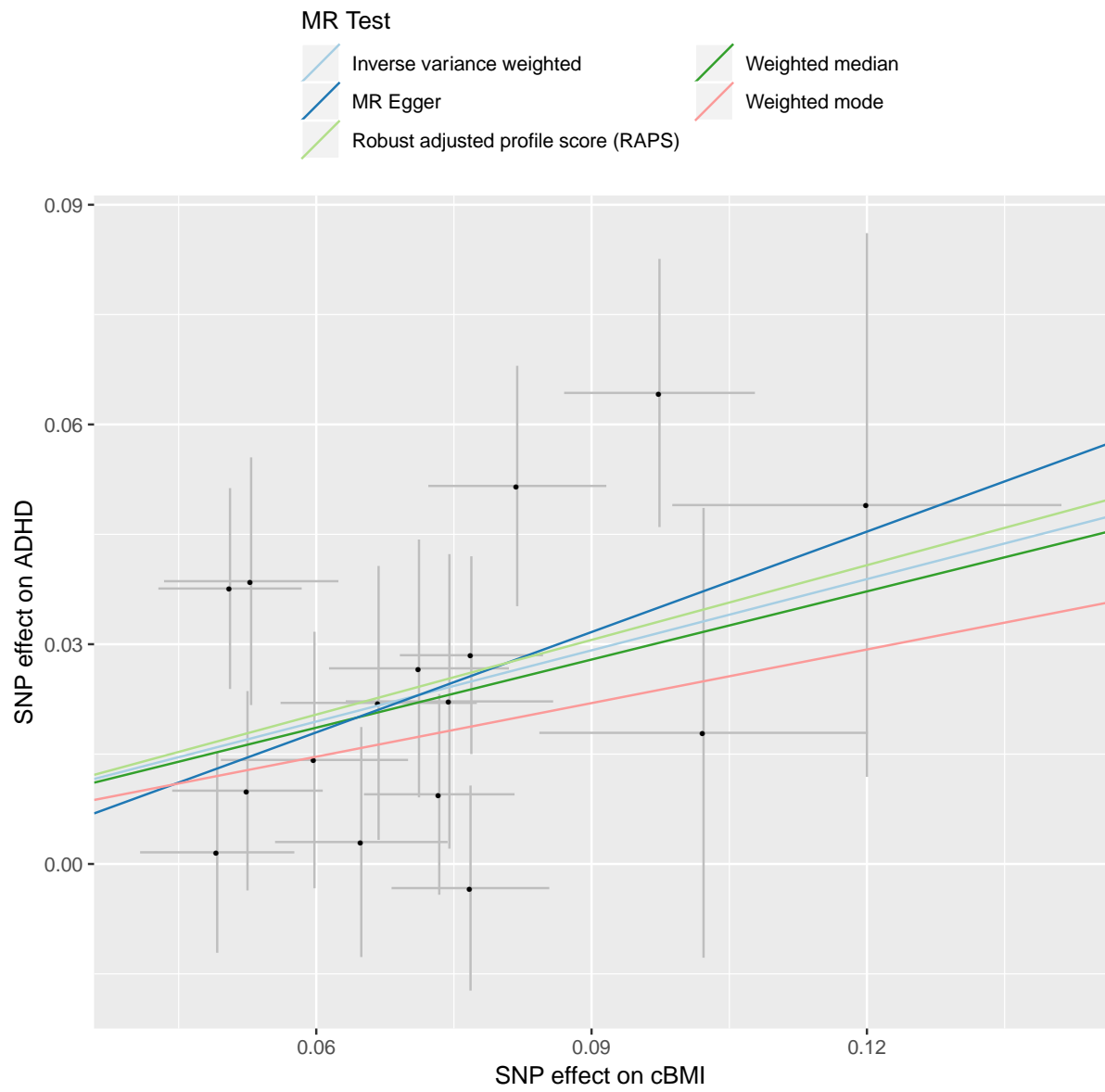
After harmonisation, 16 of the 18 SNPs selected from the childhood BMI GWA summary statistics at the threshold of $p < 5e-8$ were used as the instrumental variables. As shown in Table 5.6 and Figure 5.6, different MR estimators identified that higher childhood BMI increases liability to ADHD except for MR-Egger regression. The estimate of MR-IVW (IVW OR=1.383, 95%CI 1.219-1.568, $p < 0.001$) suggested that a one SD unit increase in childhood BMI increased the odds of ADHD around 1.4 folds. MR-Egger intercept provided little evidence of unbalanced horizontal pleiotropy (intercept=-0.009, 95%CI -0.426-0.407, $p=0.664$) (Table 5.6).

The MVMR estimate also provided evidence that childhood BMI had an effect on the liability to ADHD independently of educational attainment (multivariable MR-IVW OR=1.332, 95%CI 1.190-1.491, $p < 0.001$). The test of difference indicated that the effect was not considerably attenuated after accounting for potential confounding of education ($t(13)=1.254$, $p=0.232$).

Table 5.6 Mendelian randomization results of the effects from childhood BMI to ADHD

Exposure	Outcome	Method	Univariable MR					Multivariable MR				
			nSNP	β	Lower 95% CI	Upper 95% CI	<i>p</i> -value	nSNP	β	Lower 95% CI	Upper 95% CI	<i>p</i> - value
childhood BMI	ADHD	IVW		1.383*	1.219	1.568	<0.001		1.332*	1.190	1.491	<0.001
		MR RAPS		1.405*	1.219	1.619	<0.001					
		Weighted median		1.364*	1.142	1.628	<0.001					
		Weighted mode	16	1.276*	0.895	1.821	<0.001	16				
		MR Egger		1.579*	0.867	2.875	0.158					
		MR Egger intercept		-0.009	-0.426	0.407	0.664					

Figure 5.6 Mendelian randomization results of the effects from childhood BMI to ADHD



5.3.3.4 Effect of adult BMI on the liability to ADHD

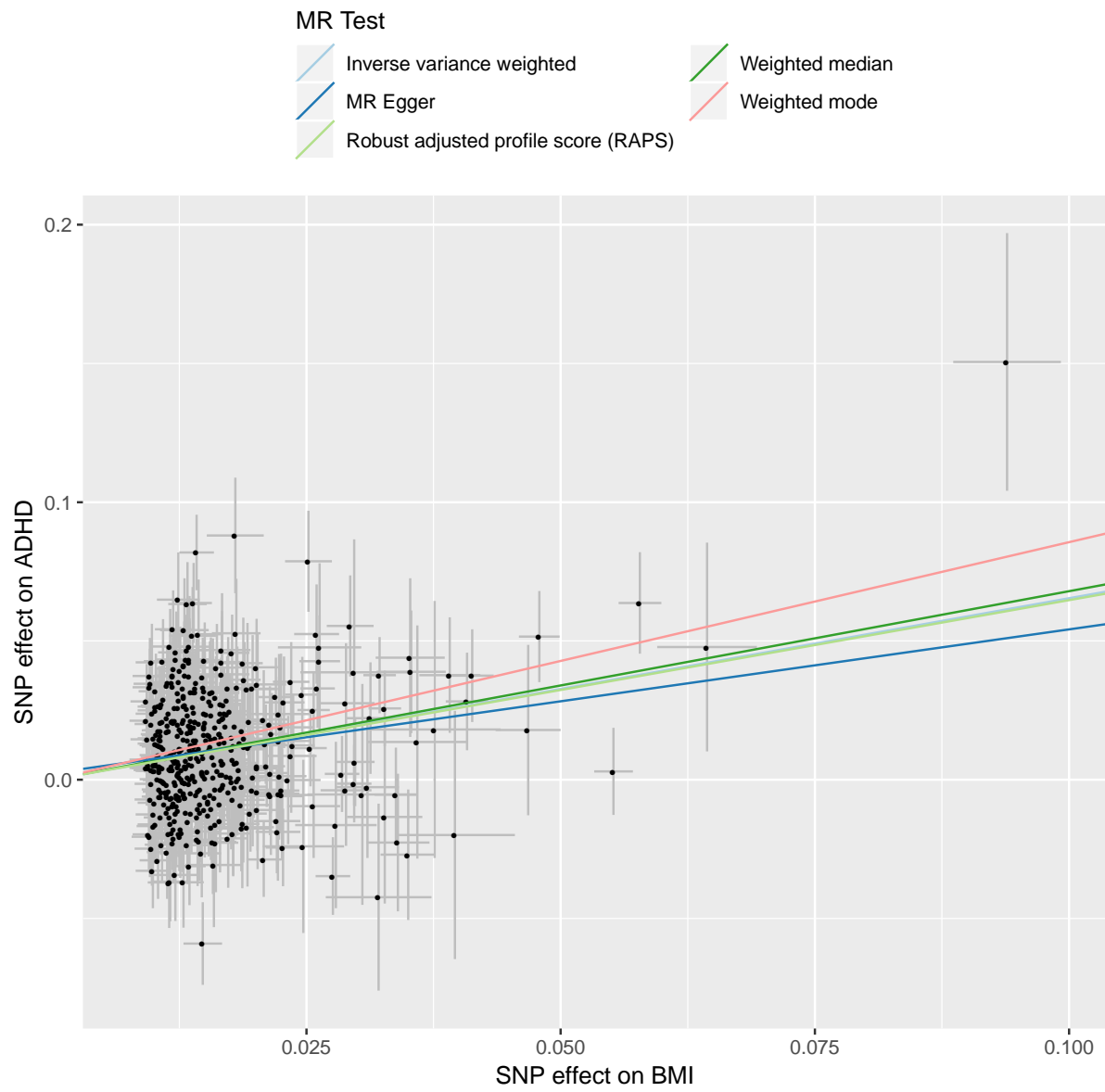
After harmonisation, 463 of the 546 SNPs selected from the adult BMI GWA summary statistics at the significance of $p < 5e-8$ were used in MR. As shown in Table 5.7 and Figure 5.7 different MR estimators consistently support that higher adult BMI increases liability to ADHD. MR-IVW (IVW OR=1.923, 95%CI 1.715-2.157, $p < 0.001$) suggested that one SD unit increase in adult BMI nearly doubled the odds of ADHD. MR-Egger intercept provided little evidence of unbalanced horizontal pleiotropy (intercept=0.002, 95%CI -0.003-0.007, $p = 0.362$) (Table 5.7).

The MVMR estimate also showed that adult BMI had an effect that is independent of educational attainment on the liability to ADHD (multivariable MR-IVW OR=1.587, 95%CI 1.395-7.583, $p < 0.001$), although the effect was attenuated as found in the test of difference ($t(456) = 5.636$, $p < 0.001$).

Table 5.7 Mendelian randomization results of the effects from adult BMI to ADHD

Exposure	Outcome	Method	Univariable MR					Multivariable MR				
			nSNP	β	Lower 95% CI	Upper 95% CI	<i>p</i> -value	nSNP	β	Lower 95% CI	Upper 95% CI	<i>p</i> - value
Adult BMI	ADHD	IVW		1.923*	1.715	2.157	< 0.001		1.587*	1.395	1.806	< 0.001
		MR RAPS		1.910*	1.699	2.147	< 0.001					
		Weighted median		1.973*	1.710	2.276	< 0.001					
		Weighted mode	463	2.353*	1.570	3.527	< 0.001	459				
		MR Egger		1.679*	1.228	2.297	0.001					
		MR Egger intercept		0.002	-0.003	0.007	0.362					

Figure 5.7 Mendelian randomization results of the effects from adult BMI to ADHD



5.4 Discussion

This chapter continued the scope of Chapter 4 and presented a study using genetically informed methods (MZ twin-differences analyses, within-family polygenic score analyses and Mendelian randomization) to investigate the nature of the relationship between ADHD and BMI across childhood and adolescence. Findings across different methods suggested a bidirectional causal and potentially age-specific relationship between ADHD and BMI. Triangulation of evidence from the three methods further indicated multiple sources of genetic and environmental confounding in the relationship between ADHD and BMI.

5.4.1 A unidirectional or bidirectional relationship?

Chapter 4 identified unidirectional effects from ADHD symptoms to subsequent BMI throughout childhood and adolescence in the cross-lagged panel analysis. However, cross-lagged twin-differences analysis in the current study found little evidence supporting that ADHD difference scores predicted subsequent BMI differences. In contrast, within-family polygenic score analysis identified bidirectional relationships between ADHD and BMI, although the effect sizes varied with age. Results of MR were also different between age groups. A unidirectional effect from BMI to ADHD was found in childhood, while a bidirectional relationship was found in adulthood.

It is noteworthy that MR findings were more consistent in the effects of adult BMI to ADHD. Nevertheless, such findings may be attributed to the more powerful genetic instruments for adult BMI compared to childhood BMI and ADHD. This can also explain discrepancy between the current study and a previous MR report, which detected no effects from ADHD to BMI when only 10 SNPs were included as the instrumental variables for

ADHD (Martins-Silva *et al.*, 2019). The current study showed that when more genetic variants were used as the instrumental variables for ADHD, herein 131 SNPs (selected at a more liberal p-value threshold), we can detect the causal effects of ADHD on adult BMI. Equally, this study found little evidence supporting an effect of ADHD on childhood BMI may also result from less powerful genetic instruments, as only 49 SNPs were available at p-value threshold of $p < 5e-5$ and 4 SNPs at $p < 5e-8$. Therefore, replication is needed when more powerful GWAS on ADHD and childhood BMI become available in the future to re-examine if there is consistent finding for the causal relationships between ADHD and BMI in childhood and adulthood.

5.4.2 A causal or a confounded relationship?

It remains unclear in extant literature whether the relationship between ADHD and overweight/obesity is causal. As demonstrated in Chapter 4, traditional longitudinal analysis may yield spurious causal claims due to unmeasured confounding. Results from different genetically informed methods highlighted genetic and environmental confounding affecting the relationships between ADHD and BMI. The heavily confounded relationship may explain why the nature of relationship between ADHD and obesity remains puzzling from epidemiological data. Explanations for mixed causal findings across methods are discussed in turn.

5.4.2.1 Twin-differences analysis

The MZ twin-differences analyses found little evidence of an effect between ADHD symptoms and BMI, suggesting that shared genetic and environmental confounding considerably accounted for the relationship between ADHD symptoms and BMI. This

finding corroborates previous studies showing that a substantial proportion of the association between ADHD and obesity was explained by shared genetic and environmental influences (Chen *et al.*, 2018a, Geuijen *et al.*, 2019). Although there were no cross-lagged effects between differences in ADHD symptoms and differences in BMI, there were substantial autoregressive relationships within both traits (e.g. association between ADHD symptom differences at age 8 and age 12 years). This suggests that twin differences analysis was able to capture phenotypic stability over time; therefore, any undetected associations between twin differences scores in ADHD symptoms and BMI may be small. Replication of the twin-differences findings in a larger twin sample is needed to verify whether small bidirectional causal effects between ADHD symptoms and BMI can be excluded. Furthermore, as discussed in Chapter 4, cross-lagged models examine reciprocal effects at specific time lags. It is possible that the effects between ADHD symptoms and BMI occur at a different time frame (e.g. immediate effects or very long-term effects), which were not picked up by the current study designs.

5.4.2.2 Within-Family polygenic score analysis

Within-family polygenic score (PS) analyses revealed that the associations between the PS for ADHD and the PS for BMI with the opposite phenotype were to some extent biased by confounding due to population stratification, assortative mating and dynastic effects. Furthermore, noticeable attenuation of the between-family estimates after controlling for parental education suggests that dynastic effects related to parental education may constitute an important source of confounding. This is in line with previous studies showing substantial confounding due to family and parental factors in polygenic score prediction for several behavioural manifestations in offspring, such as educational attainment (Bates *et al.*, 2018) and cognitive abilities (Selzam *et al.*, 2019). This study demonstrated that dynastic

effects also affect the polygenic associations between ADHD and BMI. Hence it is important to bear in mind that the PS associations can be confounded, and that a within-family design is more robust to such confounding.

5.4.2.3 Mendelian randomization

MR findings in general support bidirectional causal effects between ADHD and BMI. However, multivariable MR analysis implicated confounding in the relationship due to educational attainment. This study found that causal effects between ADHD and BMI were substantially attenuated after accounting for the genetic effects associated with educational attainment, suggesting assortative mating and dynastic effects may be involved (Brumpton *et al.*, 2020). This is in line with meta-analytic data showing that even general parenting is associated with child eating, child physical activity and child weight status (Russell *et al.*, 2016). Further work implementing a within-family MR design that accounts for shared environmental confounding may provide robust estimates of the causal effects of BMI on ADHD.

In sum, within-family polygenic score analyses and MR analyses suggest potential bidirectional relationships between ADHD and BMI. However, it is noteworthy that the genetic instruments used in polygenic scores and MR reflect long-term exposures (e.g. long-term increased liability to BMI and ADHD), which may be one important source of divergence between findings from these two methods and findings from time-sensitive cross-lagged twin-differences analysis.

5.4.3 The developmental features of the relationship between ADHD and BMI

To better understand the developmental aspects of reciprocal relationships between ADHD and BMI, I integrated age-sensitive designs for the three genetically informed methods. Using data from different ages, I tested whether effects between ADHD and BMI changed from childhood to adolescence. The twin-differences analyses showed little evidence supporting direct effects between ADHD symptoms and BMI across childhood and adolescence. However, such findings may be due to low statistical power or limitations associated with measurement.

In contrast, the polygenic score analyses showed that the genetic liability to higher BMI had stronger influence on ADHD manifestations during the childhood years. There have been an abundance of data supporting the links between obesity and neuropsychological dysfunction, including cognitive decline (Prickett *et al.*, 2015), impaired inhibitory control (Kamijo *et al.*, 2012) and aberrant reward processing (Garcia-Garcia *et al.*, 2014). A recent study also showed that obesity and higher BMI were associated with diminished prefrontal cortex thickness and impaired executive function in children (Laurent *et al.*, 2019). It is possible that obesity may influence neurodevelopmental processes and contribute to the development of ADHD symptoms starting from an early age. In the other direction, the liability to ADHD was associated with higher BMI to a larger extent in adolescence and beyond than in childhood. One plausible explanation to the increasing effects of ADHD is that the problematic eating behaviours associated with ADHD impose higher risks for weight gain in adolescence and beyond, when parental monitoring is less pronounced, and individuals are more autonomous in their food consumption patterns. However, these explanations are tentative and further investigations towards underlying mechanisms are needed.

Finally, MR analysis showed consistent evidence of the effects of BMI on the liability to ADHD in childhood and adulthood, while the liability to ADHD only had an effect on adult BMI. These findings are in line with developmental differences identified by PS analyses and suggest accumulating effects of BMI on the liability to ADHD. However, it is important to interpret with caution that the GWAS for adult BMI is much more powerful than the GWAS for ADHD and childhood BMI. The developmental differences may thus come from larger shared aetiologies between ADHD and BMI that were captured by adult BMI GWAS. Therefore, MR analyses in this study may not be sufficient enough to provide evidence for developmental changes. More powerful GWAS for ADHD and childhood BMI in the future may provide more complete insights.

5.5 Limitations

In addition to the aforementioned methodological limitations associated with each method and limitations related to statistical power, the following limitations should also be considered. As I used BMI as the studied variable for all the analyses, the interpretation may not be applicable when using obesity as study target. Similarly, ADHD symptoms were dimensionally assessed in the current study sample, so the findings may not be readily transmitted to clinical samples. Finally, as I used ADHD liability (i.e. a dichotomised measure) as the exposure variable in MR analyses to study the effect of ADHD on BMI, this may potentially lead to violation of MR assumptions if there is a continuous effect of ADHD on BMI and prevents us from estimating the actual effect (Burgess and Labrecque, 2018).

5.6 Conclusion

The three genetically informed methods converged to show that the relationships between ADHD and BMI involve multiple sources of shared genetic and environmental confounding. Polygenic score analysis and MR analysis suggest plausible bidirectional causal relationships while findings from twin-differences analysis were inconsistent. The polygenic score analysis also uncovered age-specific effects between ADHD and BMI. Future research using larger samples and developmentally sensitive designs can help to resolve apparently diverging findings. Applying innovative causal inference methods under a triangulation framework provides great opportunity to elucidate potential mechanisms and shared vulnerability behind the co-occurrence of complex diseases.

6 Chapter 6: General discussion, implications and future directions

6.1 Overview

ADHD symptoms are associated with a range of behavioural and psychosocial problems. In addition to symptom persistence and severity, the development of ADHD symptoms also affects ADHD outcomes (Pingault *et al.*, 2014). Using longitudinal analyses and genetically informed methods can help to unravel genetic and environmental factors explaining ADHD symptom development and mechanisms leading to different developmental outcomes.

This thesis set out to systematically examine the developmental pathway of ADHD symptoms across childhood and adolescence using a multimodal approach. Applying multinomial logistic regression and twin modelling on a large-scale longitudinal cohort helps to identify childhood characteristics differentiating late-onset ADHD and aetiological contributions to the developmental course and developmental outcomes of inattentive symptoms. Findings have important clinical implications as they demonstrate potential areas for intervention to curb symptom deterioration and to improve developmental outcomes of individuals with ADHD. This thesis also implemented different genetically informed causal inference methods to investigate the nature of the relationships between ADHD and BMI across different developmental stages. This approach strengthens causal inferences and provides an example of triangulation of findings using multiple designs.

6.2 Summary of findings and implications

6.2.1 The childhood characteristics and adolescent outcomes of late-onset ADHD. What childhood factors predict late-onset ADHD?

Chapter 2 presented a study investigating childhood characteristics and adolescent outcomes of individuals with ADHD symptoms emerging beyond the childhood years, namely late-onset ADHD. This study used data from the “Twin Early Development Study” (TEDS), a database from a population-based twin cohort in the UK. Different ADHD categories were assigned according to parent-rated ADHD symptoms in childhood and adolescence. Individuals with late-onset ADHD was defined as those who did not meet the DSM ADHD symptom criteria before 12 years old but crossed the threshold afterwards (American Psychiatric and American Psychiatric Association, 2013). Late-onset ADHD was further divided into de novo late-onset ADHD and subthreshold late-onset ADHD, according to childhood symptom presentations. Results showed that de novo late-onset ADHD and subthreshold late-onset ADHD were distinct from non-ADHD controls in that they showed more childhood conduct problems and more family environmental adversity. Despite differences in symptom development from childhood, the two late-onset groups experienced comparable levels of emotional and behavioural impairments as childhood-onset persistent ADHD in adolescence. The study then compared and contrasted two late-onset ADHD groups with childhood-onset persistent ADHD and non-ADHD controls to identify predictors of late-onset symptoms. Findings identified non-overlapping childhood predictors for different ADHD groups: family socioeconomic difficulty specifically predicted de novo late-onset ADHD, while other family adversity (maternal depression and harsh parenting) predicted subthreshold late-onset ADHD. Additional predictors were identified for childhood-onset persistent ADHD.

The findings of this study showed that ADHD symptoms can first emerge beyond the childhood years and can be predicted by a number of childhood characteristics. More factors predicting childhood-onset persistent ADHD followed by subthreshold late-onset ADHD and de novo late-onset ADHD suggested a dimensional distribution of risks contributing to ADHD symptom development. Non-overlapping childhood predictors between de novo late-onset ADHD and subthreshold late-onset ADHD further implied that different aetiological pathways for the late-onset symptoms may be involved. It is noteworthy that even with no or very few ADHD symptoms in childhood, de novo late-onset ADHD already exhibited levels of behavioural and emotional problems higher than non-ADHD controls. Previous research has identified that late-onset ADHD had intermediate polygenic risks for ADHD between the non-ADHD controls and childhood-onset ADHD (Riglin *et al.*, 2016). It is possible that late-onset ADHD is more likely to be found in individuals with a predisposition to ADHD or to general psychopathology. These findings also correspond to a vast amount of ADHD research showing that the indicators of ADHD (e.g. neurocognitive characteristics and behavioural manifestations) and its genetic and environmental underpinnings are dimensionally distributed in the population (Brikell *et al.*, 2018, Humphreys *et al.*, 2019). Additionally, the fact that the lower number of early childhood factors predicted de novo late-onset ADHD suggests that time-varying factors emerging across the development may better predict late-onset ADHD symptoms. To better characterise different developmental processes of ADHD symptoms, it is important to adopt a dimensional approach and a developmentally sensitive study design for risk assessments in future research.

It is noteworthy that this study challenged the conception that late-onset ADHD is scaffolded by a protective environment (Kosaka *et al.*, 2018). Contrary to that argument, I found that increased family adversities predicted late-onset ADHD. Previous studies have demonstrated that low socioeconomic status and certain family adversities were associated

with deteriorations in neurodevelopment and poor mental health outcomes in offspring (Hagan *et al.*, 2016, Sharp *et al.*, 2019). This study further demonstrated that low socioeconomic status, harsh parenting and maternal depression in the early stages of life predicted an increase in ADHD symptoms from childhood to adolescence. Together with the finding that emotional and behavioural problems were aggravated along with the increase in ADHD symptoms among late-onset individuals, this study suggested that an adverse environment may play an influential role in common psychopathological pathways or symptom feedback networks that lead to psychiatric comorbidity. Therefore, early identification and remediation for children at risk are important to curb the development of ADHD symptoms as well as other psychopathology beyond childhood.

6.2.2 Whether and how the development of inattention influences adolescent academic performance.

Chapter 3 presented a study investigating whether the genetic and environmental influences underlying the development of inattentive symptoms contribute to the developmental effects of inattentive symptoms on academic outcomes. This study applied latent growth curve modelling and twin analyses on parent-rated inattentive symptoms at ages 8, 12, 14 and 16 years and GCSE performance at age 16 years in the TEDS sample. The results of the latent growth curve model showed that both the baseline level and the developmental course (systematic change in symptoms) of inattentive symptoms predicted GCSE performance. The twin analyses uncovered independent genetic contributions to the baseline level and the developmental course of inattention. Additionally, effects of inattention on GCSE were explained largely by shared genetic influences.

These findings highlight the importance of ADHD symptom development on academic outcomes. Traditionally, research has focused on functional impairment associated with symptom severity. This study showed that the way symptoms change over time also had an effect on the outcomes. Therefore, the developmental processes of ADHD symptoms should be regarded as important outcome indicators that demand close monitoring. Unique genetic contributions to the development of inattention also inform future aetiological search for genetic risk variants specific to symptom development over time (Hannigan *et al.*, 2018). Shared genetic influences between inattentive symptom development and academic performance suggests a potential causal relationship. Alternatively, shared genetic influences may arise from unmeasured confounding or pleiotropy. A recent Mendelian randomization study found bidirectional causal relationships between ADHD and educational attainment (Dardani *et al.*, 2020). Because the genetic variants associated with educational attainment are closely associated with sociodemographic and familial indicators, it is possible that the association between inattention and academic performance involve a mixture of direct causality and confounding. Future studies with a within-family or a fixed-effect design that control for confounding can advance our understanding of causal pathways linking ADHD and poor academic performance (Pingault *et al.*, 2018).

6.2.3 Investigating potential causal relationships between ADHD symptoms and BMI across childhood and adolescence using longitudinal observational data.

Chapter 4 presented a study investigating the nature of the associations between ADHD symptoms and BMI across childhood and adolescence. This study employed the Cross-Lagged Panel Model (CLPM) and the Autoregressive Latent Trajectory with

Structured Residuals (ALT-SR) model to draw causal inferences from longitudinal observation data. The two models examined the reciprocal relationship between ADHD symptoms and BMI at a specific time lag, while the ALT-SR further tested whether the relationship can be detected at the within-individual level. The CLPM showed that higher ADHD symptoms predicted higher BMI at the adjacent time point but not the reverse. However, the ALT-SR provided little evidence supporting any reciprocal effects between ADHD symptoms and BMI at the individual level.

Meta-analytic findings based on observational studies concluded a bidirectional relationship between ADHD and overweight/obesity. However, many of the studies used cross-sectional designs, which may be subject to reverse causality and confounding (Cortese and Tessari, 2017, Nigg *et al.*, 2016). Consequently, despite a well-established link, the nature of the relationship between ADHD and obesity remains unresolved. The current study used a longitudinal design with clear temporal ordering to avoid reverse causality. The findings that earlier ADHD symptoms predicted subsequent BMI suggested potential causal effects. However, the lack of supporting evidence in the reverse direction cannot rule out that BMI is causally linked to ADHD symptoms at a different time lag, or that the causal effects were too small to be detected by the current study.

The ALT-SR specifically examined reciprocal effects between ADHD symptoms and BMI after controlling for between-individual influences. The discrepant findings between the CLPM and the ALT-SR imply that the effects of ADHD symptoms on BMI may arise from unmeasured confounding influencing the development of the two traits. However, it is noteworthy that the phenotypic relationships between ADHD and obesity have been reported to be small and unstable during childhood and adolescence (Nigg *et al.*, 2016). It may be more challenging to study the causal relationship using observational data in younger age samples. In this regard, to draw causal inferences in the relationship between ADHD and

BMI, we need to employ alternative approaches that are more robust and powerful. For example, genetically informed methods may help to strengthen causal inference and identify potential sources of confounding.

6.2.4 Investigating potential causal relationships between ADHD symptoms and BMI across childhood and adolescence using genetically informed approaches.

Chapter 5 presented a study expanding the approaches in Chapter 4 to investigate potential causal relationships between ADHD and BMI. I triangulated findings from different genetically informed methods, including twin-differences analysis, within-family polygenic score association and Mendelian randomization (MR). Additionally, I also applied developmentally sensitive designs to examine age-specific components in the potential causal relationships. The findings of the twin-differences analyses provided little evidence of reciprocal relationships between the differences in ADHD symptoms and the differences in BMI. However, the within-family polygenic score analyses found within-family polygenic effects from both directions. The between-family polygenic effects decreased significantly when parental education was controlled for in the model. Findings across different MR estimators supported bidirectional causal relationships between ADHD and BMI, although evidence for the effect of BMI was more consistent. Multivariable MR revealed confounding of educational attainment for both ADHD and BMI. Developmental differences in the relationship between ADHD and BMI were detected by polygenic score analyses and MR. Polygenic score analyses showed that the polygenic scores for ADHD had increasing effects on BMI with age, while the polygenic scores for BMI had decreasing effects on ADHD symptoms. The MR results only supported direct effects of genetic liability to ADHD on

adult BMI but not on childhood BMI. Overall, findings of this study supported bidirectionally causal and developmentally specific relationships between ADHD and BMI.

Findings of Chapter 5 are consistent with findings of Chapter 4 in that the reciprocal associations between ADHD and BMI are partly attributable to confounding. Little evidence of an effect in twin-differences analyses suggested that shared genetic and environmental factors may account for the relationship between ADHD and BMI. The polygenic scores for educational attainment have been demonstrated to capture familial effects across a number of traits including BMI (Kong *et al.*, 2018). Through the within-family polygenic score analyses, the current study demonstrated that population stratification, assortative mating and dynastic effects were potential confounding variables in the relationship between ADHD and BMI. Moreover, the multivariable MR showed that genetic effects associated with educational attainment contributed to the bidirectional causal relationships between ADHD and BMI. Hence, MR results concur with polygenic score analyses to show confounding by dynastic effects in the relationships between ADHD and BMI. Altogether, these findings corroborated previous studies showing that the association between ADHD and obesity can be largely explained by shared genetic and environmental influences (Chen *et al.*, 2018a).

Triangulation of the results of three genetically informed methods highlights multiple sources of confounding affecting the relationships between ADHD and BMI. This study demonstrated that confounding due to parental factors can be observed in the relationship between ADHD and BMI. Despite disjunction between genetically informed approaches and longitudinal statistical analyses (methods applied in Chapter 4), such mixed findings should be interpreted in complement. Longitudinal statistical designs implemented here rely on matching the specific timing of putative causal effects (e.g. changes in ADHD symptoms at age 8 years influence BMI at age 12 years). Conversely, genetic instruments reflect lifelong differences in exposures. Therefore, inconsistent findings between genetically informed

approaches and longitudinal statistical analyses suggest that the causal effects between ADHD and BMI may involve long-term accumulated exposures. However, replications on larger longitudinal cohorts are needed to verify this hypothesis. It is crucial to adopt a pluralistic approach and to obtain mechanistic evidence from functional analyses at the molecular level to better understand aetiological pathways between ADHD and obesity (Faraone and Larsson, 2019, Meijer *et al.*, 2020, Vandenbroucke *et al.*, 2016).

6.3 Implications for future directions

Findings of this thesis have generally supported the knowledge that ADHD has diverse symptom manifestations, multiple comorbidity and negative impacts across different functional domains (Faraone *et al.*, 2015). But more importantly, this thesis extends these findings specifically to the systematic developmental changes in ADHD and explained potential underlying mechanism of the developmental outcomes. Chapters 2 and 3 showed the heterogeneous nature in the development of ADHD and the importance of developmental processes on outcomes. Chapter 4 and 5 disentangled the developmental relationships between ADHD and BMI across childhood and adolescence and found bidirectional causal effects between the two conditions. Implications of each study are discussed within the relevant chapter. In the following section, I discuss possible avenues for future research and implications in clinical management and public health domains.

6.3.1 Extending current understanding of the development of ADHD

The weight of the evidence indicating symptom persistence has shifted our understanding of ADHD from a childhood disorder to a lifelong condition. Research findings in the past few years further introduce a new category of late-onset ADHD. Chapter 2 supported that ADHD symptoms can first emerge beyond the childhood years in some individuals, contrary to the conventional idea that ADHD symptoms always arise in the childhood years. Late-onset ADHD can be distinguished from non-ADHD controls and childhood-onset persistent ADHD by a number of childhood characteristics. Chapter 2 further extended current knowledge on factors that contributed to the development of late-onset ADHD. Although the underlying mechanisms driving late-onset ADHD symptoms need further investigation, I found that individuals with higher levels of general psychopathology and family environmental adversity are at higher risks for the condition. Further investigation on the interaction between genetic liability and environmental influences in relation to late-onset ADHD symptoms can shed light on the aetiology.

This thesis also highlights the importance of ADHD symptom development on the outcomes and varying factors influencing the developmental processes. Following the findings of heterogeneous age of onset, Chapter 3 demonstrated individual variation in the developmental course of inattention in relation to different academic outcomes. Specifically, Chapter 3 showed that not every individual experienced decreasing inattentive symptoms with age, and those with worsening symptoms across time had poorer academic performance. Furthermore, Chapter 3 highlighted heterogeneous underpinnings of the development of ADHD through the finding that genetic and environmental contributions to the developmental course of inattention were partly independent from those underlying the baseline symptom level. This suggests that genetic underpinnings specifically to variations in symptom development also play a part in developmental outcomes. Consequently, future

aetiological studies of ADHD should not only focus on incidence of disease but also mechanisms driving symptom development, including genetic liability, environmental factors and the gene-environmental interplay. In addition to psychological and functional outcomes, the development of ADHD also influences physical outcomes. Chapter 4 and 5 identified age-specific causal relationships between ADHD and BMI. More consistent evidence of the positive influences of ADHD on BMI with age suggests accumulating developmental effects.

Taken together, these findings suggest that the dynamic and heterogeneous nature of the development of ADHD is a function of different balances of genetic and environmental contributions. More importantly, variation in the development of ADHD can explain individual differences in a range of outcomes beyond symptom severity and duration. The pluralistic approach in this thesis provides a good example for studies that aim to study the development of a complex disorder such as ADHD.

6.3.2 Using triangulation in the study of ADHD development

Understanding causal mechanisms is a crucial step to targeted and effective intervention. This thesis investigated relationships between the development of ADHD and associated conditions using multiple approaches. Chapter 3 employed classic twin modelling and uncovered shared genetic factors underlying the contribution of inattention to GCSE performance. Nevertheless, overlapping genetic factors suggest a causal relationship only when unmediated/horizontal pleiotropy is excluded, which cannot be decided based on the twin design alone. Therefore, Chapter 4 examined if the relationships between ADHD and BMI were causal using multiple specifications of cross-lagged models that can control for unmeasured confounding. The lack of evidence supporting cross-lagged effects between

ADHD symptoms and BMI in the autoregressive latent trajectory model suggests that the relationships between ADHD and BMI are confounded. However, it is possible that there were age-dependent causal effects outside of the measured time lag that were undetected in cross-lagged analyses. Findings of Chapters 3 and 4 highlight the need of using different approaches to study causality because all methods rely on assumptions that are sometimes untestable. It is noteworthy that methods that have different sources of bias can complement one another when findings are examined under the triangulation framework (Lawlor *et al.*, 2016). Therefore, in Chapter 5 I combined longitudinal analyses and genetically informed methods to more confidently assess the possibly causal nature of the reciprocal relationships between ADHD and BMI.

Triangulation can help evidence synthesis in a number of ways. First, if findings from different approaches converge, we can be more confident in the causal claim. Second, different methodological designs can provide insights regarding the sources of bias. One such approach is to compare findings from methods that control for unrelated sources of bias, as in the current thesis or methods that provide the opposite control, where the contrary findings are expected at the presence of biases. For example, Chapter 5 used within-family polygenic score analyses and Mendelian randomization (MR) to interrogate causal relationships between ADHD and BMI. Both approaches detected bidirectional causal effects between ADHD and BMI. Furthermore, attenuation in the effect estimates in multivariable MR further indicated that the causal effects from both directions were confounded by population stratification, dynastic effects and assortative mating. Because such confounding is controlled by design in the within-family polygenic score analyses, this increases the likelihood that relationships between ADHD and BMI are partly causal, despite being affected by multiple sources of bias. Third, if findings do not align in triangulation, we can investigate what other factors may be involved by comparing limitations and bias of each

approach to uncover potential areas for future study. However, it is also important to consider measurement comparability. If measurements across different approaches tap into dissimilar exposures and outcomes, results should not converge irrespective of differences in sources of bias. Chapter 5 demonstrated how divergent findings can be informative in this regard. In contrast to the other two methods, twin-differences analyses did not detect direct effects between ADHD and BMI. However, twin differences analyses investigated temporal relationships between ADHD symptoms and BMI phenotypes withing a defined measurement interval (as cross-lagged models). In contrast, polygenic score analyses and MR used genetic instruments to examine the effects of lifetime exposure on the outcomes. Discrepant findings suggest that timing of the effects should be further investigated in the relationship between ADHD and BMI.

Chapter 5 demonstrated how triangulation can be employed to study causal relationships in the development of ADHD. It also highlighted that all designs rely on assumptions that cannot be tested explicitly within the design itself but can, potentially, be (partially) ruled out in complement with other designs. Therefore, in addition to statistical adjustment for potential confounding and adjustment by study design, the practice of triangulation should be widely adopted when unpacking the puzzling relationships between multifactorial complex conditions. Furthermore, careful scrutiny and triangulation of evidence with a pluralistic approach (Vandenbroucke *et al.*, 2016) are needed before drawing inferences and translating knowledge into practice. Although not explored in this thesis, triangulation can also help to formally compare the magnitude of causal effects and pin down key elements in causal pathways (Lawlor *et al.*, 2016). It requires great efforts to ensure comparability between different approaches and to reconcile measurement differences, but the findings could be immensely informative and useful.

6.3.3 Implications for clinical and public health initiatives:

Findings from this thesis identify potential areas for preventive intervention to tackle undesirable outcomes associated with ADHD. First, Chapter 2 found that family environmental adversity may drive the increase in ADHD symptoms for some individuals, leading to a late-onset ADHD diagnosis. The finding that late-onset ADHD rarely arose in the absence of behavioural and emotional problems in childhood also suggests that early detection of at-risk individuals is crucial. Similarly, Chapter 3 highlighted that changes in inattentive symptoms can influence future academic outcomes. Corroborating previous reports, children with a rising developmental course of inattention were more likely to have poor educational performance (Breslau *et al.*, 2010, Pingault *et al.*, 2011). The finding of shared genetic underpinnings between the development of inattention and its effects on academic performance suggests that specific genetic liability may be identified for children who have higher risk developing worse outcomes. Finally, Chapters 4 and 5 identified bidirectional causal relationships between ADHD and BMI. The age-dependent effects between ADHD and BMI indicate that different strategies are needed to meet the developmental need. In addition, the two studies also identified shared genetic and environmental confounding affecting the co-occurrence of ADHD and BMI, suggesting family environmental factors can be a target of intervention to curb the comorbidity.

6.4 Limitations

Findings of this thesis should be considered in the context of some methodological limitations. Limitations of the individual study have been discussed in the chapter concerned. This section will describe general limitations shared across different studies.

6.4.1 Result generalisability and sample representativeness

Data analysed in this thesis were drawn from the “Twins Early Development Study” (TEDS) cohort. This is a population-representative twin cohort in the UK with predominantly white participants (Haworth *et al.*, 2013). Therefore, the results may not be directly transferable to populations from different ethnicities. In addition, the use of twin data may limit result generalisability to samples of singletons or of the general population. For example, higher rates of preterm delivery and perinatal complications were found with twin pregnancies (Rao *et al.*, 2004). Intrauterine growth restriction and lower birth weight are also more common in twins than in singletons (Hiersch *et al.*, 2019). As perinatal complications and low birthweight have been associated with increased risk for ADHD (Lim *et al.*, 2018), our twin samples may represent a high-risk subgroup with greater disease susceptibility. However, the prevalence of childhood-onset persistent ADHD identified in Chapter 2 fell within the range reported in other population-based studies (August *et al.*, 1996) (Riglin *et al.*, 2016), suggesting reliability in the study estimates. Moreover, the developmental trajectories of externalising behaviours and emotional problems of the TEDS sample were also comparable with findings from other epidemiological surveys (Hannigan *et al.*, 2018, Tick *et al.*, 2016).

Second, for the purpose of investigating the development of ADHD, this thesis excludes twin pairs with complete data missing on ADHD symptom assessment in childhood

(ages 8 and 12 years) or adolescence (ages 14 and 16 years). For each study, additional exclusions were applied for different research objectives. However, excluding participants with missing data may create systematic bias that affects sample representativeness. For example, participants who remain in the follow-up usually have higher socioeconomic background, better family support and better psychosocial functioning (Young *et al.*, 2006). Therefore, our study sample may be under-representative of deprived individuals or those who experience more psychosocial distress. Although such caveats are common among longitudinal population-based research (Ng *et al.*, 2016), our findings should be interpreted with caution and replication with other samples is needed.

Third, one of the common methodological problems that may affect sample representativeness in longitudinal studies is attrition, and the TEDS sample is no exception. Attrition may be due to dropouts or missing observations on repeated measurements. According to the official summaries, there were almost 14,000 families in the initial TEDS sample but only 5123 families provided data when the twins were 16 years old (Study, 2019). However, despite attrition, the TEDS sample still remains fairly representative of the general UK population up till adolescence (Haworth *et al.*, 2013). In Chapter 2 and 3, I also demonstrated that our study sample (after attrition and applying exclusion criteria) was adequately representative of the TEDS initial sample and general UK population (findings presented in the Appendix 1.1 and Appendix 2.1). As for missing data, I used full information maximum likelihood (FIML) estimation throughout this thesis to minimise bias due to incomplete observation. FIML estimation has been shown to provide less biased estimates for latent variable structural equations (Cham *et al.*, 2017) and multiple regression models (Enders, 2001) when data are missing completely at random (MCAR) or missing at random (MAR).

6.4.2 Limitations of the Measurements

The measurement of ADHD symptoms used across this thesis is the Revised Edition of Conners' Parent Rating Scale (CPRS-R). Although the CPRS-R provides a comprehensive assessment of ADHD-related behaviours, the questionnaire does not assess functional impairment, symptom chronicity and symptom pervasiveness (Conners *et al.*, 1998). In general, when the aforementioned criteria (e.g. functional impairment and symptom pervasiveness) are considered, a noticeable variation in the prevalence of ADHD emerges (Dopfner *et al.*, 2008). However, high correlations between the ADHD diagnosis based on the CPRS-R results and clinical interviews supports the use of the CPRS-R for ADHD assessment (Demaray *et al.*, 2003). Therefore, our findings may still reliably inform risks and outcomes associated with ADHD.

Second, informant-related bias should be considered when interpreting the findings in the studies. The CPRS-R ratings used in this thesis were obtained primarily from mothers. I did not include self-report or teacher-report symptoms to ensure consistency in reporting because the diagnosis of ADHD may vary across different informants (Barkley *et al.*, 2002). In addition, evidence shows that parent-reported ADHD symptoms have higher agreement with clinical assessments during childhood and adolescence (Chang *et al.*, 2016, Du Rietz *et al.*, 2016), and that parent-reported ADHD symptoms are associated with the polygenic scores for ADHD in both childhood and adulthood (Riglin *et al.*, 2020). Another informant-related issue when using parent-reported data in twin samples is the “contrast effect”, where lower resemblance than expected (intraclass correlation between one twin and the co-twin) is found for dizygotic (DZ – non-identical) twins (Saudino *et al.*, 2000). Contrast effects may exaggerate differences in DZ twins, and hence inflate heritability estimates in twin analysis in

the context of equal environment assumption (Merwood *et al.*, 2013). However, the intraclass correlations of inattention ratings in DZ twins were around 50% of the values in monozygotic (MZ – identical) twins in our sample, suggesting parent-reported ADHD symptoms were not severely affected by contrast effects.

6.4.3 Statistical limitations in studying the development of ADHD

This thesis employed longitudinal statistical analyses and genetically informed methods to study factors associated with the development of ADHD, and whether and how the development influences outcomes. Potential pitfalls and statistical limitations pertinent to each method have been discussed in the concerning chapters. Here, I describe overarching limitations shared among different approaches when studying factors associated with the development.

6.4.3.1 The missing counterpart: time-varying risk factors

First, ADHD development is a dynamic process influenced by various biological and environmental factors (Sonuga-Barke and Halperin, 2010). Some of the factors are stable across life, but some factors are changing and have varying effects over time. However, most studies do not include changes in the risk factors and their accompanying effects on the development of ADHD, because to model jointly the co-development of ADHD and associated risk factors is highly subject to data availability. Instead, risk factors are often treated as either a transient exposure or a static state. Such an approach conflates effects associated with the variation in risk factors and fails to capture the developmentally dynamic processes that constantly occur. For example, a recent study shows that a decreasing household income, regardless of the initial income band, predicts childhood diagnosis of

ADHD (Choi *et al.*, 2017). This suggests that changes in risk factors may be as important in the development of ADHD, if not more so, than the presence of such risks. Consequently, developmental prediction analyses without incorporating time-varying risks may have inadequate performance and explain fewer individual differences in the developmental pattern and outcome. Findings of Chapter 2 and Chapter 4 demonstrated limitations when time-varying risks were not available in the models. In brief, the fewer number of childhood factors predicting de novo late-onset ADHD in Chapter 2 was possibly because late-onset ADHD symptoms were more attributable to time-varying risk factors across childhood and adolescence. Similarly, little evidence for the prospective effects of BMI on ADHD symptoms from the cross-lagged panel model in Chapter 4 may be due to such effects happening at a different time lag, but the data were unavailable in our sample.

Equally, polygenic score analysis and Mendelian randomization use genetic variants as instrumental variables to reflect lifelong differences in risk exposure in relation to the outcomes. Therefore, findings of polygenic score analyses and Mendelian randomization in Chapter 5 were not necessarily informative about effects associated with the timing, duration and changes of the ADHD symptoms on BMI and vice versa. Although I implemented a cross-lagged design in the twin-difference analyses, the findings suffered from same limitations as in the cross-lagged panel model. Future research in the field of developmental psychopathology should incorporate a co-developmental concept in the study design, which not only focuses on changes in mental disorders (outcomes) but also changes in associated factors (risks).

6.4.3.2 Unidirectional or bidirectional? Reverse causation between the exposure and the outcomes

In the above section, I discussed statistical limitations due to missing information on the dynamic characteristics of risk factors. We need also to consider the interactive nature between the development of ADHD and the development of associated factors. More specifically, the development of ADHD may in turn influence changes in the risk factors, introducing reverse causal effects. Reverse causation can complicate causal claims from observational data in different areas of epidemiological research. Although a longitudinal design with repeated data collection can minimise such bias, it is not possible to fully exclude reverse causality (Sattar and Preiss, 2017). Therefore, findings of Chapters 2, 3 and 4 were potentially subject to reverse causality bias because the statistical analyses were based mainly on longitudinal observations. In contrast, genetic information can provide causal estimates more robust to reverse causation (Lawlor *et al.*, 2008). Hence, to overcome the statistical limitations when studying factors associated with the development of ADHD, a favourable approach would be to combine and compare longitudinal statistical analyses and genetically informed methods. Such a design can detect causal effects via genetic instruments and the timing of the effects via observed data. To be successful, it is crucial to include repeated assessments of different associated factors along with the study phenotypes to better capture the developmental relationships.

6.5 Conclusion

Findings of this thesis suggest that 1) developmental processes of ADHD comprise variation in age of onset, systematic change in symptom levels and impact of developmental trends on long-term outcomes; 2) specific genetic and environmental risks contribute to different

ADHD developmental patterns and how they relate to the outcomes; 3) associations between ADHD and different outcomes reflect both multiple sources of confounding and putative causal effects; 4) it is important to adopt a pluralistic approach to triangulate evidence regarding causal mechanisms for clinical and public health purposes.

Altogether, these findings contribute to a more complete and systematic understanding of different developmental aspects of ADHD.

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Appendices

Appendix 1.1

Sample representativeness of the UK population in the study of late-onset ADHD

	Returned data (individuals)	Male	MZ	White	Mothers with A-level or higher	Mother employed	Father employed
UK Census	-	-	-	93%	32%	49%	89%
TEDS initial sample	25186	49.5%	33.8%	91.6%	34.8%	42.9%	82.6%
Current study sample	9875	45.8%	36.7%	93.8%	44.7%	47.2%	88.1%

Note. UK data from the 2000 General Household Survey (Walker *et al.*, 2001) were used rather than more recent data because they provided more appropriate comparisons for TEDS twins who were born from year 1994 to 1996. A-levels are the national educational exam taken at 18 years of age in the UK. MZ, monozygotic twins.

Appendix 1.2

Number of participants with different ADHD symptom levels in childhood and adolescence

Inattentive or hyperactive/impulsive symptom count	adolescence			
	Childhood	0-2	3-5	6-9
Symptom counts				
0-2	6509	470	123	
3-5	1264	443	164	
6-9	384	230	288	

Note. A total of 9875 participants had CPRS-R ratings in childhood and in adolescence and met the inclusion criteria. 7084 participants were included in the final analyses, including non-ADHD controls (n=6509); late-onset ADHD with low childhood symptom level (de novo late-onset ADHD, n=123); late-onset ADHD with subthreshold childhood symptom level (subthreshold late-onset ADHD, n=164); childhood-onset persistent ADHD (n=288).

Appendix 2.1

Sample representativeness of the UK population in the study of inattention development and GCSE scores

	Returned data (N pairs)	Male (%)	MZ (%)	White (%)	Mothers with A- levels or higher (%)	Mother employed (%)	Father employed (%)
UK Census	-	-	34.3	93%	32%	49%	89%
TEDS initial sample	13722	49.9%	33.2%	91.7%	35.5%	43.1%	91.6%
Current study sample	5634	46.7%	36.5%	93.5%	45.1%	48.7%	94.5%

Note. UK data from the 2000 General Household Survey (Walker *et al.*, 2001) were used rather than more recent data because they provided more appropriate comparisons for TEDS twins who were born from year 1994 to 1996. A-levels are the national educational exam taken at 18 years of age in the UK. MZ, monozygotic twins.

Appendix 2.2

CPRS-R inattention ratings of twin pairs with GCSE scores and twin pairs without GCSE scores

	Twin pairs with GCSE scores (N=5634)	Twin pairs without GCSE scores (N=2089)	Statistics		
	mean (SD)	mean (SD)	t	p value	Cohen d
Age 8	4.91 (\pm 4.71)	6.09 (\pm 5.55)	7.61	<0.001	0.24
Age 11	5.15 (\pm 4.77)	6.42 (\pm 5.62)	6.64	<0.001	0.26
Age 14	4.73 (\pm 4.91)	6.21 (\pm 5.74)	5.09	<0.001	0.30
Age 16	3.84 (\pm 4.51)	5.60 (\pm 5.84)	6.96	<0.001	0.38

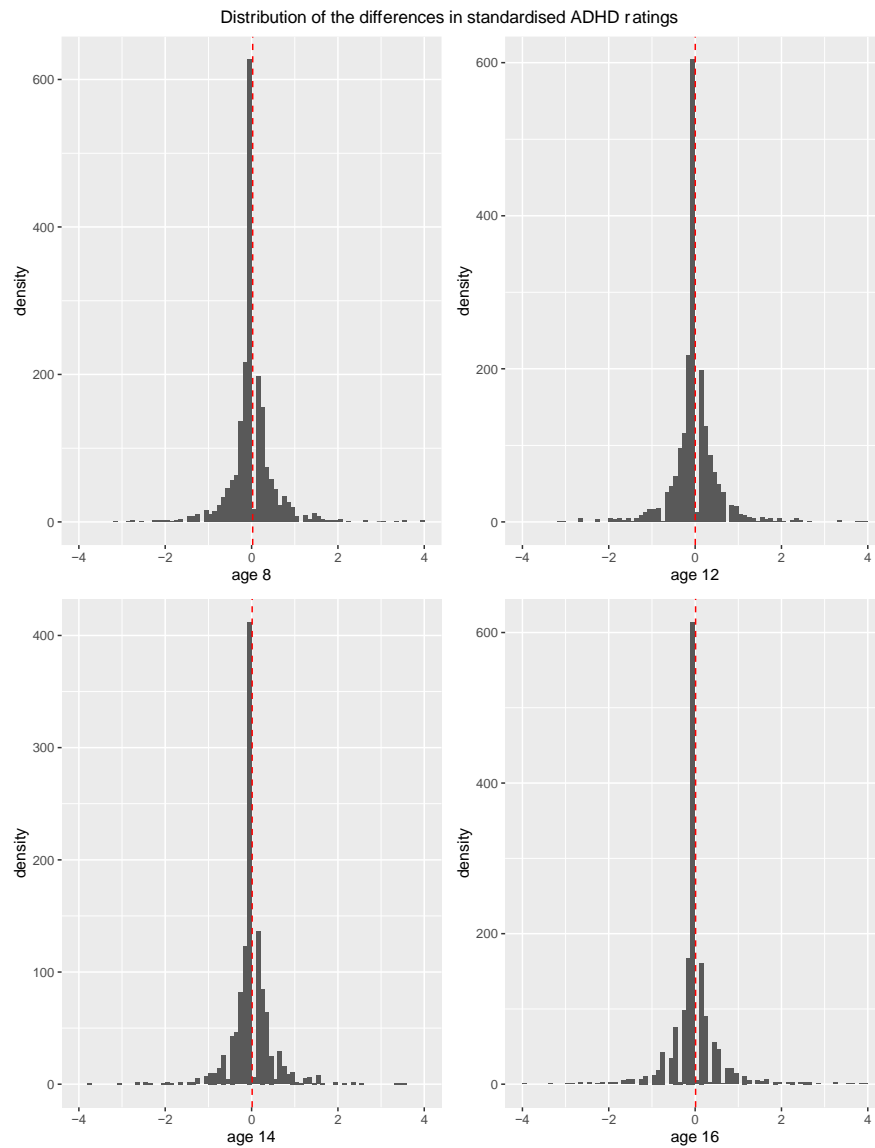
Appendix 3.1

The values of 1% and 99% percentile of BMI at the four time points

	raw BMI (kg/m ² , mean, sd)	1% percentile	99% percentile	winsorise BMI (kg/m ² , mean, sd)
Age 8	15.86 (2.61)	10.91	25.21	15.85 (2.50)
Age 12	17.85 (3.14)	12.96	27.68	17.82 (2.99)
Age 14	19.56 (3.14)	14.18	30.02	19.54 (3.02)
Age 16	20.93 (3.29)	15.23	31.95	20.91 (3.17)

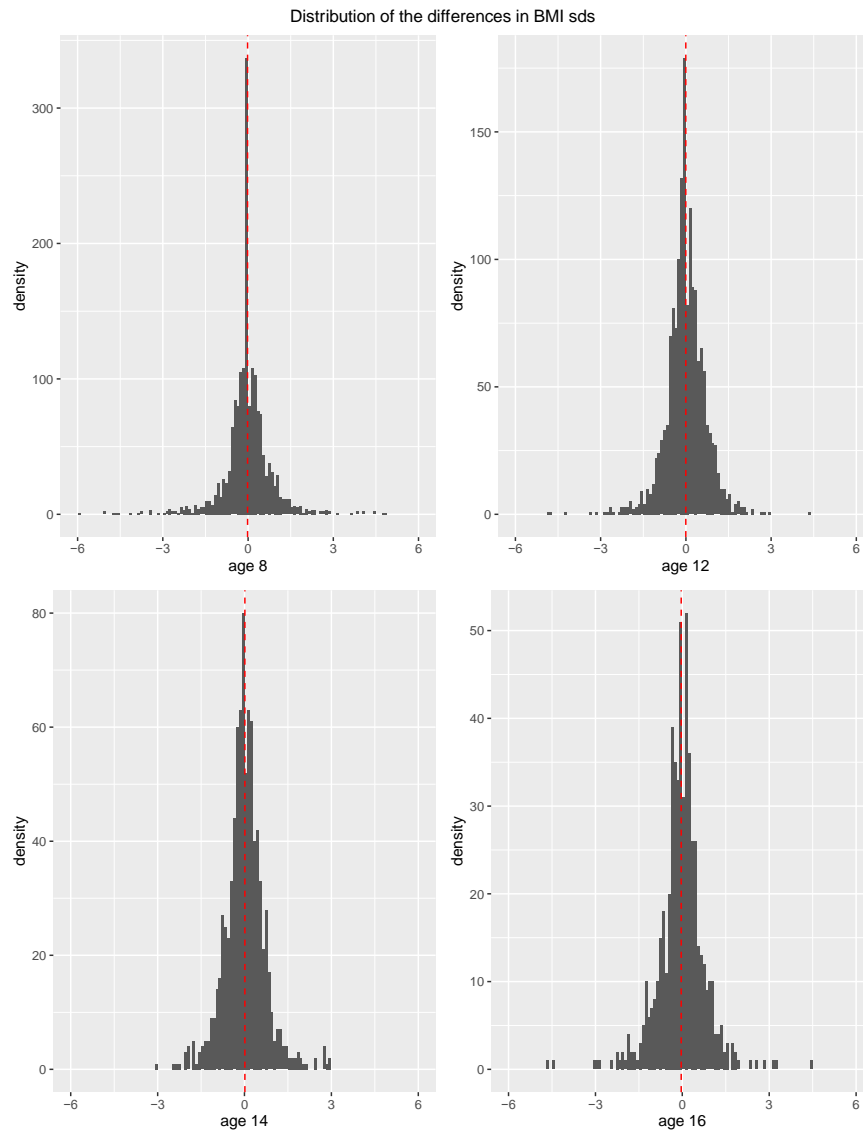
Note. a 98% winsorising transformation sets extreme values in BMI below the 1% percentile to the 1% percentile and data above the 99% percentile to the 99% percentile.

Appendix 4.1

Distribution of the twin differences in ADHD ratings

Note. Ratings of ADHD symptoms were derived from the sum of the Conners' Parent Rating Scale-Revised (CPRS-R).

Appendix 4.2

Distribution of the twin differences in BMI SDS

Note. BMI SDS represents Body Mass Index converted to standardised deviation score (SDS) based on the British 1990 growth reference.

Appendix 4.3

Mendelian randomization results of the effects from ADHD to childhood BMI (SNPs selected at $p < 5e-8$)

Exposure	Outcome	Method	Univariable MR					Multivariable MR				
			nSNP	β	Lower 95% CI	Upper 95% CI	p -value	nSNP	β	Lower 95% CI	Upper 95% CI	p - value
ADHD	childhood BMI	IVW		0.065	-0.087	0.217	0.129		0.119	-0.452	0.690	0.684
		Weighted median		0.075	-0.057	0.206	0.366					
		Weighted mode	4	1.161	-0.104	0.365	0.973	4				
		MR Egger		0.130	-3.447	5.770	0.440					
		MR Egger intercept		-0.086	-0.448	0.276	0.687					

Note. A total of 11 SNPs of $p < 5e-8$ were identified in the ADHD GWAS, among which 5 were found in childhood BMI GWAS. After harmonisation, 1 ambiguous SNP was removed due to strand ambiguity, leaving 4 SNPs as the instrumental variable for ADHD.

Appendix 4.4

Mendelian randomization results of the effects from ADHD to adult BMI (SNPs selected at $p < 5e-8$)

Exposure	Method	Univariable MR					Multivariable MR				
		nSNP ¹	β	Lower 95% CI	Upper 95% CI	p -value	nSNP	β	Lower 95% CI	Upper 95% CI	p - value
ADHD	IVW	7	0.064	0.004	0.125	0.036	7	0.069	0.016	0.122	0.011
	Weighted median		0.044	0.001	0.078	0.001					
	Weighted mode		0.024	-0.048	0.097	0.533					
	MR Egger		-0.003	-0.308	0.301	0.983					
	MR Egger intercept		0.006	-0.020	0.032	0.655					

Note. A total of 11 SNPs of $p < 5e-8$ were identified in the ADHD GWAS, among which 8 were found in BMI GWAS. After harmonisation, 1 ambiguous SNP was removed due to strand ambiguity, leaving 7 SNPs as the instrumental variable for ADHD.

