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ADHD and Physical Health: Comorbidity and Risk Factors

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Thesis for the degree of Doctor of Philosophy

May 2026

Thesis DOI – https://doi.org/10.5258/SOTON/PG/T167

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Abstract

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Research has shown that ADHD is associated with several different physical health conditions, spanning a range of physiological mechanisms. The relationship between ADHD and physical health is complex and research is often cross-sectional or overlooks the impact of many environmental factors associated with ADHD. As ADHD is highly heritable, understanding these associations whilst considering genetic and environmental influences is crucial. The papers in this thesis utilised Millennium Cohort Study data to explore longitudinal and cumulative relationships between ADHD and physical health conditions in childhood. Paper 1 (Chapter 2) examined associations between cumulative numbers of similar physical conditions across childhood and ADHD symptoms in adolescence, adjusting for cumulative environmental risk. Cumulative sensory and neurological, but not atopic, conditions were significantly associated with ADHD symptoms. Cumulative cardiometabolic conditions were largely driven by higher obesity prevalence in the sample. This cluster of conditions was not associated with ADHD symptoms once environmental risk was adjusted for. Building on these findings, Paper 2 (Chapter 3) explored how the relationship between ADHD and weight changes throughout childhood from birth to adolescence. Cohort members with an ADHD diagnosis/high symptoms were typically lighter at birth, then more likely to have obesity from age 5. Path analyses, adjusted for environmental risk, showed that ADHD symptoms at ages 7-14 predicted BMI at the subsequent time point (age 11-17). In males, this association appeared only in early adolescence. Both Papers 1 and 2 found significant results after adjusting for environmental risk indicating a role of genetic liability. Paper 3 (Chapter 4) found associations between ADHD polygenic scores and obesity, epilepsy and asthma. Polygenic scores were also associated with earlier onset of epilepsy and asthma and with BMI from age five. Genetic nurture effects were explored by analysing the relationship between non-inherited parental genetic liability and children's physical health outcomes, but no significant associations were found. Together, the findings presented in this thesis highlight the complex relationship between ADHD and physical health and demonstrate the interplay of numerous genetic and environmental influences across development.

Keywords: ADHD, Physical Health, Genetic Liability, Environmental Factors

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Research Thesis: Declaration of Authorship

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   Reed, C., Cortese, S., Larsson, H., Galéra, C., Cotton, J., & Brandt, V. (2024). Longitudinal Associations Between Physical Health Conditions in Childhood and Attention-Deficit/Hyperactivity Disorder Symptoms at Age 17 Years. *Journal of the American Academy of Child & Adolescent Psychiatry*, *63*(2), 245-254. https://doi.org/10.1016/j.jaac.2023.06.016

   Reed, C., Cortese, S., Golm, D., & Brandt, V. (2024). Longitudinal associations between ADHD and weight from birth to adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2024.09.009

Signature: Date:

Acknowledgements

I first want to acknowledge the Millennium Cohort Study members and their families as without them, this thesis would not exist. Thank you for sharing so much of your lives so that this research was possible.

I am so very grateful, and so very lucky, to have had such a brilliant supervisory team in Dr Valerie Brandt, Dr Dennis Golm and Prof. Sam Cortese. I can't fully express how much I have appreciated their combined support, guidance and expertise over the past four years.

I also want to thank my family and friends as I couldn't have done this without their encouragement, advice and willingness to listen to my petulant complaints about formatting - for that I will be eternally grateful. In particular, I would like to thank my husband Nic for his constant unconditional support and unwavering belief in me which has seen me through the many ups and downs of the last few years. Last, but by no means least, thank you to my daughters Lara and Amber. Your enthusiasm and curiosity about Mummy's research has kept me focused and reminded me why it's so important. At the same time, you have kept me grounded and you are absolutely the best kind of distraction.

Definitions and Abbreviations

ADHD……Attention-Deficit/Hyperactivity Disorder

BMI……Body Mass Index

CRI……Cumulative Risk Index

DSM-5…….Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

GWAS…….Genome-Wide Association Study

ICD-11…….International Classification of Diseases 11th Revision

MCS……..Millennium Cohort Study

NVQ……..National Vocational Qualification

PGS……Polygenic Score

SDQ……..Strengths and Difficulties Questionnaire

SES……Socioeconomic Status

rGE……Gene-Environment Correlation

Chapter 1 Introduction

1.1 ADHD Overview and Epidemiology

1.1.1 Diagnosis

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition characterised by persistent and impairing symptoms of inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013). Diagnosis is given based on the results of a clinical interview with a specialist health care professional trained to administer ADHD assessments. Although there are several biological markers associated with ADHD, none are robust enough to indicate the condition in isolation (Faraone et al., 2024). In the UK, NICE guidelines (NHS England, 2018) state diagnostic assessments for both adults and children should ensure that symptoms meet the DSM-5 (American Psychiatric Association, 2013) diagnostic criteria and that assessments should consider the patient's full developmental and psychiatric history, family circumstances and any comorbidities. The DSM-5 diagnostic criteria separates symptoms by trait and specifies three subtypes; combined, predominantly inattentive and predominantly hyperactive/impulsive. For children, a combined diagnosis requires six or more symptoms of inattention and hyperactivity/impulsivity to be present, whereas the other two subtypes require six symptoms of one trait allowing fewer of the other to be exhibited. For adults, only five or more symptoms of each trait are required for diagnosis. For all subtypes, symptoms must be persistent and cause moderate or severe impairments across multiple areas of life such as educational/occupational and social settings. Inattentive symptoms detailed in the DSM-5 include making careless mistakes, avoiding tasks requiring sustained mental effort and being easily distracted and forgetful. Hyperactivity symptoms include fidgeting, a feeling of restlessness, and excessive talking. Impulsive symptoms may present as blurting out answers before the end of the question and struggling with turn-taking. Although the diagnostic criteria details broad examples of symptoms, presentation varies significantly between individuals and traits can be expressed in numerous ways.

ADHD is also associated with many strengths and positive aspects. Many people with ADHD report positive traits associated with their experience of the condition, such as high

levels of creativity and flexibility (Schippers et al., 2022). Although the diagnostic criteria for ADHD focus on inattention, people with the condition often report the ability to hyperfocus and sustain attention for a significant period of time as a particular strength (Schippers et al., 2024). ADHD is associated with many negative outcomes, and research which aims to ameliorate serious consequences is crucial. Due to the numerous adverse outcomes associated with many physical health conditions as well, this thesis inherently approaches the comorbidity between ADHD and physical health through a negative lens in alignment with a medical model of ADHD rather than a social model of disability. However, the heterogenous nature of ADHD also extends to individuals' experiences and attitudes and research should aim not to further stigmatise the condition.

1.1.2 Prevalence and Diagnostic Challenges

ADHD is the most common neurodevelopmental disorder (Coghill et al., 2023) with worldwide prevalence estimates of 5-8% in children (Ayano et al., 2023; Cortese et al., 2023). NHS England reports that 2.5 million people in England have an ADHD diagnosis, with over 700,000 of those being under 24 years of age (NHS England, 2018). ADHD symptoms are typically higher during childhood and decrease as individuals enter adolescence and adulthood (Niina et al., 2022). ADHD symptoms continue to decline across adulthood (Song et al., 2021), however recognition and treatment of ADHD has improved significantly over recent years but it is still under identified in older adults (Vos & Hartman, 2022).

The ratio of males to females with ADHD varies between 4:1 in clinical settings and 2:1 in the general population (Martin, 2024). Analyses of ADHD associated genetic variants have reported no significant differences between males and females (Demontis et al., 2023), however having a female sibling with ADHD appears to confer a higher risk of ADHD than having a male sibling with ADHD (Martin et al., 2018). Beyond genetic factors there are many hypothesised reasons for the disparity in prevalence between the sexes, including possible different phenotypic presentation of symptoms (Young et al., 2020). The expression of fewer hyperactivity/impulsivity traits in girls, and consequently lower levels of disruption may lead to a general under recognition of the condition, resulting in lower diagnosis rates (Martin, 2024; Young et al., 2020). Underdiagnosis extends to many populations, and research including systematic reviews has identified several key barriers to recognition and diagnosis (French et al., 2019; McKenna et al., 2024). A commonly reported theme is a lack of

education and awareness of ADHD symptoms in parents, teachers and primary health care professionals (French et al., 2019; McKenna et al., 2024). Parents who do not have adequate knowledge of ADHD symptoms may not seek assessment, or may do so later than parents who are able to recognise ADHD traits in their children (McKenna et al., 2024). Even if parents are concerned by certain behaviours or symptoms, research has found that many are not sure of the next steps when seeking help (Spencer et al., 2021). A second theme identified as a significant barrier to diagnosis is the stigma associated with ADHD (Paidipati et al., 2022). Parents who fear judgement from teachers, health care professionals or within their social circles may delay or avoid diagnosis for their child. Another key factor in underdiagnosis of ADHD is a lack of resources to cope with the number of new referrals in recent years resulting in long waiting times for assessment. The average time children wait for an assessment in the UK is almost 18 months and this can often be considerably longer in certain areas or if children have additional complex health needs (Maciver et al., 2025).

1.2 ADHD Aetiology

1.2.1 A Biopsychosocial Framework

Before outlining what is currently known about ADHD and its relationship with several physical health conditions, relevant aetiological context should be considered. ADHD is a very heterogenous condition with a complex aetiology and it would be unfeasible for this thesis to fully describe every pathway and mechanism involved. With this in mind, this section will use a Biopsychosocial framework to ensure that the multifaceted nature of the condition is recognised, and multiple influential factors are taken into account. The Biopsychosocial Model (BPS) (Engel, 1977) was created to acknowledge the biological, psychological and social factors which impact a medical condition, as well as the overlap between them. The BPS has been adopted to provide a theoretical explanation for many different health conditions. A key advantage of this model is that it acknowledges complexity and heterogeneity by recognising the numerous different biological and environmental factors which can influence a person's experiences of a health condition. The BPS also takes into account physical symptoms which do not in themselves meet the threshold for a diagnosis or follow a clear clinical pathway, as well as psychosocial factors which may be harder to quantify (Førde et al., 2022).

In the context of ADHD, the BPS offers a framework which recognises the high heritability of the condition (Faraone et al., 2024), whilst also acknowledging the influence of psychosocial factors associated with symptom development and expression. Viewing ADHD through a biopsychosocial lens addresses many important points within the literature (Cooper, 2009). Historically, ADHD as a diagnosis has received much criticism and scepticism with many believing a medical diagnosis of ADHD legitimises and excuses poor behaviour. Although this opinion is thankfully less common in recent years, Cooper (2009) highlights the negative consequences of restricted views which neglect to consider either biological or psychosocial factors related to ADHD aetiology and phenotypic expression. Claims that ADHD results purely from adverse environmental factors disregard a wealth of genetic and neurobiological evidence within the literature. Counter to this, an overfocus on biological factors ignores the many psychosocial factors associated with ADHD prevalence and symptom expression. Even though research may often skew towards a genetic, neurobiological or psychosocial perspective, it is nonetheless necessary to acknowledge the interplay of many factors which may contribute to the development, maintenance and differences in expression of ADHD symptoms.

Later sections (see 1.3 and 1.4) will discuss current literature reporting on the relationship between ADHD and physical health conditions, such as asthma. However, the BPS can provide wider context taking into account not just associations between the two conditions but also overlapping features and consequences. Smoking is significantly more common in people with ADHD (Schoenfelder et al., 2014) and smoking significantly increases the risk of developing asthma (Thomson et al., 2022). Discussions on the topic of ADHD and asthma comorbidity should therefore take the full biopsychosocial picture into account and consider both genetic overlap and environmental factors, such as smoking, which may confound the relationship. Medication adherence is another area where biological and psychosocial overlap is evident. Stimulant medication is effective at reducing smoking rates (Schoenfelder et al., 2014) demonstrating that ADHD medication may have both biological and psychosocial benefits.

The inherent nature of statistical research often necessitates that human characteristics and experiences are divided and categorised as distinct variables. In real-world situations, and in particular clinical practice, it is not possible nor desirable to disentangle the

overlapping facets that make up a person's lived experiences; including but not limited to the genetic, environmental and wider societal influences we are all subject to. This section will highlight key biological, cognitive and environmental research relating to ADHD before outlining further consequences of how these separate areas overlap and contribute towards a more holistic view of ADHD aetiology.

1.2.2 Pathophysiology: Genetics and Neurobiology

Genetic factors play a large role in the aetiology of ADHD with heritability reported to be approximately 80% (Faraone et al., 2024). ADHD has a strong genetic correlation with many psychiatric disorders, such as conduct disorder, and other neurodevelopmental conditions, such as autism (Gidziela et al., 2023).

Research into the genetics of ADHD has benefitted substantially from genome-wide association studies (GWAS). The most recent ADHD GWAS (Demontis et al., 2023) discovered 27 genome-wide risk loci and identified associations between ADHD polygenic scores and other conditions and cognitive processes such as autism, educational attainment and BMI. ADHD polygenic scores (ADHD-PGS) represent a person's genetic liability towards ADHD by totalling the effect of relevant variants. They are calculated by totalling the number of risk alleles an individual has for each genetic variant and multiplying this by the effect size for each risk allele provided by GWAS. This is then repeated for all variants and totalled across them (Choi et al., 2020). Although polygenic scores are highly useful for research into the influence of ADHD genetic liability, it should be noted that PGS capture only a weak amount of genetic variance and are not robust enough to be used as a diagnostic tool (Ronald et al., 2021). Despite this, ADHD-PGS do show a significant association with ADHD symptoms as well as sub-clinical traits within the general population (Taylor et al., 2019). Therefore, symptoms are theorised to lie on a continuum with ADHD diagnoses reflecting the extreme end of this spectrum (Faraone & Larsson, 2019).

The genetic variants identified as being associated with ADHD are involved in many brain areas and processes including neuronal development and synapse formation (Faraone et al., 2024). Although the heterogeneous nature of the condition hinders a full consensus between studies (Firouzabadi et al., 2022), several abnormalities have been reported by multiple neuroimaging studies. Lower amygdala and hippocampal volumes have been

observed in people with ADHD and show an association with impulsivity symptoms and reward processing (Connaughton et al., 2024). Frontal lobe and basal ganglia abnormalities have also been observed (Firouzabadi et al., 2022) and the basal ganglia demonstrates a genetic correlation with ADHD (Bahrami et al., 2024). This region is implicated in the regulation of dopamine neurotransmission and ADHD is associated with genes expressed in midbrain dopaminergic neurons (Demontis et al., 2023). Neurotransmitter imbalance is a significant factor connecting ADHD neurobiology with phenotypic presentation. An imbalance of dopamine, acetylcholine and noradrenaline has implications for many functions including working memory, attentional control and reward processing (Bech et al., 2023; Gholami & Mortezaee, 2025).

Neurotransmitters also help to regulate connectivity between the default mode network and other areas of the brain (X. Chen et al., 2023). Connectivity between the default mode network and dorsal attention networks is disrupted in ADHD (Norman et al., 2023). Dysregulation of the default mode network has shown an association with mind wandering (Bozhilova et al., 2018), and ADHD inattention symptoms may result from default mode network dysfunction (Sutcubasi et al., 2020). These connectivity abnormalities have also shown a genetic correlation with ADHD (Liu et al., 2024) demonstrating the robust association between ADHD genetic liability and structural and functional brain differences.

1.2.3 Psychological and Cognitive Factors

Several brain differences result in cognitive and psychological functioning impairments, such as deficits in executive functioning. For example, ADHD is linked to underactivity in corticocerebellar networks which impacts several executive functions (Faraone et al., 2024). Within the wider literature, there is much debate around the definition of the term ‘executive function’ and there is no universal agreement on which processes should be included (Barkley & Murphy, 2011). Until relatively recently, research generally described executive functioning in the context of the cognitive processes involved in working towards a goal (Willcutt et al., 2005). However, it is now recognised that a significant affective component is also involved. Cognitive components include goal maintenance, inhibitory control and working memory and are often referred to as ‘cool’ executive functions (Tsermentseli & Poland, 2016). ‘Hot’ executive functions include processes with an affective component such as motivation and emotion regulation. The

anterior cingulate cortex is implicated in both affective (ventral) and cognitive (dorsal) domains (Faraone et al., 2024). There are also several links between executive functions. Working memory impairment is associated with reduced inhibitory control (Kofler et al., 2024) suggesting a cascade of executive functioning impairments. Impairments in both inhibitory control and working memory are associated with a number of physical health conditions, highlighting the cognitive symptoms shared with ADHD. In adolescents, obesity is linked to impulsive eating and research suggests there is a bidirectional link between executive dysfunction and obesity (Lane et al., 2023). Executive dysfunction is also common in people with epilepsy with research finding evidence of impairments in 30% of patients (Guerra et al., 2024). Working memory is also implicated in emotional dysregulation and this relationship is mediated by core ADHD symptoms (Groves et al., 2022). Longitudinal data has shown that emotional regulation at ages three, five and seven is associated with ADHD symptoms at age seven and may serve as a useful indicator of children who may need additional support (Murray et al., 2025). Further research has suggested that emotional dysregulation is such an intrinsic component of ADHD that it should be included as a core symptom of the condition (Soler-Gutiérrez et al., 2023). Other affective executive functions, such as motivation are also lower in people with ADHD and motivation plays a significant role in academic functioning and outcomes (Smith et al., 2020). Research has found that motivation as a measure of executive functioning mediates the relationship between ADHD and academic outcomes (Dvorsky & Langberg, 2019). Again, the heterogeneity of ADHD means that psychological and cognitive outcomes will vary between individuals and are likely to overlap with numerous biological and environmental factors.

1.2.4 Social and Environmental Factors

The high heritability of ADHD indicates a predominantly genetic aetiology, but in order to recognise a biopsychosocial perspective there are many environmental factors which should be acknowledged within both research and clinical practice. These begin even prior to conception as research has shown that maternal obesity before pregnancy is associated with ADHD symptoms in childhood (Andersen et al., 2018). Research into maternal age also reveals that ADHD risk is highest in children whose mothers are under the age of 20 (Chang et al., 2014; Min et al., 2021). A large scale umbrella meta-analysis reports notable related factors during pregnancy (Arango et al., 2021). The review found suggestive

evidence of an association between gestational diabetes and ADHD and convincing evidence of an association between hypertension or pre-eclampsia and ADHD. There was also highly suggestive evidence of the risk of maternal smoking during pregnancy, which is corroborated in other studies, including meta-analyses (Y. He et al., 2020). Many studies do not differentiate between smoking frequencies or history but there is some evidence that ADHD risk is still higher for children whose mothers smoke even if they stop smoking in the first trimester (Li et al., 2024). However, a key consideration is whether this is a true environmental effect. Previous research has suggested that the relationship between maternal smoking and child ADHD may be confounded by genetics. In a sample of mothers who had undergone fertility treatment, the relationship between smoking and child ADHD symptoms was higher in mothers and children who were genetically related (Thapar et al., 2009).

Research has also identified many relevant factors surrounding the birth and neonatal period. A caesarean delivery (Arango et al., 2021; Serati et al., 2017), breech presentation (Arango et al., 2021) and increased number of birth complications (Serati et al., 2017) are all associated with an increased risk of ADHD in childhood. Previous literature also reports an association between ADHD and premature birth (Serati et al., 2017) as well as low birth weight (Momany et al., 2018). Another environmental factor relevant to the neonatal period and beyond is breastfeeding duration. Research has found that any amount of breastfeeding is associated with a lower risk of ADHD compared with no breastfeeding (Zeng et al., 2020). The same study found that ADHD risk was lower in children who were breastfed for over one month compared to less than one month.

Associations between environmental factors and ADHD continue into the postnatal period with maternal mental health often studied in relation to childhood ADHD risk. Maternal distress is associated with ADHD both pre and post birth (Bendiksen et al., 2020) and risk is higher for continued rather than infrequent distress (Noonan et al., 2018). Meta-analytic evidence also reports an association between postnatal depression and ADHD in children (Christaki et al., 2022).

Many environmental risk factors can be categorised under broader themes, such as the prenatal factors described above. The ADHD literature includes many examples of studies exploring both individual factors and the wider umbrella they fall under. One

frequently researched example of this is socioeconomic status. Although socioeconomic status (SES) is commonly defined as a measure of economic and social status (Baker, 2014), studies including SES as an environmental confounder use numerous different measures to represent this. There are many examples in the literature demonstrating an association between ADHD and socioeconomic disadvantage (A. E. Russell et al., 2016) and SES measures often include variables such as household income (G. Russell, Ford, et al., 2014), household crowding (Flouri et al., 2017) and housing tenure (A. E. Russell et al., 2015). Frequently parental education is included as a measure of SES although the influence of parental low educational attainment has been shown to be associated with ADHD beyond shared family risk factors (Torvik et al., 2020).

Within the household, parenting and caregiving factors also show a relationship with ADHD. ADHD and childhood maltreatment demonstrate a bidirectional association (Golm & Brandt, 2024). Children with ADHD are more likely to experience maltreatment, and maltreatment is associated with increased ADHD symptoms. However, a twin study has shown that maltreatment is not causally related to neurodevelopmental disorders (Dinkler et al., 2017). Caregiving practices, along with other environmental factors, are likely to influence ADHD phenotype but their role in ADHD aetiology is undetermined.

1.2.5 The Relationship Between Genes and Environment

The BPS offers a beneficial framework acknowledging the overlap of numerous factors. ADHD research has identified numerous biological, psychological and social associations and determinants many of these are also pertinent to physical health. In addition to the overlapping influences, the interaction between genetic liability and environmental exposures should be considered. Research reporting the environmental associations described above often discuss the relationships from a linear, unidirectional perspective and often neglect to consider related environmental and genetic confounders. Two key mechanisms, gene-environment correlation and gene-environment interaction provide explanations for the relationship between genes and environment and how this affects ADHD outcomes. These can occur simultaneously and contribute to the complexity and heterogeneity of the condition.

1.2.5.1 Gene-Environment Correlation

Research often presents environmental risk as an external factor, neglecting to acknowledge the influential role of genetic liability both on ADHD and associated environmental factors. Gene-environment correlation (rGE) describes the ways in which many environmental factors are influenced by genotype (Agnew-Blais et al., 2022; Jami et al., 2021). Passive rGE occurs when parental genotype is associated with both child genotype and the family environment (Warrier et al., 2021). For example, maternal ADHD genetic liability is associated with higher levels of household chaos (Agnew-Blais et al., 2022). Parental genotype may result in children inheriting higher ADHD genetic liability and also being raised in a more chaotic environment. A second rGE mechanism, evocative rGE, occurs when a child's genotype influences their behaviour which in turn elicits a particular environmental response (Warrier et al., 2021). Using the household chaos example, evocative rGE would occur when the child's ADHD genetic liability, and resulting ADHD symptoms, also contribute to a more chaotic household (Agnew-Blais et al., 2022). Childhood temperament, including negative emotionality, shows an association with ADHD (Kostyrka-Allchorne et al., 2020) and different temperaments are also likely to elicit different environmental responses. Active rGE may also occur, especially later in development, when a child's genotype influences them to seek out particular environments (Warrier et al., 2021). The correlation between genes and environment has implications for both research and clinical settings and environmental risk factors may at least partially reflect underlying genetic liability.

1.2.5.2 Gene-Environment Interaction

Where rGE describes how genetic liability may influence environmental factors, gene-environment interaction (GxE) occurs when the impact of environmental risk differs between different genotypes (Virolainen et al., 2023). Within the ADHD literature, evidence for GxE is mixed. Children with higher genetic liability have been shown to develop more ADHD symptoms when accompanied by a larger burden of environmental risk (Leffa et al., 2024). However, other studies have not found evidence of an interaction. Both ADHD genetic liability and maltreatment are associated with ADHD symptoms, however a study exploring the interaction between them did not find a significant result (Q. He & Li, 2022). It has also been hypothesised that an interaction between ADHD genetic liability and socioeconomic status influences ADHD symptom expression, however, findings are inconsistent (Gould et

al., 2018). Gould et al. (2018) suggest that gene-environment interactions may occur in individuals with very high symptoms and not extend to subclinical traits. The heterogenous nature of findings underscores the importance of replication within research and highlights the need for a nuanced approach to understanding the interplay of numerous environmental and genetic factors.

1.3 ADHD and General Health Outcomes

In addition to the core symptomology which forms the basis of a diagnosis, ADHD is also associated with many other traits, features and comorbidities which add complexity to the condition and affect diagnosis, symptom management and quality of life. Research has shown an association between higher ADHD symptoms and lower quality of life in multiple areas including both physical and mental health, relationships, education, and self-esteem (Krauss & Schellenberg, 2022). A lower quality of life is also reported by people with elevated ADHD symptoms who do not meet the full diagnostic criteria for ADHD. (Franklin et al., 2017). The consequences of these associations are far-reaching for the individual, their families and wider society. ADHD symptoms in childhood are associated with an increased risk of mortality in adulthood (Schiavone et al., 2022). This increase is driven by unnatural causes of death, including suicide and conditions resulting from an unhealthy lifestyle. People with ADHD experience mental ill-health at rates significantly above their peers (Reale et al., 2017). In adults, ADHD and anxiety share a 25% comorbidity rate (D'Agati et al., 2019) and two-thirds of children diagnosed with ADHD additionally experience one or more psychiatric disorders such as anxiety or conduct disorder (Reale et al., 2017). A recent umbrella review reported several associations between ADHD and negative outcomes including suicide, addiction and eating disorders (French et al., 2024). As well as differing prevalences, psychiatric comorbidities also vary between males and females. Both males and females with ADHD are more likely to experience other conditions including anxiety and depression, but the difference between ADHD and non-ADHD populations is greater in women (Solberg et al., 2018).

An association has been found between childhood ADHD and poor health in adults in multiple areas, encompassing both mental and physical health (Agnew-Blais et al., 2018). Agnew-Blais et al. (2018) reported poorer physical health in adults regardless of whether childhood symptoms were remitting or continued at a clinical level into adulthood. This

suggests ADHD symptoms at key sensitive developmental periods can have far reaching negative consequences. These findings highlight the importance of early diagnosis and support for both ADHD and any comorbid conditions in order to minimise long term consequences.

The relationship between ADHD and physical health is evident across the lifespan. It is estimated that at least one comorbid condition is experienced by more than 80% of children with ADHD (Akmatov et al., 2021). Research has shown that children with ADHD participate in fewer healthy lifestyle behaviours, including meeting physical activity and sleep guidelines (Holton & Nigg, 2020). There is also substantial current literature detailing the relationship between ADHD and many individual physical health conditions such as obesity and asthma (Instanes et al., 2018) which will be explored in more detail later in the chapter (see section 1.4). These relationships are also evident in mid-late adulthood (Garcia-Argibay et al., 2022). Garcia-Argibay and colleagues report an association between ADHD genetic liability and several physical health conditions. This twin study also found a mediating effect of environmental factors such as education level and alcohol use. The confounding effect of environmental factors is an important consideration in ADHD and physical health research. Previous research has found weaker, yet still significant, associations between ADHD and poor physical health when adjusting for environmental confounders (Landes & London, 2021). It is clear that genetic liability and environmental risk are crucial factors in the relationship between ADHD and physical health but disentangling their effects is complex and multifaceted.

1.4 ADHD and Physical Health Conditions

As discussed above, ADHD has a predominantly genetic aetiology but there are key psychological and social factors to consider when diagnosing and managing both ADHD and any comorbidities. There are a myriad of different physical health conditions known to be associated with ADHD and it would not be feasible to discuss each one in this thesis. Therefore, I will focus on the conditions included in Paper 1 (Chapter 2), grouped into four categories: atopic, cardiometabolic, sensory and neurological conditions. This section will elaborate on relationships between ADHD and each group of conditions, discussing primarily the genetic and biological associations between them whilst also considering relevant psychological and social influences.

1.4.1 ADHD and Atopic Conditions

Many previous studies, including meta-analyses and umbrella reviews have reported a relationship between ADHD and atopic conditions which produce an exaggerated immune response, such as asthma, eczema and allergic rhinitis (Arrondo et al., 2022; Cheng et al., 2023), even after adjusting for confounders (Galera et al., 2023; Kaas et al., 2021). Research has also shown that ADHD and asthma often co-occur within families pointing to a shared genetic association (Sun et al., 2021). The results of a recent genetic study support this as a reverse mendelian randomisation analysis found a causal association between ADHD and childhood asthma, but not vice versa (Jiang et al., 2025). When looking at phenotypic presentation, research using data from a longitudinal cohort study found a bidirectional relationship between ADHD and asthma (Park et al., 2023). The relationship between ADHD and eczema is also suggested to be bidirectional. ADHD and eczema may co-occur due to shared genetic factors, and inflammation resulting from immune system dysfunction may disrupt normal neurotransmitter functioning (H.-F. Wang et al., 2025). The way in which the body responds to stress hormones such as cortisol may also play a role in the association. Buske-Kirschbaum et al., (2019) propose that both eczema and ADHD result from a reduced cortisol response due to hypothalamus-pituitary-adrenal (HPA) axis dysfunction. Atopic conditions are driven by hypersensitive immunological responses such as higher levels of Immunoglobulin E (IgE) antibodies. (Justiz Vaillant et al., 2025). IgE antibodies are involved in normal immune system function, but elevated levels are implicated in atopic disease pathways. People with ADHD often have higher levels of IgE antibodies (L.-J. Wang et al., 2018). Wang et al. (2018) report an increased risk of ADHD in children with multiple atopic conditions.

In addition to shared biological factors, it is possible that environmental factors mediate the relationship between ADHD and atopic conditions. Asthma has several environmental risk factors such as air pollution, second hand smoke and exposure to mould and these risk factors are often associated with poverty and poor housing conditions (Grant & Wood, 2022). It is therefore likely that some measures of socioeconomic status associated with ADHD may influence the relationship with asthma in addition to genetic factors.

1.4.2 ADHD and Cardiometabolic Conditions

ADHD is associated with many conditions involving the body's metabolism and cardiovascular system such as diabetes, hypertension, heart disease and obesity (Akmatov et al., 2021). Of particular concern is obesity as prevalences have increased significantly in recent decades and in many areas are still rising (Lister et al., 2023). Obesity is associated with many other metabolic conditions (Yang et al., 2022) and the relationships between them are complex and far reaching. This complexity extends to the relationship between obesity and ADHD (Cortese, 2019) and research in this field is vast. It is therefore beyond the scope of this thesis to cover all aspects of the association. Instead, this section will focus on what is known about the association between ADHD and weight at various childhood milestones, and the relationship with other metabolic conditions.

A relationship between ADHD and weight can be observed from birth. Children with ADHD are typically born lighter than their peers without ADHD and this relationship is not moderated by gestation (Momany et al., 2018). Throughout childhood this relationship shifts and ADHD symptoms in childhood are associated with higher BMI in adolescence (Khalife et al., 2014). The age at which associations develop is unclear, and existing research reports mixed findings. A longitudinal study examining the relationship between ADHD and BMI at various ages found that a higher BMI at 18 months of age was associated with lower ADHD symptoms at three years old (Bowling et al., 2018). This association was not seen between three and six years old but reappeared between ages six and nine indicating that the relationship between BMI and later ADHD symptoms fluctuates over early and middle childhood. When analysing the association in the opposite direction, the researchers found that higher ADHD symptoms at age three predicted later higher BMI at age six and this association was also found between ages six and nine. This study supports the presence of bidirectional associations between ADHD and weight (Cortese, 2019) but indicates that they present different patterns of association at different ages. The direction of the association between ADHD and BMI has also been explored within genetic studies. A study utilising Mendelian randomisation reported an association from BMI to ADHD but not from ADHD to BMI (Martins-Silva et al., 2019). However, the study acknowledges that ADHD genetic information was limited and these findings are contradicted by a more recent study which identified a shared genetic association between ADHD and BMI indicated by correlated

polygenic scores and shared neural correlates (Barker et al., 2021). Both ADHD and BMI polygenic scores were associated with reduced volume in the amygdala and hippocampus, which as previously discussed (see section 1.2.2) are involved in impulsivity symptoms and reward processing (Barker et al., 2021; Connaughton et al., 2024).

The intersecting influence of genes and environment is also a consideration when researching the association between ADHD and weight. Longitudinal data has shown that the influence of genes and environment may differ between males and females (Do et al., 2019). Do et al. (2019) found that the association between ADHD and BMI in males was more strongly impacted by environmental factors whereas genetic factors were more influential in females. Environmental factors have been shown to play a significant role in the relationship between ADHD and weight and, when adjusting for factors such as socioeconomic status, parental depression and smoking during pregnancy, a recent study found no significant relationship between ADHD and BMI at age 9 or 13 (Donnchadha et al., 2023).

As well as a multifaceted relationship with ADHD, obesity is associated with many other metabolic conditions with many hypothesised mechanisms (Yang et al., 2022). ADHD is associated with both type 1 and type 2 diabetes with obesity potentially acting as a significant confounder (Ai et al., 2022). The relationship between ADHD and diabetes is suggested to be bidirectional and, although obesity is a notable risk factor, maternal diabetes and dopamine dysfunction are also thought to be influential (Marcelli et al., 2025). Dopaminergic abnormalities join other neurobiological factors such as inflammation and HPA axis dysfunction in echoing processes thought to be involved in the relationship between ADHD and atopy (see 1.4.1) as well as metabolic conditions (Marcelli et al., 2025).

1.4.3 ADHD and Sensory Conditions

ADHD is often associated with sensory processing difficulties and may include either increased sensory seeking or avoidance behaviours (Rani et al., 2023). These sensory processing differences span multiple domains including visual, auditory and olfactory systems. For example, auditory difficulties may present as a hypo- or hyper- sensitivity and responsiveness to sounds. ADHD is also associated with sensory system pathophysiology. For example, children with vision problems are more likely to have ADHD (DeCarlo et al., 2016).

Within the literature, it is hypothesised that the association may in part be explained by symptoms of vision impairment mimicking or exacerbating ADHD neurocognitive symptoms (Bellato et al., 2023; DeCarlo et al., 2016). Of particular note is the role of executive dysfunction. Children with a vision impairment will experience a greater demand on their executive functioning to counter their difficulties (DeCarlo et al., 2016). This may exacerbate existing executive function impairments (see section 1.2.3) or mimic attention deficits (Cavézian et al., 2013). This hypothesis implies some people with ADHD symptoms have been misdiagnosed due to their vision impairment. However, a large-scale study of more than one million participants refutes this as their findings demonstrated an association between ADHD and increased incidences of a large number of eyesight disorders (Choudhury et al., 2024). The study found that the ADHD group was nearly two and half times more likely to have a vision impairment than those without ADHD. The researchers highlighted that this level of misdiagnosis is improbable and therefore there must be other explanations for the association between ADHD and vision disorders. Meta-analytic evidence suggests there is no association between ADHD and structural eye problems, and impairments are mainly found in functional disorders (Bellato et al., 2023). One measure that shows an association with ADHD is impaired colour discrimination. Bellato et al. (2023) suggest dopaminergic neurons may play a role in this relationship. This is supported by research which found higher odds of vision impairment in children with ADHD and describes the role of dopamine in both ADHD and visual perception (Lu et al., 2025). In addition to problems with vision, ADHD has shown an association with hearing impairments, even after adjusting for environmental confounders such as socioeconomic status (Tsur et al., 2024). Genetic studies have also shown that ADHD polygenic risk is associated with hearing impairment (Schmitz et al., 2021). In this study however, the researchers report the mediating effects of environmental factors including IQ and socioeconomic status. The influence of genetics and environment on the relationship appears to lack consensus within the literature and highlights the probability of multiple contributing factors.

1.4.4 ADHD and Neurological Conditions

In Paper 1 (Chapter 2), neurological conditions reflect an analytic grouping rather than a distinct clinical classification. The ICD-11 includes the category “Diseases of the Nervous System” which includes conditions such as epilepsy and movement disorders

(World Health Organization, 2019). In this thesis, I am also including stutter and sleep disorders under the broad umbrella of 'neurological conditions'. Although sleep disorders are classified separately in the ICD-11, research notes their relationship with other neurological and psychiatric disorders (Rémi et al., 2019) and many disorders such as restless legs syndrome have a neurological aetiology (Manconi et al., 2021). Similarly, although classified by the ICD-11 as a neurodevelopmental disorder (World Health Organization, 2019), neuroimaging studies indicate that stutter is associated with brain alterations (Neef & Chang, 2024) and can develop following neurological injury (Junuzovic-Zunic et al., 2021). Grouping these conditions together acknowledges their shared neurological underpinnings and ensures that analyses incorporate all available data.

Within the literature there are many known associations between ADHD and neurological conditions as defined above. The relationship with epilepsy is widely reported and extremely prevalent, with 30-40% of children with epilepsy also having ADHD (Ahmed et al., 2022). The association between the conditions is reported to be bidirectional (Chu et al., 2024). However, Chu et al. propose caution in assuming a bidirectional relationship as the results of their mendelian randomisation study indicated the presence of pleiotropy. More than one phenotypic presentation may result from a single gene. This complicates the aetiology as it may be that ADHD and epilepsy result from shared genetic variants as well as further influencing each other. A shared genetic association has been demonstrated in other studies which also identified common neurobiological alterations resulting from shared genetic variation (Wu et al., 2022). Amongst other alterations, ADHD and epilepsy are both associated with reduced hippocampal volume. Wu et al. (2022) propose that genetic variants associated with both conditions may affect brain development leading to shared structural and functional alterations. As with other conditions, there is not a complete consensus within the literature on the relative influence of genes and environment. A phenotypic and genetic association is well established within existing research, however a genetic study using cohort data concluded that only 40% of the relationship between ADHD and epilepsy is explained by shared genetics and environmental factors convey a stronger influence on the association (Brikell et al., 2018).

As well as associations with ADHD, many neurological conditions are associated with each other, for example children who stutter are at increased risk of sleep disturbances

(Merlo & Briley, 2019). In both ADHD and epilepsy, sleep problems are a commonly reported issue, however it is hard to isolate the direction of the relationship (Neto et al., 2016). This is a frequent theme in ADHD and sleep research in particular as children with ADHD often experience problems with sleep (Eyuboglu & Eyuboglu, 2018) and in turn, poor sleep may exacerbate ADHD symptoms including executive dysfunction by impacting cognitive function (Lok et al., 2025). Establishing the temporal order of conditions from cross-sectional research is difficult and relative onsets should be considered. There is mixed evidence of a genetic association between ADHD and sleep problems. Studies have found ADHD genetic liability is correlated with sleep disturbances (Ohi et al., 2021) however, others which adjust for environmental confounders such as socioeconomic status report no genetic association (Lewis et al., 2023). Gene-environment interaction may influence the relationship between ADHD and sleep disorders.

1.5 Thesis Aims: Addressing Current Gaps in the Literature

The current literature encompasses research into many comorbidities and risk factors associated with ADHD but there are several notable gaps which this thesis aimed to address. The following aims were examined across more than one paper, and all are addressed using longitudinal cohort data to study different aspects of the relationship between ADHD and physical health.

1.5.1 Aim 1: To Investigate the Relationship Between ADHD and Cumulative Physical Health Comorbidity

As demonstrated above, the field of ADHD and physical health research describes many associations between ADHD and individual physical health conditions. Comorbidity between related conditions is also widespread. However, less is known about the impact of multiple comorbidities and whether the burden of additional conditions has a cumulative effect on the risk of another. Wang et al. (2018) propose a shared aetiology between atopic conditions and ADHD with an increased number of comorbidities further increasing risk. Research investigating the association between ADHD and a cumulative number of other conditions however is scarce. As many conditions share similar physiological mechanisms and aetiologies, it is possible that the shared biological and environmental differences associated with two comorbid conditions additionally increase the likelihood of cumulative comorbidity.

The first aim of this thesis considered the relationship between ADHD and a cumulative number of physical health conditions. In Paper 1 (Chapter 2), this aim was addressed by analysing the association between a cumulative number of related conditions across childhood and ADHD symptoms in adolescence. After a focus on phenotypic presentation in the first study, Paper 3 (Chapter 4) looked at ADHD genetic liability and examined the association with a cumulative number of conditions across childhood.

1.5.2 Aim 2: To Investigate the Relationship Between ADHD and Physical Health Across Multiple Developmental Periods

The current literature also describes many relationships between ADHD and physical health conditions at several time points across development. ADHD is associated with low birth weight (Momany et al., 2018), childhood asthma (Kaas et al., 2021) and obesity in adolescence (Khalife et al., 2014). However, many associations are reported at single time points using cross-sectional data. The onset of each condition and how associations may change over time is also not consistently explored, particularly in genetic studies. ADHD symptoms in childhood are associated with numerous adverse health outcomes, including increased mortality, in adulthood (Agnew-Blais et al., 2018; Schiavone et al., 2022). The association between ADHD genetic liability and physical health in later adulthood has revealed significant results (Garcia-Argibay et al., 2022), however an exploration of how these relationships develop over childhood is lacking. This highlights the importance of exploring associations between ADHD and health across development in order to aid recognition and diagnosis of comorbidities with the aim of reducing negative consequences in later life. Determining the direction of association as well as how these may evolve over time is difficult in cross-sectional research. Although many studies explore bidirectional associations (Marcelli et al., 2025; Park et al., 2023), even longitudinal research often encompasses only limited developmental periods (Bowling et al., 2018).

The second aim of this thesis was to use longitudinal data to examine associations between ADHD and several physical health outcomes across childhood. This aim was primarily addressed in Paper 2 (Chapter 3) which used weight/obesity data from birth to adolescence to identify how the relationship between ADHD and weight evolves over time. This aim was also investigated in Paper 3 (Chapter 4) which analysed the relationship

between ADHD genetic liability and BMI over childhood as well as the association with epilepsy and asthma onset.

1.5.3 Aim 3: To Investigate Genetic and Environmental Influences on the Relationship Between ADHD and Physical Health and Identify Relevant Risk Factors

Many conditions share a genetic aetiology with ADHD (Barker et al., 2021; Jiang et al., 2025; Wu et al., 2022) and environmental factors also contribute significantly to some comorbid associations (Brikell et al., 2018). As with physical conditions themselves, environmental risk factors are regularly considered in isolation. Research often adjusts for individual influences, even when acknowledging that these individual factors fall under overarching themes such as socioeconomic status (Donnchadha et al., 2023; Landes & London, 2021). Some research has explored the influence of cumulative related environmental factors on ADHD risk (Keilow et al., 2020) and cumulative risk indices have been adjusted for in research examining comorbidity in other psychiatric conditions (Carr et al., 2023). In ADHD and physical health research however, cumulative risk is seldom explored. Also absent in the current literature is an investigation into the indirect influence of environmental factors on childhood health via parental genetic liability. As parents contribute both genotype and rearing environment, research is needed to examine the influence of both on the relationship between ADHD and physical health.

The third aim of this thesis was examined in several ways across the three papers. In the first two papers (Chapters 2 and 3), analyses were adjusted for cumulative environmental risk. This acknowledges and directly addresses the impact of an increased quantity of risk beyond individual factors. Genetic influences were investigated by considering both inherited genetic liability and the influence of non-inherited parental genes.

1.6 Thesis Overview

1.6.1 The Millennium Cohort Study

All three papers in this thesis utilise data from the Millennium Cohort Study (MCS) (University College London, 2024). The MCS is a large scale longitudinal cohort study involving approximately 19,000 children and their families. Cohort members were all born in

a 17-month period at the start of the Millennium (2000-2002) and were all living in the UK at nine months of age. The MCS sampling methods were complex and involved several approaches to ensure the sample was representative of the UK population. Detailed information on sampling methods is accessible online (Plewis, 2007). To maximise representation of particular groups, recruitment involved oversampling families from disadvantaged areas and ethnic minority groups. Due to the nature of longitudinal studies, participation rates varied across waves, with disadvantaged groups more likely to withdraw from the study. In order to account for attrition and to maximise representation, the MCS dataset includes standardised survey weights to be included in analyses (Centre for Longitudinal Studies, 2020).

To date, seven waves of data collection have been released capturing information from when cohort members were 9 months and 3, 5, 7, 11, 14 and 17 years old. An eighth wave of data, collected when cohort members were 23 years old, is due to be released in early 2026. At each wave, a vast quantity of information about cohort members and their families was collected, including data on physical health, household characteristics, parenting and relationships. A primary respondent from each household, in most cases the mother, completed questionnaires about the cohort member, themselves and other household members and information was also gathered from resident fathers and stepfathers. Data collected directly from cohort members varied across waves and included self-completion questionnaires from age 7 onwards, neuropsychological assessments at age 11 and activity diaries at age 14. The majority of MCS data can be accessed by interested researchers via the UK Data service website (https://ukdataservice.ac.uk/). Additional data such as biological and genetic data can be accessed on application to the Centre for Longitudinal Studies.

1.6.2 Paper 1 (Chapter 2): Longitudinal Associations Between Physical Health Conditions in Childhood and Attention-Deficit/Hyperactivity Disorder Symptoms at Age 17 Years. (*Reed, Cortese, Larsson, et al., 2024 [Hereafter referred to as 'Paper 1'])*

1.6.2.1 Background

As discussed above, previous research has predominantly focussed on the relationship between ADHD and individual physical health conditions. Paper 1 aimed to address this limitation by exploring the cumulative influence of multiple conditions. This aligns with the first aim of this thesis by examining the relationship between ADHD and cumulative physical health comorbidity. Paper 1 also addressed the third thesis aim by considering the influence of cumulative environmental risk.

Aim of paper 1: to investigate whether a cumulative number of physical disorders in childhood predicted ADHD symptoms at age 17 years, controlling for cumulative environmental risk, ADHD medication use, and ADHD symptoms reported at age 3 years.

1.6.2.2 Methodology

Stepwise multiple regression analyses were used to analyse the associations between clusters of similar physical health conditions in childhood and ADHD symptoms in adolescence, whilst also adjusting for cumulative environmental risk, ADHD medication use, and earlier ADHD symptoms at age three. The statistical methods and measures in this paper were chosen for several reasons. Within the MCS dataset, the number of cohort members with an ADHD diagnosis was substantially lower than prevalence estimates in the general population (Cortese et al., 2023). Therefore, scores on the Hyperactivity/Inattention subscale of the Strengths and Difficulties Questionnaire [SDQ] (Goodman, 1997) were also included.

The MCS dataset contains information on numerous physical health conditions collected across all seven waves. However, this was not always consistently recorded and data for some conditions were only included in two or three waves. Therefore, it was not possible to determine the total number of conditions experienced by each cohort member at each wave. As a result, binary 'ever had' variables were created to account for any report of each condition across all waves. These variables were then summed to create four cumulative variables; a sensory cluster, a neurological cluster, a cardiometabolic cluster and an atopic cluster. By creating the clusters in this way, it was possible to maximise the amount of physical health data included in the analyses. However, this meant it was necessary for the primary outcome to be ADHD symptoms at age 17 in order to avoid later physical health conditions retroactively predicting earlier ADHD symptoms. Subsequently, in order to maintain correct temporal ordering, this study analysed whether cumulative childhood

conditions predicted adolescent ADHD symptoms. However, it should be noted that this paper does not make any assertions of causality or the direction of the relationship. Additionally, to establish that any results were not confounded by earlier ADHD symptoms and to ensure the robustness of the results, ADHD symptoms at age three were added to the main model as an additional predictor.

To address a further limitation within existing research, environmental risk was adjusted for within the analyses. Individual risk factors identified within the MCS dataset were grouped according to similar risk profiles creating five cumulative risk indices (CRIs). The CRIs were included in the analyses as additional predictors to explore the impact of a cumulative burden of risk.

1.6.3 Paper 2 (Chapter 3): Longitudinal Associations Between ADHD and Weight From Birth to Adolescence. (*Reed, Cortese, Golm & Brandt., 2024 [Hereafter referred to as 'Paper 2'])*

1.6.3.1 Background

Paper 2 primarily addressed the second aim of this thesis by investigating associations across development, focusing on weight and obesity. In Paper 1, the cardiometabolic cluster (diabetes, obesity and cardiovascular disorders) was the only cluster to be affected by adjusting for environmental risk. Obesity had the third highest frequency of all conditions at 25.2% of the sample. In the UK, approximately 29% of adults are living with obesity (NHS England, 2025b) and, as adults with ADHD are more likely to be obese (Cortese, 2019), it is imperative that research focuses on identifying key risk factors and time periods in childhood which it may be most beneficial to target in clinical practice. This was the main objective of Paper 2 which takes a deeper look at the relationship between ADHD and weight, across the whole of development. Analyses in this study are split into two main parts.

***First aim of Paper 2*:** To compare an ADHD group and a control group on three measures; 1) mean birthweight, 2) mean weight at nine months, 3) the number of cohort members with obesity at each wave of data collection.

***Second aim of Paper 2*:** To investigate the direction of the association between ADHD symptoms and BMI z-scores across multiple time points.

1.6.3.2 Methodology for ADHD/Control Group Comparison

The two groups were formulated using data on both ADHD diagnosis and ADHD symptoms. As in Paper 1, ADHD symptoms were captured by the hyperactivity/inattention subscale of the SDQ to mitigate the low frequency of ADHD diagnoses in the MCS sample.

Several variables were used and created to capture data on weight throughout childhood. Cohort members' birthweight was retrospectively reported by parents in the first data sweep when children were nine months old. At every wave, cohort members' weight and height were recorded allowing BMI and BMI z-scores to be calculated at each time point. These were adjusted for age and sex and were based on the World Health Organisation growth standards (World Health Organization, 2006). At this point, it is important to clarify the language used when referring to sex differences. It is possible some individuals in the MCS dataset now identify with a gender which does not match their sex assigned at birth, however this data is not available. Therefore, in this thesis, the terms 'male' and 'female' are used to indicate sex assigned at birth and reported by parents when recruited to the study.

Obesity status was determined using the International Obesity Task Force (IOTF) cut-offs (Cole & Lobstein, 2012). Child cut-offs are provided linking BMI at each month of childhood with a corresponding BMI at age 18, with separate values for boys and girls. The IOTF defines overweight, obesity and severe obesity as an adult BMI of ≥25, ≥30 and ≥35, respectively. For example, a five-year old boy (age 60 months) with a BMI of 19.27 would have a corresponding adult BMI of 30 and fall into the obesity category (Cole & Lobstein, 2012). For the group comparison analyses, cohort members with a BMI equivalent to ≥30 at age 18 were categorised as having obesity and binary variables were created to indicate obese/not obese each wave.

1.6.3.3 Methodology for Path Analyses

In order to explore bidirectional associations between ADHD symptoms and BMI at multiple time points in childhood, extended versions (Mulder & Hamaker, 2021) of a Random-Intercept Cross-Lagged Panel Model (RI-CLPM) were conducted. Separate models for males and females were used to examine potential sex differences within the cohort. The RI-CLPM was chosen over the traditional Cross-Lagged Panel Model (CLPM) because it accounts for within-person variance as well as differences between individuals. This is an

important distinction because ADHD symptoms and BMI may differ significantly between cohort members as well as individual children experiencing fluctuations in both measures throughout childhood. The RI-CLPM estimates autoregressive pathways between subsequent measurements of each variable as well as cross-lagged paths indicating relationships between variables over time shedding light on the direction of the association. As in Paper 1, cumulative environmental risk indices were adjusted for to explore the influence of an accumulation of similar risk rather than individual effects. CRI groupings differed between Papers 1 and 2 due to data availability and associations with the outcome variables within existing literature. The CRIs were included in both models as time-invariant predictors, constrained across waves. In addition to the CRIs, ethnicity and ADHD medication were added as covariates. Only eight female cohort members were taking ADHD medication, so they were excluded from the analysis and medication was only adjusted for in the males-only analysis.

1.6.4 Paper 3 (Chapter 4): Association between ADHD polygenic scores and childhood physical health conditions. *(Hereafter referred to as 'Paper 3')*

1.6.4.1 Background

The first two papers found significant results even when adjusting for environmental factors. The path analyses revealed that cumulative prenatal factors produced the largest effect size when predicting subsequent BMI. Together, these findings highlight the importance of exploring how environmental and genetic factors interact to influence the relationship between ADHD and physical health. At age 14, cohort members and their biological parents were invited to provide DNA samples. This meant that both transmitted and non-transmitted ADHD polygenic scores could be calculated and used in analyses to explore relationships between ADHD genetic liability and physical health.

Paper 3 addressed all three of the overarching aims of this thesis. Cumulative comorbidity was examined by analysing the association between ADHD genetic liability and a cumulative total number of physical health conditions. This paper also investigated associations across development by looking at the association between ADHD polygenic scores and any reported diagnosis across childhood, BMI at each time point, and the onset of epilepsy and asthma. The overall aim of this paper aligns with the third thesis aim as it

examines the influence of genetic liability on children's physical health. Specific aims for this paper were as follows:

First aim of Paper 3: to investigate whether transmitted (ADHD-PGS_T) and non-transmitted (ADHD-PGS_{NT}) polygenic risk scores are associated with physical health conditions in childhood.

Second aim of Paper 3: To investigate whether ADHD-PGS are associated with a cumulative number of physical conditions.

Third aim of Paper 3: To investigate whether ADHD-PGS affect physical health condition onset and whether associations change over time.

1.6.4.2 Methodology

Environmental and genetic factors are intrinsically linked (see section 1.2.5.1), and it was not possible within the MCS dataset to include both polygenic scores and measured environmental risk variables within the same analysis due to gene-environment correlation. However, the inclusion of both transmitted and non-transmitted ADHD-PGS within this study meant it was possible to analyse both inherited genetic liability and the influence of non-inherited parental genes and associated environment and rearing factors (genetic nurture).

In order to examine genetic influences, only physical health conditions with a known heritability and sufficient data to ensure robust results were included. Although many other physical health outcomes are associated with ADHD, this study was only interested in those with a genetic aetiology therefore only conditions signifying a diagnosis with a known genetic basis were included. These were obesity (categorised according to IOTF cut-offs as in paper 2), epilepsy (excluding febrile seizures), asthma and food allergy.

Binary logistic regression analyses were conducted to explore whether ADHD-PGS (both transmitted and non-transmitted) were associated with 'ever had' variables for each condition. These were binary variables created to indicate whether a condition had been reported in any of the data collection waves. This method was chosen to explore the overall association between ADHD-PGS and each condition when taking into account data spanning the whole of childhood.

As no significant associations were found for non-transmitted ADHD-PGS, no further analyses were conducted using this variable. However, inherited genetic liability did show a relationship with physical health so the second part of the paper explored both cumulative associations and relationships over time. Linear regression analyses were used to investigate the relationship between transmitted ADHD-PGS and 1) the cumulative total number of conditions, and 2) BMI z-scores at waves two to seven (age 3 to 17 years). I decided to analyse the relationship with BMI at each wave following the results of Paper 2. Both the cross-sectional and path analyses indicated significant time periods in the relationship between ADHD and weight, so I wanted to explore whether genetic liability also has an impact on BMI at specific time points or whether the association is consistent across childhood. As the path analyses in Paper 2 found different results for males and females, the BMI analyses in Paper 3 were also repeated separately for males and females to establish whether the association between ADHD genetic liability and BMI is dependent on sex assigned at birth.

This paper also tested whether ADHD genetic liability is associated with epilepsy and asthma onset. However, the structure of the MCS dataset makes this less straightforward than other analyses. As the data collection waves have varying gaps between them and each wave represents data from the whole window of time since the previous data sweep, it is not possible to know the exact onset age of each condition. Interval-censored parametric survival models were used to determine whether higher transmitted ADHD-PGS were associated with epilepsy and asthma onset. The analyses explored whether higher genetic liability is associated with an earlier or later onset of each condition, rather than actual age of onset.

1.7 Author Contributions

Claire Reed was the lead author on and wrote all three papers in this thesis. Valerie Brandt and Samuele Cortese supervised completion of all aspects of Papers 1-3 and Dennis Golm supervised completion of all aspects of Papers 2 and 3. For Paper 1, co-authors Henrik Larsson, Cédric Galéra, and Joanne Cotton advised on methodology and were involved in the interpretation of the findings and editing of the final manuscript. For Paper 3, Joanna Martin created the polygenic scores used in the analyses, and was involved in the design, interpretation and editing process. Anita Thapar advised on design and methodology and was involved in the interpretation of findings and manuscript editing.

Chapter 2 Longitudinal Associations Between Physical Health Conditions in Childhood and Attention-Deficit/Hyperactivity Disorder Symptoms at Age 17 Years

This paper was published in the Journal of the American Academy of Child & Adolescent Psychiatry in 2024. https://doi.org/10.1016/j.jaac.2023.06.016

2.1 Abstract

Objective: Although evidence suggests significant cross-sectional relationships between attention-deficit/hyperactivity disorder (ADHD) and several physical health conditions, less is known about their longitudinal associations. We investigated the cumulative effect of childhood physical health conditions on ADHD symptoms at age 17 years, controlling for environmental factors, ADHD medication status, and ADHD symptoms at age 3 years.

Method: Using Millennium Cohort Study data (weighted n = 8,059), we assessed whether 4 physical health clusters (sensory, neurological, atopic, and cardio-metabolic) were associated with scores on the ADHD subscale from the Strengths and Difficulties Questionnaire at age 17 years. Environmental factors were grouped into five cumulative risk indices: prenatal, perinatal, postnatal environment, postnatal maternal well-being, and sociodemographic factors. Regression analyses determined whether each physical health cluster was associated with ADHD score while controlling for environmental factors, ADHD medication, and earlier symptoms.

Results: Sensory, neurological, and cardio-metabolic clusters were all significantly associated with ADHD symptoms (β range = 0.04-0.09, $p < .001$). The overall model explained 2% of the variance. This rose to 21% ($\Delta R^2 = 0.06$) after adjusting for confounders. The sensory (β = 0.06) and neurological (β = 0.06) clusters remained significant ($R^2 = 0.21$, $\Delta R^2 = 0.06$), but the cardio-metabolic cluster was no longer a significant predictor.

Conclusion: Sensory or neurological conditions in childhood were associated with higher ADHD symptoms aged 17 after adjustment of confounders. This was not the case for atopic or cardio-metabolic conditions. These findings have implications for the care of children with sensory/neurological conditions and future research examining ADHD etiopathophysiology.

Key words: ADHD; physical health; environmental factors; ADHD medication

2.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by developmentally atypical, pervasive, and impairing symptoms of inattention and/or hyperactivity/impulsivity (American Psychiatric Association, 2013). ADHD is a complex condition, with many comorbidities often complicating the diagnostic process, symptom management, and the quality of life of individuals with ADHD and their families (Reale et al., 2017).

There is increasing evidence that ADHD is associated not only with mental health but also with physical conditions. A recent umbrella review (Arrondo et al., 2022) encompassing 10 meta-analyses on ADHD found significant cross-sectional associations of ADHD with asthma and obesity when considering the most rigorous estimates (adjusted effect sizes). When considering unadjusted effect sizes, there was also convincing or highly suggestive evidence for an association of ADHD with rhinitis and dermatitis.

Another recent birth cohort study (Galéra et al., 2022) (n = 2,057) assessed cross-sectional associations between ADHD symptoms and a large number of physical conditions at different time points during development, from age 5 months to 17 years. Some of the associations between ADHD symptoms and several physical conditions were consistently found in early childhood, middle childhood, and adolescence (e.g., asthma, sleep problems), whereas others were present only at 1 time point, or were confounded by socioeconomic status or psychiatric comorbidities (e.g., body mass index [BMI], dental caries). It is possible that either ADHD contributes to the increased risk for physical conditions, or that, vice versa, physical conditions increase the risk of ADHD, or that common underlying factors contribute to both (Hanć & Cortese, 2018).

However, although the bulk of the studies on the links between ADHD and physical conditions have addressed cross-sectional associations, longitudinal associations shedding light on the direction of the relationship have been less explored and have focused on single physical conditions, for example, obesity/increased body mass index (Kase et al., 2021).

To address these limitations, the present study used a large-scale population-representative sample to examine the hypothesis that a cumulative number of physical health conditions across child development are associated with ADHD symptoms in adolescence.

When assessing this relationship, it is important to control for two important confounders. The first is environmental factors associated with an increased risk of ADHD. In this regard, there is meta-analytic evidence that ADHD is more common in children whose mothers smoked during pregnancy or experienced pre-eclampsia (Arango et al., 2021). Other risk factors include low birth weight and prematurity (Serati et al., 2017), and several indicators of socioeconomic disadvantage such as low family income, single-parent households, and low maternal education (A. E. Russell et al., 2016). The second important confounder is medications for ADHD that may have an impact on a number of physiologic systems; for instance, stimulants can negatively affect (at least at the beginning of the treatment) weight (Carucci et al., 2021) and sleep (Faraone et al., 2019).

To gain insight into the longitudinal relationship between physical conditions and ADHD symptom development, we explored whether a cumulative number of physical disorders in childhood predicted ADHD symptoms at age 17 years, controlling for cumulative environmental risk, ADHD medication use, and ADHD symptoms reported at age 3 years.

2.3 Methods

2.3.1 Sample

We used data from the Millennium Cohort Study (MCS), a longitudinal study that collected information from more than 19,000 UK families with children born between 2000 and 2002. To date, 7 waves of data have been collected, at ages 9 months and 3, 5, 7, 11, 14, and 17 years, respectively. In this study, as in previous research (Flouri et al., 2017), only the first sibling of each family was included (4.9% excluded) to prevent confounding effects of family membership. Participants were also excluded if data relating to their biological mother were unavailable (5.1%) or if all physical health predictor variables were missing (1.1%). As in previous longitudinal analyses (Brandt et al., 2022), only participants with non-missing outcome data at age 17 years were included in the analysis.

The number of participating families varied among waves, and households sampled from disadvantaged areas were more likely to withdraw (Mostafa & Ploubidis, 2017). As such, standardized weights were applied to ensure the sample was representative of the UK population and to account for attrition rates. Weights were calculated by multiplying the wave 1 sample design weights by the non-response weights of each wave. As data in this

study were taken from all waves, weights from the most recent data sweep were applied. Descriptive statistics for all weighted variables in the current sample for the study (n = 8,059) are reported in Tables 1 and 2. This study was approved by the University of Southampton Ethics Committee, in addition to the informed consent procedures obtained in the MCS (Shepherd & Gilbert, 2019). Parents gave written informed consent to the open use of the anonymized dataset.

Table 1.

Weighted Frequencies of Sample Demographics and Other Environmental Risk Factors

	High Risk Criteria	High Risk N (%)
SES[a] and demographics		
Sex[1]	Male	4016 (49.8)
Ethnicity[2]	Any ethnicity other than white	968 (12)
Household income[3]	Below 60% median poverty indicator	2502 (31.1)
Household crowding[4]	Fewer rooms than people (excluding bathrooms)	743 (9.2)
Housing Tenure[5]	Social housing or renting from local authority	1825 (22.7)
Prenatal factors		
Maternal pre-pregnancy BMI[b6]	>24.9	2089 (25.9)
Antenatal blood pressure[7]	Mother diagnosed with Pre-eclampsia/ Hypertension	561 (7)
Maternal diabetes diagnosis[7]	Mother has Diabetes diagnosis	159 (2)
Smoking in pregnancy [8,9]	Mother smoked 1 or more cigarettes during pregnancy	1716 (21.3)
Perinatal factors		
Birthweight[10]	<2.5kg	502 (6.2)
Gestation[10,11]	<37 weeks gestation (premature)	663 (8.2)
Delivery[7]	Caesarean section	1584 (19.7)
Presentation/lie[7]	Breech presentation/ other abnormal lie	452 (5.6)
Postnatal environmental factors		
Maternal age[12]	≤19 years	671 (8.3)
Number of parents in household[3]	1 parent living in household	1270 (15.8)
Mother's education[13,14]	Mother educated to <NVQ[c] level 3 (2 A-levels)	4847 (60.1)
Breastfeeding[15]	No breastfeeding	2480 (30.8)
Postnatal maternal wellbeing factors		
Maternal distress[16,17]	<4 on Rutter Malaise Inventory	358 (4.4)
Maternal mental health diagnosis[18]	Depression/anxiety diagnosis	2008 (24.9)
Maternal attachment[19,20]	>22 on Condon Maternal Attachment Scale	1870 (23.2)

[a] SES = socioeconomic status, [b] BMI = Body Mass Index, [c] NVQ = National Vocational Qualifications

[1](Pinares-Garcia et al., 2018), [2](Assari & Caldwell, 2019), [3](Russell et al., 2014), [4](Flouri et al., 2017), [5](Russell et al., 2015), [6](Andersen et al., 2018), [7](Arango et al., 2021), [8](Y. He et al., 2020), [9](Rougeaux et al., 2020), [10](Serati et al., 2017), [11](Murray et al., 2022), [12](Chang et al., 2014), [13](Torvik et al., 2020), [14](Hall et al., 2022), [15](Zeng et al., 2020), [16](Bendiksen et al., 2020), [17](Noonan et al., 2018), [18](Sagiv et al., 2013), [19](Storebø et al., 2016), [20](Curran et al., 2016)

Table 2. Weighted Frequencies of Individual and Clustered Physical Health Conditions, and Cumulative Risk Indices

		Number of Conditions N(%)			
	N (%)	**0**	**1**	**2**	**3**
Sensory cluster		5051 (62.7)	2515 (31.2)	493 (6.1)	
Eyesight problems	1802 (22.4)				
Hearing problems	1700 (21.1)				
Atopic cluster		3271 (40.6)	2790 (34.6)	1477 (18.3)	508 (6.3)
Asthma	1375 (17.1)				
Eczema	3411 (42.3)				
Hay fever	2482 (30.8)				
Neurological cluster		6851 (85)	1093 (13.6)	109 (1.4)	6 (0.1)
Movement problems	452 (5.6)				
Neurological disorders	41 (0.5)				
Sleeping problems	82 (1)				
Stutter	261 (3.2)				
Fits or Epilepsy	491 (6.1)				
Cardio-metabolic cluster		5983 (74.2)	2052 (25.5)	24 (0.3)	
Diabetes	22 (0.3)				
Obesity age 17	2031 (25.2)				
Cardiovascular disorders	47 (0.6)				

	Number of Environmental Risk Factors N(%)					
Cumulative Risk Indices	**0**	**1**	**2**	**3**	**4**	**5**
Prenatal factors	4336 (53.8)	2983 (37)	682 (8.5)	53 (0.7)	5 (0.1)	
Perinatal factors	5747 (71.3)	1596 (19.8)	556 (6.9)	148 (1.8)	13 (0.2)	
Postnatal environmental factors	2707 (33.6)	2535 (31.5)	1917 (23.8)	701 (8.7)	199 (2.5)	
Postnatal maternal wellbeing factors	4625 (57.4)	2719 (33.7)	622 (7.7)	90 (1.1)		
Socioeconomic status and demographics	2229 (27.7)	3175 (39.4)	1431 (17.8)	901 (11.2)	298 (3.7)	24 (0.3)

2.3.2 Measures

2.3.2.1 Outcome Measure: Parent-Reported ADHD Symptoms

The parent-reported hyperactivity/inattention subscale of the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997), measured at age 17 years, was used as a continuous dependent variable. The subscale hyperactivity/inattention is composed of five items ("restless, overactive, cannot stay still for long," "constantly fidgeting or squirming," "easily distracted, concentration wanders, "thinks things out before acting," "good attention span, sees tasks through to the end"). The SDQ items are rated from 0 to 2 points (0 = never, 1 = sometime true, 2 = certainly true or reverse coded for positive statements). Scores on the hyperactivity/inattention subscale range between 0 and 10, with a higher score indicating more ADHD symptoms. The SDQ has been found to be a valid measure with the hyperactivity/inattention subscale predicting ADHD diagnosis (C. L. Hall et al., 2019) with a Cronbach alpha of 0.88, indicating good reliability. In the current sample, SDQ scores are significantly correlated ($p < .001$) across all 6 waves (ages 3-17 years) in which they are reported.

ADHD was diagnosed in a subset of children, with n = 174 children having an ADHD diagnosis by age 17 years. The main analysis was replicated with diagnosed ADHD as the outcome variable to test robustness of the results. We found that adolescents with an ADHD diagnosis at age 17 had a significantly higher hyperactivity/inattention SDQ score (mean = 5.09) than adolescents without an ADHD diagnosis (mean = 2.38; $t_{8386} = 16.31$, $p < .001$, $d = 1.25$).

2.3.2.2 Predictors: Physical Health Conditions

At each wave of data collection (age 9 months to 17 years), parents were asked about their child's physical health. This information was gathered in several ways, including asking whether they had ever seen a health care professional about any problems and, if yes, asking to give details. Parents were also asked about specific diagnoses (e.g., "has [child's name] ever had asthma?"). Hospital admissions were also recorded along with the reason for admission, such as convulsions, fits, or epilepsy. We created variables to identify whether each child had ever experienced the condition. Physical conditions for which a diagnosis could be given repeatedly and on a temporary basis, such as infection or diarrhoea, were excluded.

We grouped the physical conditions into 4 clusters, according to similar physiological mechanisms, reflecting their grouping in the *International Classification of Diseases, Eleventh Revision* (*ICD-11*) (World Health Organization, 2019), as well as existing empirical evidence (M.-H. Chen et al., 2014; Eklund et al., 2018; Garcia-Argibay et al., 2022; Merlo & Briley, 2019; Pruett et al., 2021): (1) sensory cluster (eyesight problems and hearing problems); (2) atopic cluster (eczema, asthma, and hay fever); (c) neurological cluster (fits and epilepsy, sleeping problems, stutter, movement problems, and other neurological disorders); and (4) cardio-metabolic cluster (obesity [at wave 7 only, to exclude the natural weight fluctuations of young children], diabetes, and any reported heart or circulation condition including congenital heart disease). Cohort members' cumulative physical risk was therefore indicated by the number of conditions that they had ever had in each cluster.

2.3.2.3 Control Variables: Cumulative Risk Indices and Age 3 Years SDQ score

Informed by previous evidence (Table 1) a total of 20 environmental risk factors for ADHD were identified and controlled for within the available MCS data (University Of London, 2024). Data were collected during interviews with parents at the first data sweep (age 9 months). Individual risk factors were classified as either "high risk" or "low risk" (e.g., caesarean delivery yes/ no). Continuous variables were assigned a cut-off with reference to previous literature (Table 1). Risk factors were grouped and totalled to create five cumulative risk indices (CRIs) as follows:

(1) prenatal risk index, including maternal pre-pregnancy BMI, blood pressure problems in pregnancy, maternal diabetes, and smoking during pregnancy;

(2) perinatal risk index, including birth weight, gestation, delivery method, and pregnancy lie/presentation;

(3) postnatal risk (environment) index, including maternal age, number of parents in the household, maternal education, and breastfeeding;

(4) postnatal risk (maternal well-being) index, including maternal distress, maternal depression/anxiety, and maternal attachment. Maternal distress was assessed using a 9-item short form version (Dex & Joshi, 2004) of the Rutter Malaise Inventory (Rutter et al., 1970). The highest loading items in the first principal factor were used to create the 9-item

scale measuring psychological distress. Mothers were asked a series of questions requiring a yes/no response such as “Do you often feel miserable or depressed?” High-risk maternal distress was indicated by a score of ≥4 (Noonan et al., 2018), and psychometric properties are reported to be good (McGee et al., 1986). A diagnosis of depression and/or anxiety was also included in the maternal well-being index, along with maternal attachment measured, using a 6-item modified version of the Condon Maternal Attachment Questionnaire (Condon & Corkindale, 1998). In this scale, mothers are asked about their feelings in different situations, such as when they are caring for or having to leave their infant. Responses were recoded to ensure that all items followed the same scale of 1 to 5, which was then summed to give a total score out of 30. In line with previous literature (Curran et al., 2016), high risk was categorized as the 25% of scores with the lowest attachment.

(5) The fifth CRI comprised socioeconomic status and demographic risk index, including sex, ethnicity, household income, housing tenure, and overcrowding.

To account for ADHD symptoms experienced at a younger age, the SDQ score reported by parents at age 3 years was added as an additional predictor.

2.3.2.4 ADHD Medication

Only at wave 6, when cohort members were 14 years of age, parents were asked if their child was taking any prescribed medication for ADHD. A list of possible medications was given, including both stimulants and non-stimulants, and the variable was coded as yes if parents indicated their child was taking any medication on the list.

2.3.3 Statistical Analysis

Stepwise multiple regression analysis was conducted using IBM SPSS Statistics for Windows (version 28.0) to analyse the relationship between the physical health clusters and ADHD symptoms at age 17 years before and after controlling for cumulative environmental risk, ADHD medication, and age 3 SDQ score. SDQ scores on the hyperactivity/inattention subscale at age 17 years were entered as the dependent variable in all 4 regression models. The predictors entered into each model were as follows: model 1, physical health clusters; model 2, physical health clusters and cumulative risk indices; model 3, physical health clusters, cumulative risk indices, and ADHD medication; and model 4, physical health clusters, cumulative risk indices, ADHD medication, and SDQ score at age 3 years. Variance

inflation factor values did not indicate multicollinearity for any of the variables. To ensure correct temporal ordering of the regression model, physical health diagnoses from all timepoints were used to predict ADHD symptoms and diagnosis at age 17 years. However, to confirm robustness of the findings when accounting for earlier ADHD symptoms, we included in the main analysis a fourth regression model with an SDQ score at age 3 years as an additional predictor. To show further robustness of the results, model 3 was repeated as a binary logistic regression with ADHD diagnosis (yes/no) as the outcome.

2.4 Results

Weighted frequencies of physical health clusters and cumulative risk indices are reported in Table 2. As clusters were formed based on physiological similarity, they consisted of differing numbers of conditions and proportional frequencies. For example, the cardio-metabolic cluster consisted of 3 conditions with obesity markedly more prevalent than the other 2 disorders, whereas the sensory cluster consisted of 2 conditions with similar frequencies. In total, 91 children (1%) were taking ADHD medication, and the average SDQ score at age 17 was 2.64 (SD = 2.34). Skewness and kurtosis were found to be within the normal range.

Model 1 (physical health clusters only) was overall significant ($F_{4,5411}$ = 29.37, p < .001) and explained 2% of the variance. As individual predictors, the sensory (β = 0.08, p < .001), neurological (β = 0.10, p < .001), and cardio-metabolic (β = 0.04, p < .001) clusters all significantly predicted ADHD symptoms at age 17 years. Model 2 (physical health clusters + CRIs) was also statistically significant ($F_{9,5406}$ = 61.59, p < .001), with 10% of the variance explained (R^2_{adj} = 0.09 , ΔR^2 = 0.07). Again, the sensory (β = 0.08, p < .001) and neurological (β = 0.09, p < .001) clusters were significantly associated with ADHD symptoms, but the cardio-metabolic cluster was no longer a significant predictor. This remained unchanged in model 3 ($F_{10,5405}$ = 96.37, p < .001), with only the sensory (β = 0.07, p < .001) and neurological (β = 0.09, p < .001) clusters significantly predicting ADHD symptoms at age 17 years. Overall, model 3 explained 15% of the variance (R^2_{adj} = 0.15, ΔR^2 = 0.06). Model 4 was again overall significant ($F_{11,5404}$ = 129.27, p < .001). The model explained 21% of the variance (R^2_{adj} = 0.21, ΔR^2 = 0.06) with the sensory (β = 0.06, p < .001) and neurological cluster (β = 0.06, p < .001) significantly predicting age ADHD symptoms at age 17 years. The atopic cluster was not a significant predictor in any of the 4 regression models. The CRIs all

significantly predicted ADHD symptoms in both model 2 and model 3 (β range = 0.03-0.18). In model 4, all CRIs significantly predicted ADHD symptoms except perinatal factors. A summary of the regression statistics can be found in Table 3. The mean SDQ scores for each cumulative number of conditions in each cluster are shown in Figure 1.

Table 3.

Regression Statistics for all Models with SDQ[a] Score at Age 17 as the Outcome Variable.

	R^2	R^2 change	B	β	95% Confidence Interval LL	UL
Model 1	.02	.02				
Constant			2.10**		2.00	2.20
Clusters						
Sensory			0.31**	0.09	0.22	0.41
Neurological			0.50**	0.09	0.36	0.64
Atopic			0.05	0.02	-0.02	0.11
Cardio-metabolic			0.17**	0.04	0.04	0.31
Model 2	.09	.07				
Constant			1.27**		1.15	1.39
Clusters						
Sensory			0.28**	0.08	0.19	0.37
Neurological			0.44**	0.08	0.38	0.64
Atopic			0.04	0.02	-0.03	0.09
Cardio-metabolic			0.04	0.01	-0.08	0.16
CRIs[b]						
Prenatal risk			0.22**	0.07	0.14	0.30
Perinatal risk			0.09*	0.03	0.01	0.16
Mother environment			0.26**	0.12	0.26	0.38
Mother wellbeing			0.18**	0.05	0.15	0.31
SES[c] & demographics			0.40**	0.18	0.31	0.42
Model 3	.15	.06				
Constant			1.34**		1.23	1.46
Clusters						
Sensory			0.28**	0.08	0.17	0.34
Neurological			0.40**	0.08	0.35	0.60
Atopic			0.02	0.01	-0.05	0.07
Cardio-metabolic			0.05	0.01	-0.06	0.17
CRIs						
Prenatal risk			0.19**	0.06	0.11	0.27
Perinatal risk			0.08*	0.03	0.01	0.15
Mother environment			0.23**	0.10	0.24	0.36
Mother wellbeing			0.14**	0.04	0.11	0.27

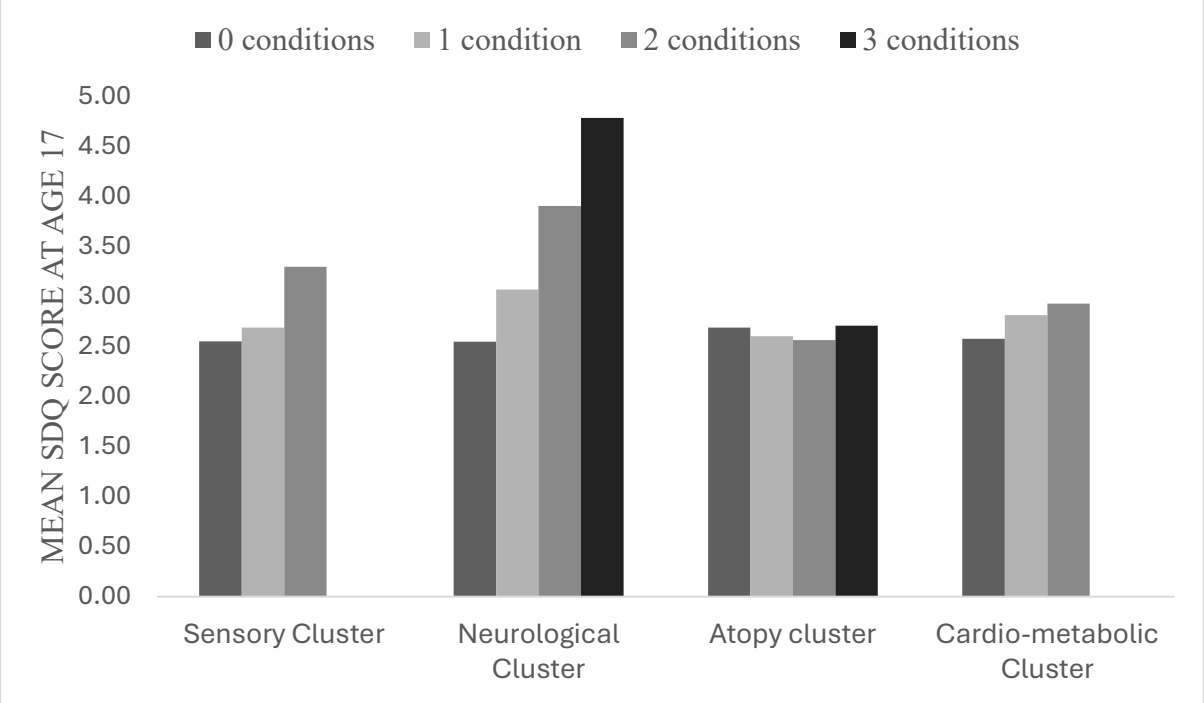
SES & demographics			0.36**	0.16	0.27	0.38
ADHD[d] medication			4.86**	0.24	4.35	5.27
Model 4	.21	.06				
Constant			0.70**		0.56	0.84
Clusters						
Sensory			0.22**	0.06	0.13	0.31
Neurological			0.32**	0.06	0.20	0.45
Atopic			0.01	0.00	-0.05	0.07
Cardio-metabolic			0.01	0.00	-0.11	0.13
CRIs						
Prenatal risk			0.16**	0.05	0.08	0.24
Perinatal risk			0.07	0.02	-0.01	0.14
Mother environment			0.16**	0.07	0.10	0.22
Mother wellbeing			0.08*	0.02	0.001	0.16
SES & demographics			0.27**	0.12	0.21	0.32
ADHD Medication			4.39**	0.22	3.91	4.87
SDQ score at age three			0.25**	0.25	0.22	0.27

* p < .05, ** p < .001

[a] SDQ = Strengths and Difficulties Questionnaire, [b] CRIs = Cumulative Risk Indices, [c] SES = Socioeconomic Status, [d] ADHD = Attention Deficit/Hyperactivity Disorder

Figure 1.

Weighted Mean SDQ Scores for Cumulative Numbers of Conditions in Each Physical Health Cluster.



A binary logistic regression with ADHD diagnosis as the outcome variable showed that the sensory cluster significantly predicted ADHD diagnosis (b = 0.27, p = .020, OR = 1.31; 95% CI = 1.04, 1.65).

The neurological cluster also significantly predicted ADHD diagnosis (b = 0.66, p < .001, OR = 1.94; 95% CI = 1.48, 2.53). Each additional neurological condition almost doubled the odds of an ADHD diagnosis.

2.5 Discussion

This is the first study to analyse the longitudinal association between a broad range of physical conditions in childhood and ADHD symptoms at age 17 years, controlling for cumulative environmental risk factors for ADHD, ADHD medication status, and earlier ADHD symptoms. The sensory and neurological clusters were both significant predictors of hyperactivity/ inattention symptoms at age 17 years and remained so after controlling for confounders. Moreover, the odds of having an ADHD diagnosis at age 17 years was almost twice as likely when adolescents had predating neurological issues. The atopic cluster was not a significant predictor in any of the regression models, and, after controlling for environmental risk and ADHD medication, the cardio-metabolic cluster was also not a significant predictor.

Children with more sensory conditions had higher hyperactivity and inattention symptoms at age 17 years. This is in line with previous studies showing that both eyesight and hearing problems increase the risk of ADHD (DeCarlo et al., 2016; Hancock et al., 2017; Su et al., 2019). Our findings build on this known association between ADHD and eyesight and hearing problems by showing that the likelihood of hyperactivity and inattention symptoms increases as the number of sensory conditions increases. DeCarlo *et al.* proposed that sensory disorders place a large demand on executive functioning. Sensory problems may deplete executive functioning skills, leading to a reduced ability to successfully perform tasks known to be impaired in ADHD, such as those requiring organization and concentration. It follows, therefore, that an increased number of sensory conditions may exacerbate inattention or hyperactivity symptoms in people who may already struggle with executive functioning.

This raises the question as to which should be explored in future research, of whether hearing and eyesight problems magnify existing symptoms, mimic ADHD symptoms that may otherwise not be present, or whether ADHD and sensory problems may share neurobiological underpinnings (Bellato et al., 2023). Our findings suggest that, to maintain quality of life, people with sensory disorders may need support with symptoms beyond those primarily associated with their health condition, because people with high levels of ADHD symptoms often experience a poorer quality of life, even if they do not meet the criteria for a diagnosis of ADHD (Franklin et al., 2017).

A higher number of neurological conditions during development also significantly predicted ADHD symptoms at age 17 years when controlling for risk factors, medication, and earlier ADHD symptoms. This is in line with previous studies reporting associations between ADHD and individual neurological conditions, such as stutter (Druker et al., 2019) and epilepsy (Brikell et al., 2018). Sleep problems, stutter, and epilepsy are all known to individually predict ADHD, as well as each other (Merlo & Briley, 2019). Our results expand this knowledge by showing that a cumulation of neurological conditions further increases the likelihood of experiencing ADHD symptoms and an ADHD diagnosis later on in adolescence.

Previous literature has suggested that this relationship may be bi-directional (Chou et al., 2013), as ADHD and conditions such as epilepsy may have shared risk factors or a shared neurobiological origin, with each predicting an increased risk of the other. Previous studies have found a shared genetic association between ADHD and neurological conditions, such as epilepsy (Wu et al., 2022), and sleep problems (Carpena et al., 2021). It is possible that some genetic variants affect several neurological as well as mental conditions increasing polygenic risk (The Brainstorm Consortium et al., 2018).

Neurological conditions such as epilepsy are also known to have an impact on executive functioning networks (Allone et al., 2017) that may modulate ADHD symptom expression. Executive functions involve the frontal cortex (Friedman & Robbins, 2022), which is associated with both epilepsy and ADHD (Wu et al., 2022). Alterations in executive functioning networks that are associated with ADHD and neurological conditions may offer another explanation of the comorbidity between the conditions.

Contrary to previous research (Sun et al., 2021), atopic disorders were not significantly associated with higher ADHD symptoms. This result was surprising, considering the wealth of evidence to support an association between atopic conditions and ADHD. Both eczema and hay fever had frequencies higher than expected and notably higher than other conditions (42.3% and 30.8%, respectively). It may be that these conditions were over-reported in the sample, which influenced the results. Future research using clinical diagnoses rather than parent-reported physical conditions may reduce measurement error and shed light on the association between cumulative atopic conditions and ADHD symptoms. Another possible explanation for our findings is that individual conditions predict ADHD symptoms, but that an accumulation of conditions does not increase the likelihood further.

This may also be the case for cardio-metabolic disorders, as the cardio-metabolic cluster also produced different results from the sensory and neurological clusters. The cumulative effect of cardio-metabolic conditions significantly predicted ADHD symptoms in the first regression model but not when controlling for environmental risk or ADHD medication. Previous research has reported an increased likelihood of developing diabetes in young people with ADHD, even after controlling for medication and demographic factors (M.-H. Chen et al., 2018). Our findings suggest that this relationship may not be bi-directional, as cardiometabolic conditions did not predict an increase in hyperactivity/inattention symptoms. Rather than an accumulation of cardiometabolic conditions being associated with an increase in hyperactivity/inattention symptoms, it may be that environmental factors, or even other ADHD-related features such as impulsive decision making, are driving this relationship. These findings add weight to the complexity of the association between physical health and ADHD, demonstrating the influence of environmental risk on this relationship. For cardio-metabolic conditions at least, an individual's environment may play a larger part in determining the nature of the relationship.

All cumulative risk indices were themselves significantly associated with ADHD symptoms at age 17 years. The postnatal mother environment and socioeconomic status/demographics indices had the largest effect size, and both consisted of environmental factors that are considered to reflect mainly psychosocial rather than biological influences

compared to the other indices. For example, gestation and birth weight are irreversible factors that affect a child's biology at a fixed point in time, potentially with long-term consequences. Factors affecting the whole household, such as income or housing tenure, have a greater effect on a child's physical environment, but they are also subject to greater fluctuation, and their influence may vary, depending on changes over time. This suggests that further investigation is warranted to explore how different environmental factors affect the relationship between cumulative physical conditions and ADHD.

This study has several strengths. It used a large sample, weighted to represent the general population. Data were obtained longitudinally, allowing analysis of environmental risk before the age of 3 years as a predictor of ADHD symptoms in later adolescence. It is also the first study to control for both environmental risk and medication use while examining the cumulative effect of several physical health conditions. The results further our insight into the pathophysiology of ADHD and point to associations that may eventually inform clinical practice in terms of implementation of additional support programs. A key area for future research would be to explore the effects of early treatment and support for physical conditions on later development of ADHD symptoms. However, when considering their possible clinical implications, our findings should be interpreted with caution. Although the SDQ differentiated well between children with and without an ADHD diagnosis, it is not a screening instrument for ADHD. The sensitivity analyses that we conducted with ADHD diagnosis are limited by only a subset of children having been evaluated for ADHD; therefore, our figures are likely underestimated. However, the consistency of the results in our sensitivity analysis indicates that our findings may extend to cases with a categorical diagnosis. There are some additional limitations to consider. First, the analyses were restricted by the amount and variety of physical health and environmental data available. Second, this study looked at physical health only as a predictor of ADHD symptoms and did not explore the reverse relationship or the possibility of a bi-directional association. Third, because of a lack of data, it was not possible to analyse the effect of parental history of ADHD or physical health. ADHD is known to be highly heritable (Faraone & Larsson, 2019), as are many physical health conditions. Therefore, it is likely that a parent's health and neurodiversity may have an impact on both ADHD symptoms and the physical health of their child, as well as the home environment.

In summary, this study found a significant relationship between a number of cumulative physical disorders diagnosed during childhood and ADHD symptoms in adolescence. The results indicated that sensory disorders and neurological disorders predicted ADHD symptoms even when relevant environmental risk was controlled for, suggesting possible biological commonalities, including genetic association.

Chapter 3 Longitudinal Associations Between ADHD and Weight From Birth to Adolescence

This paper was published in the Journal of the American Academy of Child & Adolescent Psychiatry in 2024. https://doi.org/10.1016/j.jaac.2024.09.009

3.1 Abstract

Objective: Attention-deficit/hyperactivity disorder (ADHD) is associated with lower birth weight, but also with obesity in childhood. Findings on the direction of this association are mixed. This study investigated the relationship between weight and ADHD from birth across development.

Method: We used data from the Millennium Cohort Study (MCS), collected at 7 time points between age 9 months and 17 years. ADHD diagnosis status and scores on the Strength and Difficulties Questionnaire (SDQ) were used to create an ADHD group and a control group. Random intercept cross-lagged panel models were conducted in female individuals (n = 4,051) and male individuals (n = 3,857) to examine bidirectional associations between body mass index (BMI) *z* scores and SDQ scores between ages 3 and 17 years. Analyses were adjusted for common risk factors for ADHD and obesity, such as sex assigned at birth, multiple births, and ADHD medication status.

Results: Children in the ADHD group were significantly lighter in weight at birth than the control group (t[5674] = 2.65, 95% CI = 0.02, 0.14, p = .008) and were significantly more likely to have obesity at age 5 years onward (odds ratio range = 1.57-2.46, relative risk range 0.98-2.29). Path analyses conducted separately for male and female individuals showed that higher ADHD symptoms in female individuals at ages 7, 11, and 14 years significantly predicted higher BMI *z* scores at ages 11, 14, and 17 years, respectively. In male individuals, this association was seen only between ages 11 and 14 years (β = 0.07; 95% CI = 0.04-0.10, p < .001).

Conclusion: Results suggest that interventions for children with ADHD, and their parents, should begin as soon as possible, ideally prenatally. Developmental sex differences should be considered.

Key Words: ADHD; obesity; environmental factors; ADHD medication

3.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD), characterized by persistent and impairing inattention and/or hyperactivity and impulsivity (American Psychiatric Association, 2013), is the most common neurodevelopmental condition. Global prevalence estimates range between 5% and 11% (Cortese et al., 2023; Danielson et al., 2024; Salari et al., 2023) in childhood and adolescence. Diagnostic rates are more than twice as high in male individuals than in female individuals (Polanczyk et al., 2007), with possible reasons for the disparity including diagnostic bias, differing symptom presentation, or biological differences (Martin et al., 2018).

The relationship between ADHD and body weight, despite being largely investigated, is still unclear (Cortese, 2019). Children with increased ADHD symptoms are typically lighter in weight at birth than their peers (Momany et al., 2018), but are later more likely to have obesity (Khalife et al., 2014). Research into the "when and why" regarding this turning point is scarce. It is unclear when children with ADHD experience the shift from underweight to overweight during their development, and at what age preventive measures might be usefully implemented. As both ADHD and high body mass index (BMI) are associated with numerous negative health outcomes, including asthma, diabetes, and cardiovascular disorders (Arrondo et al., 2022; Horesh et al., 2021), the relationship between the 2 conditions has important clinical implications.

The longitudinal direction of the association between ADHD and overweight and the mechanisms involved is also unclear. Some studies have suggested that high BMI leads to an increase in ADHD risk (Martins-Silva et al., 2019), whereas others have found that childhood ADHD symptoms predict obesity in adolescence (Khalife et al., 2014). One longitudinal cohort study (Bowling et al., 2018) assessing the bidirectional relationship between body composition and ADHD in children aged 18 months to 9 years found that higher ADHD symptoms predicted higher weight from age 3 years onward; however, this was not investigated for boys and girls separately.

When investigating the relationship between weight and ADHD, it is important to take into account not only cohort members' sex but also common risk factors, including factors prior to conception, such as mothers' BMI (Andersen et al., 2018), and family

demographics, such as socioeconomic disadvantage (A. E. Russell et al., 2016). ADHD medication may also confound the relationship, as stimulants are known to have an effect on weight, particularly at the start of treatment (Carucci et al., 2021).

Importantly, although substantial previous literature describes the relationship between ADHD and numerous weight measures at different times during development, much of this research is cross-sectional or assesses only a short time period in childhood.

Shedding light on the longitudinal relationships between ADHD and body weight during the developmental period is crucial to inform preventive programs. In the present study, we used data from a large, population-representative, UK sample with data from birth to late adolescence (age 17 years), to explore the relationship between weight and ADHD in male and female individuals, across childhood and adolescence, while adjusting for relevant environmental risk factors. The main aims were to investigate the following: (1) at what age underweight shifts toward overweight in the ADHD group compared to the control group; (2) the bidirectional associations between ADHD symptoms and BMI across childhood; and (3) whether this association is different in male and female individuals.

3.3 Methods

3.3.1 Sample

We used data from the Millennium Cohort Study (MCS), a longitudinal cohort study involving more than 19,000 families with children born between 2000 and 2002. Data have been collected at 7 time points to date, when cohort members were 9 months, and 3, 5, 7, 11, 14, and 17 years of age. Cohort members taking ADHD medications (n = 141) were excluded from the comparison analyses and adjusted for in the longitudinal analysis, as stimulants may lead to decreased weight (Carucci et al., 2021).

As is common in longitudinal cohort studies, participation rates varied across survey waves, with families joining and withdrawing at different time points. The random-intercept cross-lagged panel model (RI-CLPM) sample (combined N = 7,908) included only cohort members who had participated at every wave and excluded those missing all environmental risk data. Survey weights, stratification, and cluster variables were also included in the analysis because of the MCS complex sampling methods (Centre for Longitudinal Studies,

2020). In addition to the informed consent procedures of the Millennium Cohort Study (Shepherd & Gilbert, 2019), this research was approved by the University of Southampton Ethics Committee.

3.3.2 Measures

3.3.2.1 ADHD Diagnosis and Symptoms

As in previous studies (Bisset et al., 2019), cohort members were identified as having ADHD based on diagnosis and/or scores above the clinical threshold on the Strengths and Difficulties Questionnaire (SDQ) hyperactivity/inattention subscale(Goodman, 1997) . At waves 3 to 6 (age 5-14 years), parents were asked if their child had been diagnosed with ADHD. The SDQ was completed by parents at waves 2 to 7 (age 3-17 years). The hyperactivity/inattention subscale requires parents to indicate whether the following 5 statements are "not true," "somewhat true," or "certainly true" about their child: "restless, overactive, cannot stay still for long," "constantly fidgeting or squirming," "easily distracted, concentration wanders," "thinks things out before acting," and "sees tasks through to the end, good attention span." Each of the 5 questions receives a score of 0, 1, or 2 (positive statements are reverse coded), resulting in a total score out of 10.

The ADHD group (n = 442) comprised cohort members with a reported ADHD diagnosis at any wave and/or SDQ scores ≥8 in at least 5 of 6 waves. This cut-off corresponds to the 4-band categorization of the SDQ, with a score of 8 considered "high" and scores of 9 or 10 considered "very high" (Youth In Mind, 2016). The control group (n = 5,398) comprised cohort members with no ADHD diagnosis and SDQ scores <8 at every wave.

3.3.2.2 Weight

Parents reported their child's birth weight in the first data sweep, and cohort members' weight was directly measured during each wave of data collection. As in previous research (Dos Santos et al., 2020), outliers 5 SDs above or below the mean were excluded from the data (3.1%). A binary variable was created to indicate whether cohort members had obesity or not, using the International Obesity Task Force (IOTF) cut-off points (Cole & Lobstein, 2012).

3.3.2.3 Covariates

We created 4 cumulative risk indices (CRIs), each including 3 environmental factors identified in previous research as having an association with ADHD and/or obesity

(Table 4). Data were collected during interviews with parents at the first data sweep (age 9 months). For each of the 12 individual factors, cohort members were classified as “high risk” or “low risk.” Cut-offs used in previous literature (Table 4) were used to create binary variables from continuous environmental factors. Individual risk factors were grouped and totalled to account for the accumulation of environmental risk at similar developmental stages. The 4 CRIs were as follows (high risk criteria in parentheses): (1) prenatal risk: mother’s pre-pregnancy BMI (>24.9), antenatal blood pressure (preeclampsia/other related diagnosis), smoking status in pregnancy (≥1 cigarette); (2) birth and neonatal risk: birthweight (<2.5 kg), gestation (<37 weeks), breastfeeding (none attempted); (3) socioeconomic status: household income (below 60% median poverty indicator), household crowding (fewer rooms than people, excluding bathrooms), housing tenure (social housing/renting from local authority); (4) home environment: mother’s educational attainment (<NVQ level 3), number of parents in household (single-parent family), mother’s mental health (depression/anxiety diagnosis or high maternal distress; high maternal distress was categorized as scoring ≥4 on a 9-item short form version (Dex & Joshi, 2004) of the Rutter Malaise Inventory (Rutter et al., 1970)).

In the RI-CLPM, the 4 CRIs, along with the following, were included as time-invariant predictors because of their association with either ADHD or weight; ethnicity (coded as “any ethnicity other than White”/White), whether children were part of a multiple birth, and ADHD medication status. At the sixth data sweep only (age 14 years), parents were given a list including both stimulant and non-stimulant medications for ADHD and asked whether their child was taking any of the listed prescribed medications for ADHD. Responses were used to create a binary variable indicating ADHD medication status (yes/no).

Table 4.

Weighted Frequencies of Individual Environmental Risk Factors and Physical Health Conditions in the Males and Females Random Intercept Cross Lagged Panel Model Samples Combined, with Reference to the Associated Literature.

Environmental risk factors	High Risk Criteria	N = 7908
Prenatal factors		
Mother's pre-pregnancy BMI[a1]	>24.9	2180 (27.6%)
Antenatal blood pressure[2]	Pre-eclampsia/Hypertension diagnosis	605 (7.7%)
Smoking in pregnancy[3,4]	Mother smoked 1 or more cigarettes during pregnancy	1342 (17%)
Birth and neonatal factors		
Birthweight[5]	< 2.5kg	556 (7%)
Gestation[5,6]	<37 weeks (premature)	580 (7.3%)
Breastfeeding[7]	No breastfeeding	1925 (24.3%)
Socioeconomic status		
Household income[8]	Below 60% median poverty indicator	2043 (25.8%)
Household crowding[9]	Fewer rooms than people (excluding bathrooms)	703 (8.9%)
Housing tenure[10]	Social housing or renting from local authority	1398 (17.7%)
Home environment		
Mother's education attainment[11,12]	<NVQ[b] level 3 (2 A-levels)	3447 (43.6%)
Number of parents in household[8]	1 parent living in household	796 (10.1%)
Mother's mental health[13,14,15]	Depression/anxiety diagnosis/<4 on Rutter Malaise Inventory	2238 (28.3%)

[a]BMI: Body Mass Index; [b]NVQ: National Vocational Qualification.

[1](Andersen et al., 2018), [2](Arango et al., 2021), [3](Y. He et al., 2020), [4](Rougeaux et al., 2020), [5](Serati et al., 2017), [6](Murray et al., 2022), [7](Zeng et al., 2020), [8](Russell et al., 2014), [9](Flouri et al., 2017), [10](Russell et al., 2015), [11](Torvik et al., 2020), [12](H. A. Hall et al., 2022), [13](Noonan et al., 2018), [14](Bendiksen et al., 2020), [15](Sagiv et al., 2013)

3.3.3 Statistical Analysis

We used R packages “anthro” (Schumacher, 2019) and “anthroplus” (Schumacher, 2021) to calculate BMI and associated z-scores, adjusted for age and sex assigned at birth, based on the World Health Organisation Child Growth Standards (World Health Organization, 2006).

Two independent-samples *t*-tests were conducted to compare mean birth weight as well as mean weight at 9 months in the ADHD group and control group. Chi-squared tests were conducted to compare the number of cohort members with obesity in the ADHD group and control group. Assumptions were met and analyses were performed in IBM SPSS Statistics for Windows (Version 28.0).

Extended versions of a RI-CLPM with time-invariant predictors (Mulder & Hamaker, 2021) were conducted for male and female individuals in MPlus version 8.10 (Muthen LK & Muthen BOM, 2017). The models were used to explore bidirectional associations between SDQ scores and BMI *z*-scores at 6 time points (ages 3, 5, 7, 11, 14, and 17 years). The RI-CLPM builds on a traditional cross-lagged panel model by accounting for both within-person and between-persons variance over time. The random intercepts also account for stable, trait-like differences between individual cohort members. The model determines both autoregressive paths (associations between different time points of a variable; e.g., age 3 SDQ score to age 5 SDQ score) and cross-lagged paths (associations between a variable at 1 time point and another variable at the subsequent time point; e.g., age 3 SDQ score to age 5 BMI *z*-score). The 4 CRIs plus ethnicity, multiple births, and ADHD medication (in male individuals only) were specified as time-invariant predictors, constrained across waves. To account for missing data and non-normality of data, we used a maximum likelihood estimator with robust standard errors (MLR). Goodness of fit of the model was determined by the root mean square error of approximation (RMSEA) and the comparative fit index (CFI). Values below 0.05 (RMSEA) and above 0.95 (CFI) are considered good.

3.4 Results

Descriptive statistics of participants can be found in Tables 4 and 5. Cohort members taking ADHD medication were excluded from the comparison analyses (n = 141) and adjusted for in longitudinal analyses (n = 83).

Table 5.

Unweighted Statistics for Variables in the Random-Intercept Cross-Lagged Panel Models.

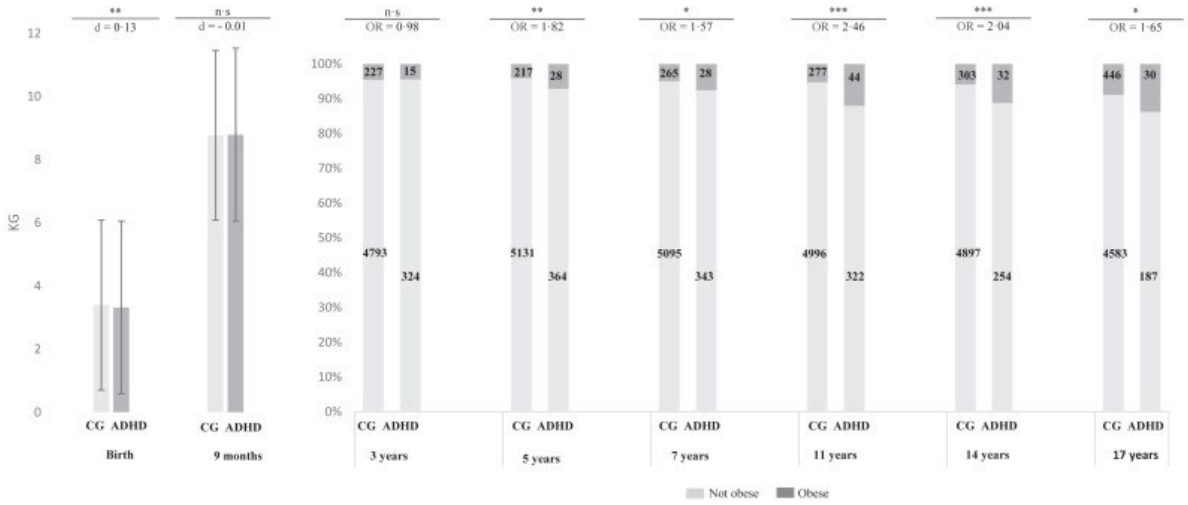
		Female Cohort Members (n=4,051)	Male Cohort Members (n=3,857)
		M (SD)	
SDQ[a] Score			
	Age 3	3.43 (2.21)	4.00 (2.36)
	Age 5	2.77 (2.18)	3.46 (2.41)
	Age 7	2.75 (2.31)	3.62 (2.53)
	Age 11	2.50 (2.19)	3.40 (2.52)
	Age 14	2.37 (2.15)	3.26 (2.49)
	Age 17	2.05 (2.04)	2.73 (2.35)
BMI[b] z-score			
	Age 3	0.79 (1.01)	0.92 (1.05)
	Age 5	0.51 (0.97)	0.63 (1.03)
	Age 7	0.45 (1.08)	0.44 (1.16)
	Age 11	0.51 (1.19)	0.55 (1.22)
	Age 14	0.47 (1.11)	0.33 (1.23)
	Age 17	0.50 (1.17)	0.30 (1.31)
		N (%)	
Part of Multiple Birth		104 (2.57)	82 (2.1)
Ethnicity other than white		620 (15.3)	563 (14.6)
Cumulative Risk Indices			
Prenatal	0 risks	2304 (56.9)	2161 (56)
	1 risk	1417 (35)	1370 (35.5)
	2 risks	320 (7.9)	308 (8)
	3 risks	10 (0.2)	18 (0.5)
Birth and Neonatal	0 risks	2699 (66.6)	2690 (69.7)
	1 risk	1103 (27.2)	960 (24.9)
	2 risks	198 (4.9)	172 (4.5)
	3 risks	51 (1.3)	35 (0.9)
Socioeconomic Status	0 risks	2642 (65.2)	2602 (67.5)
	1 risk	729 (18)	659 (17.1)
	2 risks	569 (14)	503 (13)
	3 risks	111 (2.7)	93 (2.4)
Home Environment	0 risks	1627 (40.2)	1589 (41.2)
	1 risk	1599 (39.5)	1536 (39.8)
	2 risks	710 (17.5)	615 (15.9)
	3 risks	115 (2.8)	117 (3)

[a]SDQ: Strengths and Difficulties Questionnaire (Hyperactivity/Inattention subscale). [b]BMI: Body Mass Index. M: Mean; SD: Standard Deviation.

The cross-sectional results of each time point (Figure 2) showed that children in the ADHD group (mean = 3.32 kg) had significantly lower birth weight than children in the control group (mean = 3.39 kg); *t*[5674] = 2.65, 95% CI = 0.020-0.135, *p* = .008), although the effect size was very small (Cohen *d* = 0.13). By 9 months, the difference between the ADHD group (mean = 8.79 kg) and the control group (mean = 8.77 kg) was no longer significant (*t*[5595] = −0.26, 95% CI = −0.147 to 0.112, *p* = .79, Cohen *d* = −0.01). Children in the ADHD group (excluding those on medication) were significantly more likely to have obesity from age 5 years onward. Odds ratios ranged from 1.57 to 2.46, indicating small to medium effect sizes across time points (Table 6).

Figure 2.

Effect Sizes and Frequencies and Percentages of Children in the Attention-Deficit/Hyperactivity Disorder Group and Control Group at Different Ages



Note: Weight in kilograms is displayed on the left for children in the ADHD group and the control group. The right side shows absolute numbers and the percentage of children in the ADHD group and control group with obesity at different ages. Error bars represent standard error. ADHD = attention-deficit/hyperactivity disorder; CG = control group; d = Cohen d effect size; OR = odds ratio.

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

Table 6.

Unweighted Descriptive Statistics and t/ χ2 Coefficients for Weight Variables

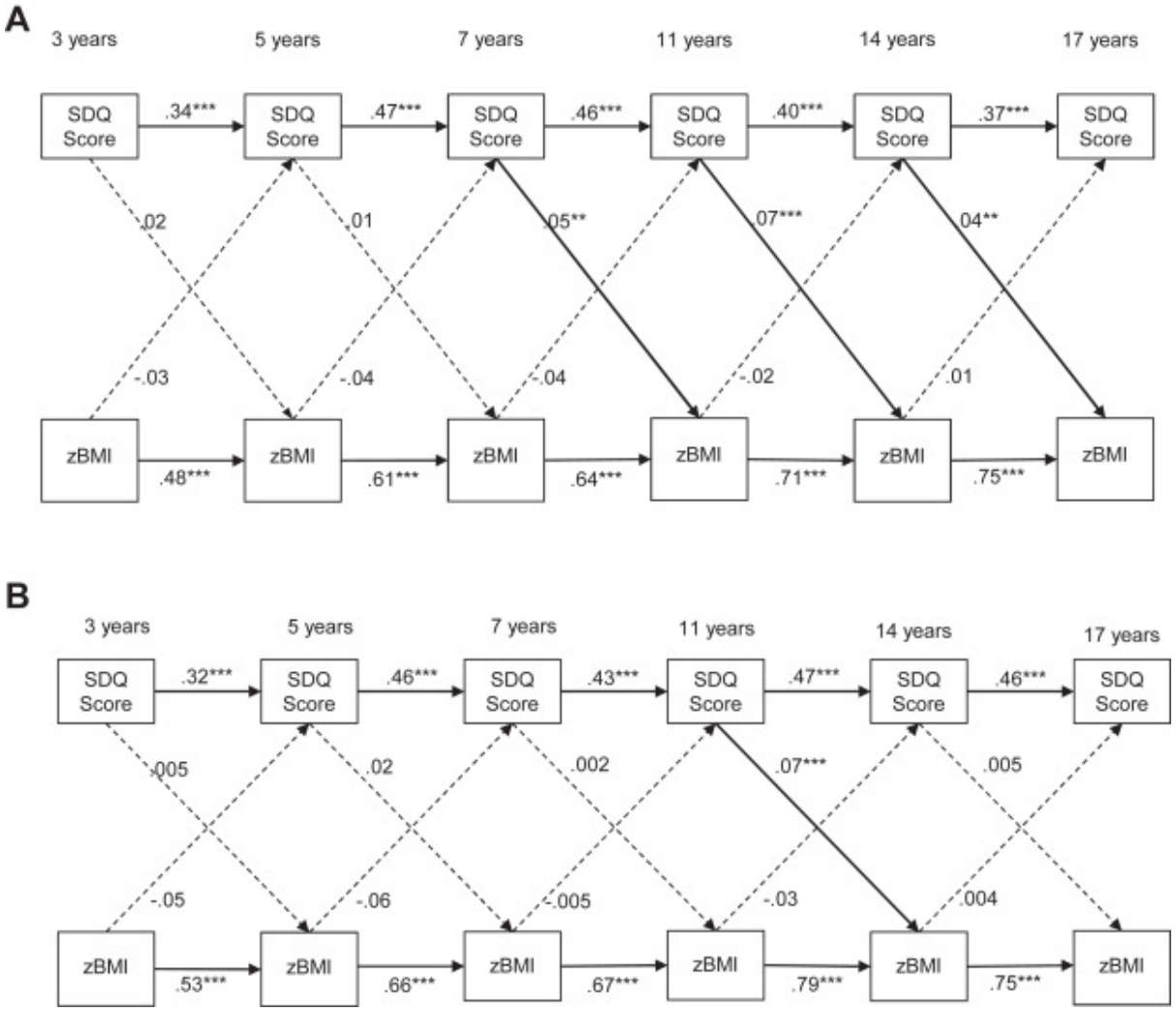
	ADHD group (n=442)	Control group (n=5398)				
	M (SD)		t	*p*	Cohen's d	
Birth weight	3.32kg (0.62)	3.39kg (0.58)	2.65	**.008**	.13	
9 months weight	8.79kg (1.55)	8.77kg (1.23)	-0.26	.79	-.01	
Number of cohort members with obesity	N (% of valid data)		χ^2	*p*	**Odds Ratio (95% CI)**	**Relative Risk (95% CI)**
Age 3	15 (4.42)	227 (4.21)	0.01	.93	0.98 (0.57, 1.67)	0.98 (0.59, 1.63)
Age 5	28 (7.14)	217 (4.06)	8.51	**.004**	1.82 (1.21, 2.73)	1.76 (1.20, 2.57)
Age 7	28 (7.55)	265 (4.94)	4.85	**.03**	1.57 (1.05, 2.35)	1.53 (1.05, 2.22)
Age 11	44 (12.02)	277 (5.25)	29.21	**<.001**	2.46 (1.76, 3.45)	2.29 (1.70, 3.09)
Age 14	32 (11.19)	303 (5.83)	13.59	**<.001**	2.04 (1.39, 2.99)	1.92 (1.36, 2.71)
Age 17	30 (13.82)	446 (8.87)	6.19	**.01**	1.65 (1.11, 2.45)	1.56 (1.11, 2.20)

ADHD: Attention Deficit Hyperactivity Disorder; M: Mean; SD: Standard Deviation; CI: Confidence Interval.
Significant associations indicated in bold.

To explore the longitudinal associations between weight and ADHD, RI-CLPMs were conducted to explore the relationship between SDQ score and BMI *z*-score in female (n = 4,051) and male (n = 3,857) individuals separately. Only 8 female individuals (<2%) were taking ADHD medications; therefore, these cohort members were excluded, and ADHD medication was not entered as a covariate in the analysis of female subjects. In both models (Figure 3), all autoregressive paths were significant ($p < .001$). Goodness-of-fit indices indicated a good model fit for both (female individuals: CFI = 0.988, RMSEA = 0.041; male individuals: CFI = 0.986, RMSEA = 0.045). BMI *z*-score did not significantly predict subsequent SDQ score at any time point in either model. In the female individuals–only model, SDQ score at ages 7, 11, and 14 years significantly predicted BMI *z* score at ages 11, 14, and 17 years, respectively. In the male individuals–only model, the SDQ score at age 11 years significantly predicted the BMI *z* score at age 14 years only. Additional model statistics can be found in Appendices A1 and A2 . A further RI-CLPM with male and female individuals combined can also be found in Appendix A3. Covariate statistics for this combined model are reported in Appendices A4.1-4.8. The MPlus code for the combined model can also be found in Appendix A5.

Figure 3.

Auto-Regressive and Cross-Lagged Associations Between Body Mass Index z Score and Strengths and Difficulties Questionnaire (SDQ [Hyperactivity/Inattention Subscale]) Score in Female Individuals (A) and Male Individuals (B) After Adjusting for Covariates



Note: Significant paths are indicated by a solid line and non-significant paths by a dotted line. (Random intercepts and covariance parameters not shown.) zBMI = body mass index z score.

∗p < *.05,* ∗∗ p < *.01,* ∗∗∗ p < *.001*.

A sensitivity analysis, with the ADHD group consisting of only those cohort members with an ADHD diagnosis, found a similar pattern of results (Appendix A6). Results at age 17 years did not reach a level of significance; however, effect sizes did mirror those in the main analyses.

3.5 Discussion

The current study explored, for the first time, longitudinal associations between ADHD and weight using data from a large cohort sample at multiple time points between birth and 17 years. Overall, children with an ADHD diagnosis/consistently high ADHD symptoms had lower birth weight than children in the control group. Although the rate of obesity did not differ between children with and without high ADHD symptoms at age 3 years, children in the ADHD group were more likely to have obesity from the age of 5 years onward. As children with ADHD are typically lighter in weight at birth than children without ADHD, our results suggest there may be a sensitive time period between the ages of 3 and 5 years during which this association reverses and higher ADHD symptoms become associated with obesity.

However, ADHD symptoms did not directly predict increased BMI until age 7 years in female and age 11 years in male individuals. This indicates that the shift from underweight to overweight during ages 3 to 5 years likely is not directly accounted for only by ADHD symptoms. Higher BMI at age 5 years was significantly predicted mainly by prenatal factors, namely, mothers' pre-pregnancy BMI, antenatal blood pressure, and smoking during pregnancy (Appendix A4.1). It is possible that there is a common genetic background to both ADHD and overweight (Barker et al., 2021), or, as parents with ADHD are more likely to have children with ADHD (Faraone & Larsson, 2019), this may have an impact on executive function skills involved in parenting, such as planning healthy meals, which in turn may influence weight status. Parents with an increased genetic risk may be influencing their child's home environment in ways that compound inherited risk. Future research should explore this interaction between direct heritability and genetic nurture, possibly through an adoption or twin study.

Several theories concerning underlying common mechanisms of ADHD and obesity have been discussed in previous literature. Genetic factors, executive function deficits, and environmental factors such as stress and disordered sleep may all offer potential explanations for the association (Hanć & Cortese, 2018).

It has also been hypothesized that differences in brain energy consumption during early childhood may be responsible for later increased obesity risk (Kuzawa & Blair, 2019). In

addition, children with ADHD may show altered function in the ability to convert glucose into energy for the brain, instead of storing it in fat cells (Killeen, 2019). As well as being a potential explanation for the executive function deficits associated with ADHD, this may also explain why higher obesity levels are found in children with ADHD. Our results are also consistent with the thrifty phenotype hypothesis (Hales & Barker, 2001), which suggests that prenatal factors, including poor nutrition, have long-lasting metabolic effects and may increase the risk of conditions such as diabetes. This suggests that future research into ADHD and weight may benefit from exploring insulin resistance resulting from prenatal factors. The complexity of the relationship posits that there is no simple explanation provided by a single factor, and further research is needed to determine the interactions among multiple mechanisms.

Longitudinally, we found that higher SDQ scores in girls predicted later higher BMI *z*-scores from age 7 years onward, whereas in boys this association was seen only between ages 11 and 14 years. With increasing age, and attending school, children will gain increasing independence regarding food choices, and those with higher levels of impulsivity may be less likely to make healthier choices. The interaction between genes and environment may amplify this. Indeed, a recent study found a correlation between BMI polygenic risk scores and ADHD polygenic risk scores (Barker et al., 2021). Comorbidity may be explained by a shared genetic risk if the same genes are implicated in multiple conditions. That study also reported that BMI and ADHD both demonstrated differences in brain areas responsible for reward processing, inhibitory control, and cognitive control. Children experiencing impairments in this area may be more likely to overeat, particularly at a time when they are undergoing significant changes in their lives, such as school transitions.

Interestingly, we found an earlier association between ADHD symptoms and obesity in girls than in boys. Obesity is known to affect the age of onset of puberty, with the mechanisms and effects differing between boys and girls (Huang et al., 2020). Differences in body composition between boys and girls in puberty may be amplified in children with ADHD, who may show abnormal functioning in converting glucose to energy. The weight changes in girls additionally seemed to be more long lasting, whereas the observed changes in boys seemed to be transitory. However, follow-up data are missing, so it is unclear whether these associations continue into young adulthood. The current findings, however,

suggest that early intervention programs targeting healthy eating and weight management are more indicated for girls than for boys with ADHD to inform prevention strategies. A stepped-care approach may be beneficial and could consider targeted interventions at critical stages. Results suggest that for prospective parents, support maintaining a healthy weight before pregnancy is important, as prenatal factors, including mothers' pre-pregnancy BMI, had a significant impact on children's weight at age 5 years. Given the heritability of ADHD and parental ADHD as a risk factor for child ADHD, this may be a particularly relevant secondary prevention strategy for parents with ADHD. Increasing the support for adults with ADHD in maintaining a healthy weight may benefit their future children. Continuing this support into the postnatal period could include offering increased weight monitoring for children during infancy and education on healthy eating habits for parents and caregivers. For children diagnosed with ADHD, clinicians should consider incorporating weight interventions or increased monitoring into treatment plans to ensure that the specific needs of each individual are considered at each stage of development.

This study has several strengths. We explored the relationship between ADHD and weight at multiple time points, from birth to adolescence. We used a large sample, weighted to be representative of the UK population, with relevant environmental risk accounted for in the longitudinal analyses. To our knowledge, this is the first study on the relationship between ADHD and weight to encompass a wide age range and to differentiate between male and female individuals.

It is important to note several limitations. As with all secondary research, frequencies in the sample do not always correspond with population estimates, as reflected in the low number of cohort members with an ADHD diagnosis. Although we attempted to mitigate this by including children with consistently high SDQ scores in the group analyses and by using SDQ score in the path analyses, our results should be interpreted with caution, as the SDQ is not a diagnostic tool. In addition, the SDQ subscale combines both hyperactive and inattentive traits and does not allow for an investigation of differential effects of individual symptom dimensions. Although both domains are associated with emotional overeating (Fuemmeler et al., 2020), hyperactivity and inattention may have differential effects on obesity via lifestyle factors. A large Swedish cohort study found that inattention symptoms in childhood predicted less physical activity in adolescence, with the opposite pattern found for

hyperactivity (Selinus et al., 2021). Future studies should therefore explore the contribution of both symptom domains on obesity and should investigate relevant mediators of this effect, such as exercise behaviours.

This study uses data across childhood; however, interpretation of the results should take into consideration the gap between each time period. Although the results shed light on the developmental period in which associations occur, we acknowledge that smaller gaps between time points would allow for a more precise interpretation. Future research may also adjust analyses for additional environmental factors, which we were unable to include in this study because of model complexity, such as comorbid child psychopathology. Further information about long-term medication use would also be beneficial in future studies, as ADHD medication status was available only at age 14 years, and we were therefore unable to account for children who were not taking ADHD medication, but who had done so previously.

In summary, the current study shows that the weight shift from underweight to overweight in children with ADHD starts between the ages of 3 and 5 years. ADHD symptoms were directly associated with later obesity from age 7 years in girls and from age 11 years in boys in the United Kingdom, whereas obesity did not affect ADHD symptoms. This study further clarifies the direction of the association between ADHD and weight, although the mechanisms underlying weight gain in children with ADHD remain to be further explored.

Chapter 4 Association Between ADHD Polygenic Scores and Childhood Physical Health Conditions

4.1 Abstract

Objective: Numerous physical health conditions are associated with ADHD. Although some conditions share a genetic overlap with ADHD, it is unclear whether this association is driven by transmitted genetic risk or influenced by non-transmitted parental genes which shape a child's environment. This study tested the relationship between transmitted and non-transmitted ADHD polygenic scores (PGS) and several physical health conditions across childhood.

Methods: Transmitted (N=6,118) and non-transmitted (N=2,742) ADHD-PGS were derived from genotyped DNA samples provided by Millennium Cohort Study cohort members and their biological parents. Analyses examined associations between ADHD-PGS and physical health conditions in childhood (obesity, epilepsy, asthma, and allergy), cumulative number of conditions, BMI z-scores and age of first reported asthma and epilepsy.

Results: Transmitted ADHD-PGS were associated with childhood obesity (OR, 1.13; 95% CI, 1.07-1.19), epilepsy (OR, 1.25; 95% CI, 1.07-1.47), asthma (OR, 1.06; 95% CI, 1.00-1.12) and cumulative number of conditions (β, 0.06; 95% CI, 0.03-0.08, $p < .001$). Transmitted ADHD-PGS were also associated with earlier onset of epilepsy (HR, 1.25; 95% CI, 1.07-1.46) and asthma (HR, 1.06; 95% CI, 1.01-1.11). Higher BMI z-scores from age five were significantly predicted by transmitted ADHD-PGS (β range, 0.04-0.08). Non-transmitted ADHD-PGS were not associated with any outcome.

Conclusions: The results suggest that transmission of ADHD-PGS, rather than rearing effects influenced by parental genetic liability (genetic nurture), drives the relationship between ADHD and physical health conditions. These results highlight the importance of early continued monitoring of the physical health of children with ADHD, especially those with ADHD liability.

4.2 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental condition, with a global prevalence of 5-8% (Ayano et al., 2023; Cortese et al., 2023) in children. ADHD is highly heritable (Faraone & Larsson, 2019). Genome-wide association studies (GWAS) have identified multiple common ADHD-associated variants (Demontis et al., 2023) enabling the creation of polygenic scores (PGS) that represent an individual's common genetic liability towards ADHD. Given the polygenic nature of ADHD, parents who may or may not meet the clinical cut-off for an ADHD diagnosis themselves, may pass genetic risk variants onto their children. Even if a child does not inherit a specific trait or condition through direct transmission, their parents' genes may still impact them indirectly via environmental or rearing factors- a concept known as genetic nurture (Kong et al., 2018). For example, studies have shown that children's educational attainment is influenced by both direct genetic transmission and genetic nurture (Kong et al., 2018). Non-transmitted parental genes shape the child's learning environment via parental behaviours and outcomes in addition to inherited genes.

In addition to the core symptoms of developmentally atypical and impairing levels of inattention and/or hyperactivity/impulsivity, more than 80% of children with ADHD have at least one comorbid condition (Akmatov et al., 2021). Although psychiatric and behavioural disorders are the most prevalent, several physical domains are also common comorbidities. For example, Akmatov et al. (2021) report respiratory system disorders in 30% of children in the ADHD sample. Previous studies found robust associations between ADHD and numerous physical health conditions (Arrondo et al., 2022; Reed, Cortese, Larsson, et al., 2024). Several of these physical comorbidities may result from shared genetic factors. Genetic correlations have been found between ADHD and obesity (Barker et al., 2021) and epilepsy (Wu et al., 2022) for example. However, within the ADHD literature, research on the relationship between ADHD and physical health largely focuses on shared genetics and direct genetic transmission and little is known about the influence of non-inherited parental genes on children's health. Previous research into genetic nurture has instead largely explored core symptoms or psychiatric outcomes and comorbidities of ADHD. For example, ADHD traits are predominantly a result of genetic transmission (Pingault et al., 2023) (Pingault et al., 2023) and parents' non-transmitted alleles do not significantly impact child ADHD traits. Some

physical health conditions are known to be influenced by environmental and rearing factors. For example, socioeconomic disadvantage increases exposure to environmental factors associated with higher asthma risk (Grant & Wood, 2022). The present study examined the relationships between physical health and ADHD, considering both inherited genetic liability and genetic nurture. Additionally, we investigated whether these relationships vary throughout childhood. Previous studies have shown that associations between ADHD and physical health conditions may develop at key time points in childhood (See Chapter 3: Reed, Cortese, Golm, et al., 2024)(Reed, Cortese, Golm, et al., 2024) and a higher cumulative number of some conditions are associated with higher ADHD symptoms (See Chapter 2: Reed, Cortese, Larsson, et al., 2024).(Reed, Cortese, Larsson, et al., 2024) The current study builds on these findings by examining whether a genetic liability for ADHD, rather than diagnosis or symptom expression, also elicits different associations with physical health throughout childhood. Gaining insight into these aspects is crucial to inform preventive programs that may be highly relevant from a clinical and public health standpoint

The specific aims of this study were to investigate whether: 1) transmitted (ADHD-PGS_T) and non-transmitted (ADHD-PGS_{NT}) polygenic risk scores are associated with physical health conditions in childhood; 2) ADHD-PGS are associated with a cumulative number of physical conditions; and 3) ADHD-PGS affect physical health condition onset and whether associations change over time.

4.3 Methods

4.3.1 Sample

The Millennium Cohort Study (MCS) is a longitudinal cohort study involving approximately N=19,000 children born in 2000-2002 in the United Kingdom. To date, seven waves of data collection have been released including information about cohort members and their families when the children were 9 months, 3, 5, 7, 11, 14, and 17 years old. When cohort members were 14 years old, they were invited to provide a DNA sample for genotyping and transmitted ADHD-PGS were calculated (N=6,118). Cohort members' biological parents were also invited to provide a DNA sample, and for those with data from both parents, non-transmitted ADHD-PGS were calculated (N=2,742)**.** The final sample included only the eldest child in the family and excluded those missing data on all physical health variables (3.3%). This research was approved by the University of Southampton Ethics

Committee in addition to the informed consent procedures of the Millennium Cohort Study (Shepherd & Gilbert, 2019).

4.3.2 Measures

4.3.2.1 ADHD Polygenic Scores

Polygenic scores (PGS) were created using genotyped data from cohort members and their biological parents. A summary of this process is given below; further details can be found in a previous publication (Shakeshaft et al., 2024). Pre-existing discovery summary statistics from the largest ADHD GWAS available at the time (Demontis et al., 2019) were used (N=20,183 cases, N=35,191 controls). GWAS data were processed for Quality Control (QC) filtering. Single nucleotide polymorphisms (SNPs) were aligned with the Haplotype Reference Consortium reference panel (The International HapMap 3 Consortium, 2010), and converted to a standardized format using an R pipeline (available at https://github.com/CardiffMRCPathfinder/summaRygwasqc).

ADHD-PGS were calculated using the polygenic risk score continuous shrinkage (PRS-CS) method using PLINK software (Ge et al., 2019). This method incorporates all available HapMap-3 SNPs (The International HapMap 3 Consortium, 2010) adjusting per-SNP effect sizes based on GWAS associations and linkage disequilibrium (LD), using pre-computed LD data from the European ancestry subset of the 1000 Genomes Phase 3 reference. PGS were computed by summing allele counts (weighted by adjusted effect sizes) across all SNPs for each individual. The PRS-CS-auto method, which detects the genetic architecture sparsity for each phenotype, was applied. A total of 608,646 common autosomal SNPs were included, with a weighted mean shrinkage parameter phi of 1.2E-04.

Ancestry for cohort members (CMs) and their biological parents was identified using the GenoPred pipeline (https://github.com/opain/GenoPred/tree/master/GenoPredPipe), which infers ancestry through principal components analysis (PCA) including the 1000 Genomes reference sample. An elastic net model predicted ancestry based on these principal components (PCs). The model assigned individuals to the most likely ancestral group, excluding those with <50% probability of assignment. Individuals of East Asian (EAS), American (AMR), South Asian (SAS), and African (AFR) ancestry were excluded due to insufficient sample size.

Further QC was performed on the European ancestry subgroup, with K-means clustering used to identify and remove outliers based on cluster distance. PCA was repeated on the final sample, extracting the top 10 PCs. The PGS were regressed on these PCs, and the resulting standardized residuals were used in the main analysis.

4.3.2.2 Physical Health Conditions

At each data sweep (from 9 months to 17 years), parents were asked questions about their child's physical health; including whether they had ever seen a health care professional for any reason as well as questions relating to specific conditions (e.g. "has [child's name] ever had asthma?"). Cohort members' weight and height were measured at each wave and BMI was calculated. The International Obesity Task Force (IOTF) cut points (Cole & Lobstein, 2012) were used to determine whether cohort members had obesity or not at each wave. Binary variables were then created based on whether cohort members had ever had a specific condition throughout childhood. Numerous physical health conditions were identified but only those with sufficient data and known heritability were considered for the present study. These were obesity (Loos & Yeo, 2022), asthma (Han et al., 2020) epilepsy (Stevelink et al., 2023) and food allergy (Kanchan et al., 2021). Additionally, we used R packages "Anthro" (Schumacher, 2019) and "Anthroplus" (Schumacher, 2021) to calculate BMI and associated z-scores, adjusted for age and sex assigned at birth, based on the World Health Organisation Child Growth Standards (World Health Organization, 2006). Onset variables for asthma and epilepsy were also created by identifying the first wave in which each condition was reported ('age at onset'). Food allergy data were only reported at two waves of data collection, so analyses at multiple time points were not possible.

4.3.3 Statistical Analyses

All analyses were conducted in Jamovi (The jamovi project, 2024) unless otherwise stated. Transmitted and non-transmitted ADHD-PGS were analysed separately to examine direct genetic pathways as well as genetic nurture. To investigate the relationship between ADHD-PGS and individual health conditions, we ran binary logistic regression analyses with each condition entered separately as an outcome variable. Linear regression models were then used to analyse the relationship between transmitted ADHD-PGS and BMI z-scores at waves two to seven (3 years to 17 years) as well as the cumulative number of physical health conditions reported throughout childhood.

As the exact onset of each condition between waves is unknown, to test the association between ADHD-PGS_T and epilepsy/asthma onset, we used interval-censored parametric survival models in R using the icenReg package (Anderson-Bergman, 2017) to determine both the overall risk of developing asthma/epilepsy over time as well as the relationship between ADHD-PGS_T and the onset of each condition.

4.4 Results

Transmitted ADHD-PGS were calculated for N=6,118 cohort members, of which 50% were female. Non-transmitted ADHD-PGS were calculated for complete trios with genetic data available from both biological parents (N=2,742; 49.3% female). Physical health condition descriptives can be found in Table 7.

Table 7.

Number of Cohort Members with each Physical Condition in both Transmitted and Non-Transmitted ADHD-PGS Samples.

	ADHD-PGS_T[a] (N=6118)		**ADHD-PGS_{NT}[b] (N=2740)**	
	N	**(%)**	**N**	**(%)**
Asthma	1621	26.5	632	23
Obesity	1707	27.9	752	27.4
Epilepsy	153	2.5	57	2.1
Allergy	191	3.1	92	3.4

[a]ADHD-PGS_T: Transmitted Polygenic Scores for Attention-Deficit/Hyperactivity Disorder,
[b]ADHD-PGS_{NT}: Non-transmitted Polygenic Scores for Attention-Deficit/Hyperactivity Disorder.

4.4.1 ADHD-PGS_T

Regression analyses showed significant positive associations between ADHD-PGS_T and reported obesity, asthma, and epilepsy across all waves, but not allergy (Figure 4). ADHD-PGS_T were also associated with a higher cumulative number of physical health conditions (β, 0.06; 95% CI, 0.04-0.08). ADHD-PGS_T were associated with BMI z-scores from age five onwards (β range, 0.04-0.08). Survival analyses revealed that the risk of developing asthma increased with age, but those with higher ADHD-PGS_T were more likely to develop

asthma earlier in childhood. Conversely, the risk of developing epilepsy decreased with age; however, ADHD-PGS_T were again associated with an earlier onset (see Table 8).

Figure 4.

Odds Ratios Showing the Association Between Transmitted ADHD-PGS and Individual Physical Health Conditions.

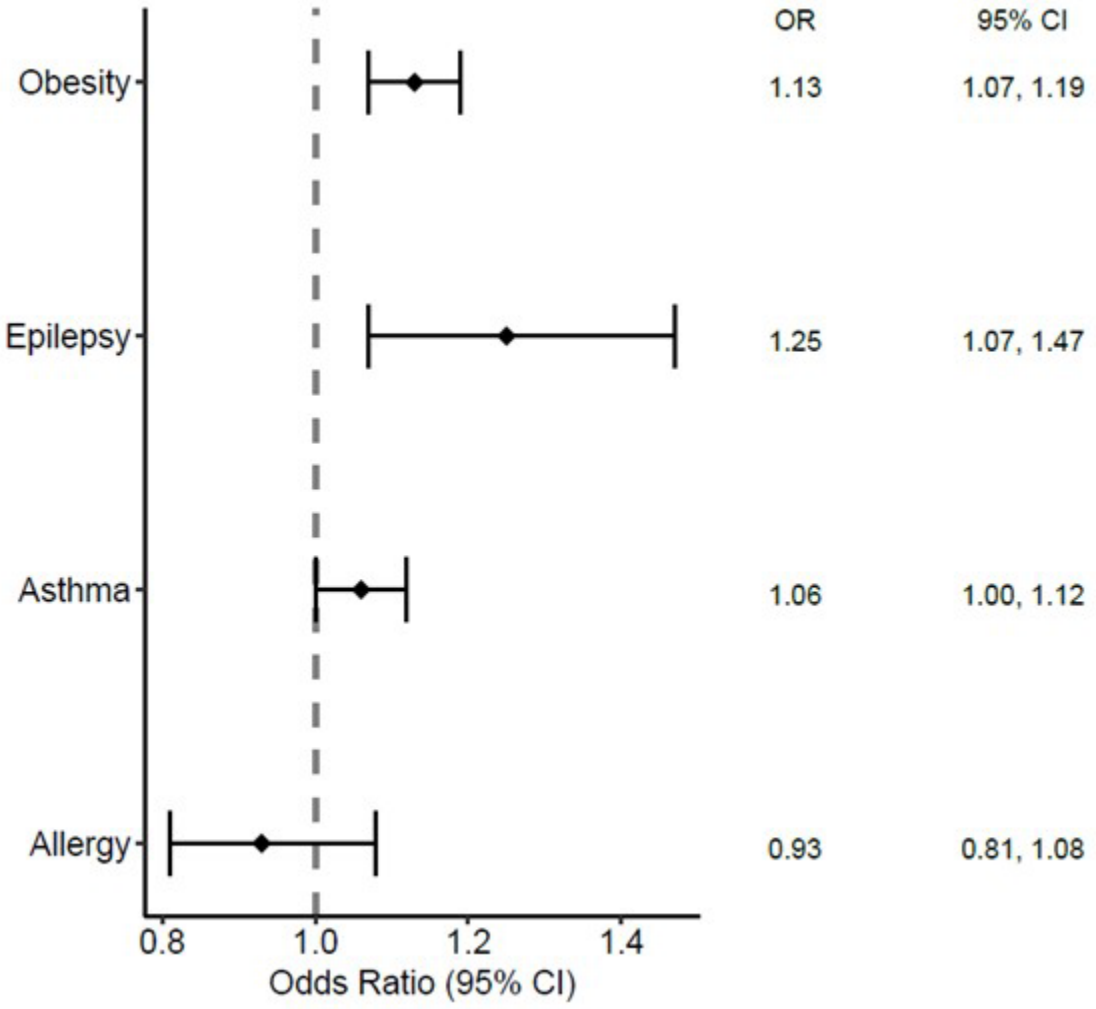


Table 8.

Coefficients for Linear Regression and Interval-Censored Parametric Survival Analyses with Transmitted ADHD-PGS[a] Predicting Asthma/Epilepsy Wave of Onset, BMI[b] z-Scores at Each Wave and Cumulative Number of Physical Health Conditions.

	HR[c]	**95% CI[d]**	***p-value***	**Weibull log shape (se)**
Asthma onset	1.06	1.01-1.11	0.021	0.197 (0.024)
Epilepsy onset	1.25	1.07-1.46	.006	-2.96 (0.081)
	β	**95% CI**	***p-value***	
BMI age 3	0.01	-0.01, 0.04	.319	NA
BMI age 5	0.04	0.01, 0.06	**.004**	NA
BMI age 7	0.05	0.02, 0.07	**< .001**	NA
BMI age 11	0.07	0.04, 0.09	**< .001**	NA
BMI age 14	0.07	0.05, 0.10	**< .001**	NA
BMI age 17	0.08	0.05, 0.11	**< .001**	NA
Cumulative number of conditions	0.06	0.03, 0.08	**<.001**	NA

[a]ADHD-PGS: Polygenic Risk Scores for Attention-Deficit/Hyperactivity Disorder, [b]BMI: Body Mass Index, [c]HR: Hazard Ratio, [d]CI: Confidence Interval.

4.4.2 ADHD-PGS$_{NT}$

Regression analyses showed ADHD-PGS$_{NT}$ were not associated with any of the physical health conditions: obesity (OR, 1.07; 95% CI, 0.98-1.16), asthma (OR, 0.99; 95% CI, 0.91-1.08), epilepsy (OR, 0.91; 95% CI, 0.70-1.19), or allergy (OR, 0.95; 95% CI, 0.77-1.18). Subsequently, no further analyses were conducted with non-transmitted ADHD-PGS.

4.4.3 Secondary Analyses

As previous research has indicated the relationship between ADHD and BMI may differ between sexes (Reed, Cortese, Golm, et al., 2024)(Reed, Cortese, Golm, et al., 2024) we ran linear regression analyses between ADHD-PGS$_T$ and BMI z-scores again separately for males and females (sex assigned at birth). ADHD-PGS$_T$ were associated with BMI z-scores in both males and females from the age of five onwards (Table 9) with effect sizes generally higher in females (β range, 0.04-0.10) than males (β range, 0.04-0.06). However, a linear

mixed model analysis testing whether biological sex moderated associations between ADHD-PGS_T and BMI over time found no significant interaction (F(5, 27120) = 0.71, p = .616).

Table 9.

Secondary Analyses Coefficients for BMI[a] z-score at each Wave Predicted by Transmitted ADHD-PGS[b] in Males and Females Separately.

	Female Cohort Members			**Male Cohort Members**		
	β	**95% CI[c]**	***p***	**β**	**95% CI**	***p***
BMI z-score at age 3	0.01	-0.03, 0.05	.510	0.02	-0.02, 0.06	.382
BMI z-score at age 5	0.04	0.00, 0.08	**.035**	0.04	0.00, 0.08	**.038**
BMI z-score at age 7	0.05	0.01, 0.09	**.007**	0.04	0.01, 0.08	**.024**
BMI z-score at age 11	0.07	0.04, 0.11	**< .001**	0.06	0.02, 0.10	**.002**
BMI z-score at age 14	0.08	0.05, 0.12	**< .001**	0.06	0.02, 0.10	**< .001**
BMI z-score at age 17	0.10	0.06, 0.14	**< .001**	0.06	0.02, 0.11	**.002**

[a]BMI: Body Mass Index, [b]ADHD-PGS: Polygenic Risk Scores for Attention-Deficit/Hyperactivity Disorder, [c]CI: Confidence Interval.

4.5 Discussion

We examined the relationship between ADHD-PGS and physical health conditions across childhood. Transmitted ADHD-PGS were associated with any reported obesity, epilepsy or asthma but not allergy, earlier asthma/epilepsy onset, total cumulative number of conditions, and higher BMI from age five.

Higher ADHD-PGS_T were associated with higher likelihood of children developing obesity at any point in childhood (9 months to 17 years). Previous literature reports a correlation between PGS for ADHD and obesity as well as shared differences in brain areas responsible for reward processing and inhibitory control (Barker et al., 2021). Our results support this as ADHD-PGS convey an increased risk of obesity at any point in childhood and, specifically, a relationship with higher BMI from age five. An overlap of genetic variants may give children a genetic predisposition for both ADHD and obesity, and associated neurobiological differences may lead to the development of both conditions. This may also explain why ADHD-PGS_T were also significantly associated with developing a higher

cumulative number of physical health conditions. A common genetic predisposition and related neurobiological differences may explain this increased comorbidity if the same genetic variants lead to an increased liability for several conditions.

We also found an association between ADHD-PGS$_T$ and BMI from age five onwards. This complements previous research in the same cohort, which reports an association between ADHD diagnosis/symptoms and obesity, also from age five (Reed, Cortese, Golm, et al., 2024). However, in the previous study, an association between ADHD symptoms and later BMI was only apparent from age seven in girls and 11 in boys. This suggests that prior to ADHD symptoms influencing weight, the association may be better explained by genetic predisposition and environmental factors. Obesity, like ADHD, has a strong genetic component but is subject to rearing, family, social economic factors (Broadbent et al., 2024). Global prevalence rates are high and in some countries rising (Lister et al., 2023) thus research into the association with comorbid conditions is crucial. Our secondary analyses did not find any marked differences between males and females in the associations between ADHD-PGS$_T$ and BMI. Although effect sizes were marginally larger in girls from age seven, biological sex did not significantly moderate the association over time. For both males and females, an association between transmitted ADHD-PGS and BMI was significant from age five onwards.

We found no association between non-transmitted ADHD-PGS and any physical health condition. Due to the nature of the dataset, the epilepsy and asthma variables were binary, with parents only reporting that their child had received a diagnosis. Therefore, it is possible that, although non-transmitted ADHD-PGS do not predict the condition, they may influence severity or symptom expression. Although our results do not support a role of genetic nurture in the association between ADHD and physical health, environmental factors likely do still contribute. Genetic nurture includes only those aspects of environment or rearing that are associated with parental ADHD genetic liability (that is not transmitted to their child). This is sometimes known as passive gene-environment correlation. Also, ADHD-PGS do not capture all ADHD genetic liability. Many environmental risk factors, such as socioeconomic disadvantage (A. E. Russell et al., 2016), are associated with ADHD and also a wide range of physical health conditions. As well as representing increased genetic liability, transmitted ADHD-PGS will influence a child's environment due to active and evocative

gene-environment correlation (rGE) (Agnew-Blais et al., 2022). The earlier associations between ADHD and weight may result from shared genetic influences or environments shaped by parents' genotypes (passive rGE) (Agnew-Blais et al., 2022). Parents with a high genetic liability for ADHD may influence their child's weight if executive function challenges act as a barrier to maintaining healthy food and exercise behaviours in their children. As children grow and gain independence, their own genetic liability and subsequent ADHD symptoms may reflect active rGE in which children's own genotypes also shape their environments (Warrier et al., 2021). For example, a child with a genetic predisposition for impulsive behaviour may make fewer healthier food choices. Separating the individual effects of genetics and environment is complex and, due to genetic confounding, it was beyond the scope of this paper to include measured environmental factors in our analyses. Further research, including testing interventions, is warranted to explore the role of environmental factors in the associations between ADHD-PGS and physical health.

We also found an association between ADHD-PGS_T and developing epilepsy in childhood. Similar brain differences have been found in ADHD and epilepsy as well as a significant overlap in genetic variants associated with both conditions (Wu et al., 2022). We also found a significant association between ADHD-PGS_T and earlier epilepsy onset. Previous research has reported similar findings, noting that patients with epilepsy and comorbid ADHD often experience seizures earlier than those without ADHD (Ohta et al., 2025). It has been suggested that this earlier epilepsy onset increases inflammation markers which contribute to ADHD symptom development (Elhady et al., 2022). Our results challenge the direction of this relationship. Inflammation resulting from epileptic seizures may impact ADHD symptom expression, but the underlying association between the two diagnoses appears to be influenced by genetic pathways. Shared overlap of genetic variants may account for the earlier onset of epilepsy, with phenotypic presentation of both conditions, as well as environmental factors reinforcing this relationship throughout childhood.

Our results further showed an association between ADHD-PGS_T and asthma. A relationship between ADHD diagnosis/symptom presentation and asthma is well-documented within the literature (Arrondo et al., 2022). While previous research has reported an association between ADHD and subsequent asthma (Jiang et al., 2025), this could not be replicated in studies controlling for PGS for ADHD or asthma (Leffa et al., 2022).

The present study did, however, find an association between ADHD-PGS_T and asthma symptoms/diagnosis. Differing methodology, including how conditions are defined, may account for some inconsistencies, but future research should aim to disentangle the relationship further. Our results also indicated that the risk of developing asthma generally increases over time, but children with higher ADHD-PGS_T are more likely to develop asthma earlier than those with lower ADHD genetic liability. This highlights the importance of early ADHD diagnosis to ensure children receive increased monitoring and timely support for comorbid conditions.

Unexpectedly (Xu et al., 2019), no significant association was found between ADHD-PGS_T and food allergy. However, due to differences in data collection across the seven waves of the MCS, data on food allergies were limited. Food allergies often resolve in infancy and early childhood. For example, nearly half of all children with an allergy to egg grow out of it by 2 years old (Neeland et al., 2018). Allergy data in the present study may only reflect cohort members with an active allergy at the time of data collection and may not include those with a previous allergy. It is possible that capturing data across every wave may have produced different results. Future research should explore the association between ADHD genetic liability and the timing of allergy development .

This study has several strengths. Notably, both transmitted and non-transmitted ADHD-PGS using parent-child trios were included allowing us to examine both direct genetic pathways and genetic nurture. We used data from a large longitudinal cohort allowing us to investigate the relationship between ADHD-PGS and physical health conditions at multiple ages as well as the overall association in childhood.

Interpretation of the results of this study should also consider some limitations. Physical health conditions were reported by parents with no clinical confirmation of diagnosis. Although variables in this study accounted for parent and child polygenic risk, and child physical health, we were not able to account for parental physical health history. Future research in this area should consider parental history of conditions such as epilepsy or asthma, to adjust for confounding effects. Additionally, non-transmitted ADHD-PGS could only be created in families with two participating parents. The non-transmitted ADHD-PGS sample is consequently much smaller than the transmitted ADHD-PGS sample, reducing the statistical power of those analyses. Effect sizes for all analyses were small, and results should

be interpreted taking into account the weak amount of genetic variance captured by ADHD-PGS which may mask the true scale of the associations (Ronald et al., 2021). Another limitation of this study is that the sample was limited to cohort members of European ancestry only due to low sample sizes of other ancestries. Results can therefore not be generalised across all ethnicities and backgrounds.

In terms of our study implications, although ADHD-PGS are not a diagnostic tool, our findings emphasise the importance of early diagnosis and support for individuals with a higher genetic risk who do develop ADHD. There may be multiple opportunities at key developmental milestones to identify additional risk factors and consider management and mitigation strategies. Parents or prospective parents with ADHD should receive extra support, including education on healthy food and exercise choices. Additionally, raising awareness of ADHD symptoms and physical health conditions such as epilepsy and asthma would benefit both parents and children, and ensure comorbidities are identified and treated as soon as possible. When a child is diagnosed with ADHD, it would be beneficial to consider not only the ADHD family history but any physical health comorbidities that may be present as well as monitoring any that develop later. As genetic liability for ADHD can be associated with obesity before ADHD symptoms develop, ongoing initiatives such as, in the UK, universal infant free school meals for all children in key stage one (Education and Skills Funding Agency & Department for Education, 2025) can ensure all children have access to nutritious food, including those at greater genetic ADHD risk who are yet to display symptoms at a clinical level.

Chapter 5 General Discussion

Research into the relationship between ADHD and physical health in childhood spans multiple conditions, populations and developmental periods. However, the size and complexity of the topic means there are several notable gaps yet to be explored in the current literature. This thesis aimed to address some of these gaps using longitudinal data to focus on comorbidity and the influence of genetics and environment. The main aims of this thesis were as follows:

1. To investigate the relationship between ADHD and cumulative physical health comorbidity

2. To investigate the relationship between ADHD and physical health across multiple developmental periods

3. To investigate genetic and environmental influences on the relationship between ADHD and physical health and identify relevant risk factors.

This chapter will discuss the key findings of each paper related to each aim, the broader context of these results within the existing literature and consider the implications of key findings for future research and clinical practice.

5.1 Cumulative Comorbidity

The first aim of this thesis was to investigate associations between ADHD and physical health conditions in childhood using data from a longitudinal cohort study. In Paper 1, 13 different conditions were grouped into four clusters based on their classification in the ICD-11 (World Health Organization, 2019) or previous literature which utilised similar groupings (M.-H. Chen et al., 2014; Eklund et al., 2018; Garcia-Argibay et al., 2022; Merlo & Briley, 2019; Pruett et al., 2021). The sensory (eyesight and hearing problems) and neurological (movement problems, neurological disorders, sleeping problems, stutter and epilepsy) clusters were significantly associated with ADHD symptoms at age 17. In Paper 3, transmitted ADHD-PGS were significantly associated with the cumulative comorbidity variable consisting of four conditions (obesity, epilepsy, asthma and allergy) which span multiple physiological mechanisms.

ADHD presentation is highly heterogenous and varies significantly between individuals (Faraone et al., 2024). However, research has identified many structural brain differences involved in ADHD and comorbid physical conditions. ADHD is associated with reduced basal ganglia volume (Faraone et al., 2024) and dysfunction in this region has been linked to many conditions associated with ADHD including stutter and sleeping problems (Merlo & Briley, 2019). Impairments in certain brain areas may account for comorbid associations between ADHD and multiple other conditions. ADHD and epilepsy for example are both associated with reduced amygdala and hippocampal volume (Wu et al., 2022). Neurotransmitters such as dopamine may also play a role in comorbidity. The dopaminergic system is involved in many ADHD related processes such as attention regulation and reward processing (Faraone et al., 2024). Although non-academic sources, including social media, often report misleading claims that ADHD is a result of dopamine deficiency, research from multiple disciplines instead suggests dysfunction in the dopaminergic system may play a role in ADHD aetiology (MacDonald et al., 2024). Dopaminergic dysfunction may impact other body systems leading to the development of multiple comorbidities. Dopamine is involved in numerous systems and processes in the body, affecting immune responses, cardiac output and the regulation of breathing (Bellitto et al., 2025). The dopaminergic system is also involved in food related reward processing, energy regulation and disordered eating (Teixeira et al., 2025). Both structural brain differences and neurotransmitter alterations may result from shared genetic variants, leading to atypical development and consequently multiple comorbidities (Barker et al., 2021; Teixeira et al., 2025; Wu et al., 2022).

Genetic associations have been found between ADHD and eczema (Cao et al., 2024) as well as ADHD and asthma (Sun et al., 2021), although research concerning the latter has found mixed results (Leffa et al., 2022). However, in Paper 1, the atopic cluster was not associated with ADHD symptoms. This finding seems to contradict the theory that shared mechanisms may lead to comorbidity between ADHD and other conditions, with additional conditions further increasing this risk. It also contrasts with previous research which found an association between ADHD and a higher number of allergic conditions (L.-J. Wang et al., 2018). There is a strong relationship between atopic conditions (asthma, allergies and eczema). All are associated with chronic inflammation and there is often a progression from one condition to another throughout development, known as ‘Atopic March’ (Yaneva &

Darlenski, 2021). The high overlap between atopic conditions may explain why a cumulative number is not associated with increased ADHD symptoms, despite associations with individual conditions. Atopic conditions may be too similar to act as distinct disorders when considering cumulative effects. There is tentative evidence of an association between ADHD and inflammation (Dunn et al., 2019; Verlaet et al., 2019). It may be that underlying mechanisms involved in atopy are associated with ADHD and additional conditions do not influence this relationship further.

Although conditions were assigned to the sensory or neurological clusters in Paper 1 based on similar classification, they may be different enough that each condition adds an individual contribution to the cumulative effect of the cluster. The results in Paper 3 add further weight to this theory and together the two papers suggest that ADHD is associated with multiple systems of the body, both individually and with a cumulative effect. This may also explain why the cardiometabolic cluster was no longer significantly associated with ADHD symptoms once adjusting for cumulative environmental risk. Although research has demonstrated an association between obesity, diabetes and cardiovascular disorders, many environmental risk factors are known to influence these relationships (Pastore et al., 2020). Adjusting for cumulative environmental risk may obscure the association and reduce the variance between conditions.

5.2 Associations Across Development

The second aim of this thesis was to investigate associations between ADHD and physical health across multiple stages of development. As it would not be feasible to discuss every possible physical health condition experienced in childhood, it was necessary to consider which conditions should be focused on. Furthering our understanding of the relationships between conditions is crucial, especially when consequences affect substantial numbers of children for long periods of time. In the UK, 15% of children between 2 and 15 years old are obese (NHS England, 2025a). When including those who are overweight, this number rises to 27%. In addition to ADHD, childhood obesity is associated with numerous poor health outcomes (Horesh et al., 2021) as well as an increased risk of obesity in adulthood (Llewellyn et al., 2016). It is therefore vital for research to identify risk factors and time points when preventative strategies and support will have the most impact. In order to

focus on those conditions with the highest prevalences, this chapter will also focus on analyses including asthma, as the most common long-term medical condition in children (Ferrante & La Grutta, 2018) and epilepsy, as the most common long-term neurological condition (Royal College of Paediatrics and Child Health, 2020).

5.2.1 Weight

Previous research reports the relationship between ADHD and weight at many distinct time points in childhood and adolescence (Bowling et al., 2018; Khalife et al., 2014; Momany et al., 2018). This thesis adds to the current literature by considering how these relationships change and progress across development. Papers 2 and 3 both found that age five appears to be a significant age in the association between ADHD and weight. Cohort members who later receive an ADHD diagnosis and/or have high symptoms are more likely to have obesity by the age of five than their peers. As path models demonstrated that high ADHD symptoms do not predict later higher BMI until age seven in girls and eleven in boys, it is clear that ADHD symptoms themselves are not driving this association. The results of Paper 3 support the robustness of these findings by finding comparable results across different predictors and analysis methods. Transmitted ADHD-PGS were associated with BMI from age 5 and additional analyses show this to be the case even when adjusting for ADHD symptoms (Appendix G). Transmitted ADHD-PGS were not associated with BMI at age 3. Additionally, non-transmitted ADHD-PGS were not significantly associated with physical health outcomes which suggests that non-inherited parental factors may not play a mediating role. However, a child's environment is shaped by both inherited and non-inherited parental factors. Within Paper 3, it was not possible to identify the influence of inherited genetic factors on environmental factors nor the subsequent effects on physical health. However, the development of a significant association with BMI from age 5 suggests there may be a crucial window in which support for children and parents should be offered before children start school. Current National Institute for Health and Care Excellence guidelines in the UK recommend weighing babies at 8, 12 and 16 weeks, and at 1 year (NICE, 2025). Research also reports that conversations around weight between parents and health care professionals are a contentious issue and best practice is not always achieved due to high demand and lack of resources (Coates et al., 2024). Once children start school, their weight and height are measured twice (at ages 4/5 and 10/11) as part of the National Child

Measurement Programme (NCMP, 2025). Although the programme addresses the important subject of child obesity, the findings in this thesis suggest that by the time they start school, children with ADHD are already more likely to weigh more than their peers. Preventative interventions may be more indicated for children with a family history of ADHD who might need additional support earlier than other children. The Department for Education has recently issued new guidance for nurseries, childminders and other early years providers caring for children aged 0-5 (Department For Education, 2025). Although this hopefully has a positive impact on pre-school children's overall health, it should be noted that many children do not attend an early years setting and those who don't are more likely to live in low income households (Kuang et al., 2024). As children from lower income households are more likely to have ADHD (A. E. Russell et al., 2016), additional strategies may be needed to target at-risk groups, either by improving the affordability of childcare or providing support at home.

Natural weight fluctuations in young children often lead to deceptive measurements (Wright et al., 2025) and in many healthy children, weight gain is not a cause for concern. Consequently, health care practices in infancy often focus instead on slower growth or weight loss (NICE, 2017). A further complication may arise due to children with ADHD typically weighing less at birth than children without ADHD, as discussed in Chapter 3. Further analyses found that transmitted ADHD-PGS also predicted lower birthweight (Appendix G). If children with ADHD have a low birth weight, or slower growth in the postnatal period, this may offer false reassurance once children reach a healthy weight. All conversations about weight should be handled sensitively with new parents and support should be tailored to individual circumstances. For families with a history of ADHD, this should include offering additional education aimed at ensuring healthy lifestyle behaviours are established as early as possible.

Analysis of environmental factors in Paper 2 showed that cumulative prenatal factors (mother's pre-pregnancy BMI, antenatal blood pressure and smoking during pregnancy) elicited the largest effect sizes when predicting BMI at age 5. Based solely on this analysis, it could be theorised that maternal behaviours alone are responsible for children's higher BMI, with ADHD playing either a secondary or far less significant role. However, the combined results of papers 2 and 3 suggest that parental genetic liability for ADHD, when transmitted

to their child, is an influential factor in the development of obesity, whether or not children go on to develop ADHD symptoms. The effect of maternal characteristics and behaviours may reflect gene-environment correlation (rGE). If mothers themselves are more likely to struggle with their weight and health if they have ADHD, the separate effects of these environmental factors and inherited genetic liability are impossible to disentangle with the current data. This highlights the importance of offering support to people with ADHD before they become parents. Antenatal care in the UK is often inconsistent. NICE guidelines specify that pregnant women and their partners should be offered free and accessible antenatal classes to include support on feeding and nutrition (NICE, 2021). However, a patient survey of UK maternity services found that 29% of pregnant women were not offered these classes and only 30% chose to attend (NHS Patient Survey Programme, 2020). The planning and implementation of future antenatal care policies may benefit from exploring ways to increased uptake of antenatal education, particularly in groups who may experience difficulties with executive functioning.

Adults with ADHD are also more likely to be obese (Cortese et al., 2016) and although there are likely to be many factors involved in this association, including genetic factors, it is possible that some parents with ADHD may struggle with the executive functioning skills needed to model healthy lifestyle behaviours to their children. Difficulties with motivation and emotional regulation (Tsermentseli & Poland, 2016) may add additional challenges and impact parents' abilities to follow consistent healthy eating patterns or encourage routine physical activity. To compound these difficulties, children with ADHD are more likely to be picky eaters (Kaşak et al., 2025; Thorsteinsdottir et al., 2021). This may add further complications to an already challenging task.

Path model analyses in Paper 2 found that ADHD symptoms predicted later BMI from age 7 in girls and 11 in boys. Increased independence, combined with children's own ADHD symptoms including impulsivity, may result in children making fewer healthy choices, especially if healthy eating and exercise behaviours have not been established and encouraged in earlier years. When children are diagnosed with ADHD, it may be beneficial to both the individual, their families and their own potential future children, to offer support in these areas if indicated, particularly if there is a family history of ADHD and obesity. Analyses in Papers 1 and 2 adjusted for ADHD medication use. Stimulant medications in particular are

associated with small but statistically significant effects on growth and common side effects include appetite suppression (Carucci et al., 2021). The MCS dataset recorded medication use at only one time point so it would be beneficial for future research to explore the longitudinal influence of medication on the relationship between ADHD and weight.

5.2.2 Asthma and Epilepsy

Cohort members' weight and height were measured at each wave of data collection. This provides valuable data and the ability to explore the relationships between ADHD and weight longitudinally. However, epilepsy and asthma data were not quite as comprehensive or consistent (see 5.4). Nevertheless, the results of analyses in Paper 3 contribute to building a picture of the association with ADHD across childhood. Transmitted ADHD-PGS were not only associated with any reported asthma or epilepsy in childhood but also with an increased likelihood of developing each condition at an earlier age. The current literature examining the relationship between ADHD and age of asthma onset is sparse, however research has found a relationship between later onset asthma and subsequent ADHD symptoms (Goodwin et al., 2013). These findings contradict those in Paper 3, as ADHD-PGS were associated with earlier asthma onset. However, asthma is often diagnosed at a younger age than ADHD (Kaas et al., 2021) and many studies may not take into account the influence of genetic liability and early symptoms prior to diagnosis. If associations are only considered once children are diagnosed, the true extent of the relationship may be missed. By demonstrating that ADHD genetic liability is associated with earlier asthma onset, Paper 3 highlights that cross-sectional research relying on diagnosis or current clinical symptoms may underestimate the relationship.

The association between ADHD-PGS and epilepsy onset also corroborates previous research which has found that children with ADHD were likely to experience the onset of seizures earlier than children without ADHD (Elhady et al., 2022; Ohta et al., 2025). Both cited studies suggest that seizures may lead to abnormal brain function, perhaps as a result of increased inflammation. As Paper 3 found an association between earlier epilepsy onset and ADHD genetic liability, rather than symptom load, this challenges the hypothesised direction of this relationship. Epilepsy may have an effect on the phenotypic presentation of ADHD, but the results in this thesis suggest that the association has a genetic origin. This, however, does not preclude the presence of a bidirectional relationship between the

conditions. A shared genetic or neurobiological origin (see section 5.1) may lead to the conditions co-occurring earlier than when experienced individually. It is also possible that the relationship between ADHD and epilepsy is influenced by mediating environmental factors. ADHD is associated with preterm birth (Serati et al., 2017) which in turn is associated with epilepsy onset (Walsh et al., 2017). Overlapping biological and psychosocial factors may influence this relationship and the direction and interplay of these factors should be explored in future research.

5.3 Genetic and Environmental Influences

The third aim of this thesis was to explore environmental and genetic influences on associations between ADHD and physical health conditions. In Papers 1 and 2, environmental factors were included as cumulative risk indices in order to examine increased quantity of risk rather than the effects of individual factors. In Paper 3, environmental influence was explored via genetic nurture alongside inherited genetic influences.

When adjusting for cumulative environmental risk, a higher number of sensory or neurological conditions was associated with both higher ADHD symptoms and ADHD diagnosis. By controlling for numerous environmental risk indices, the results suggest that genetic or other biological factors are driving the association. Conversely, cumulative cardiometabolic conditions were not significantly associated with ADHD symptoms when analyses adjusted for environmental confounders. These findings show that environmental factors do not exert the same influence on the relationship between ADHD and every group of physical conditions. Some associations may be more rooted in genetic origin, and some may be more susceptible to environmental factors or the interaction between them. This susceptibility may also change over time. In the path models conducted in Paper 2, cumulative environmental risk indices were included as time-invariant predictors with their effects constrained across all time points. This was necessary in order to include environmental variables which were only measured once but future research should explore the impact of fluctuating environmental risk over time.

As non-transmitted ADHD-PGS were not associated with any physical health outcome, the analyses did not provide any evidence for genetic nurture. If an association

had been found, this would have indicated that parental genes are associated with their children's physical health outside of any inherited risk. We know that several environmental factors on a household and wider societal level impact health, for example adults with ADHD are more likely to experience social disadvantage (Landes & London, 2021). Socioeconomic disadvantage itself is associated with additional risk factors for asthma such as increased exposure to pollution (Grant & Wood, 2022). It was a reasonable hypothesis therefore that parental ADHD liability might influence children's health through genetic nurture in addition to direct transmission. However, not only do ADHD-PGS in general capture a weak amount of genetic variance (Ronald et al., 2021), but ADHD-PGS are also known to be overtransmitted (Martin et al., 2022). This means the associated genetic variants are passed on to children at a greater than expected level which may further impact the strength of non-transmitted PGS. Additionally, in a different sample, Martin et al. (2022) reported that complete trios, i.e. the child and both their parents, had more socioeconomic advantages than incomplete trios. As non-transmitted PGS combine the PGS not passed on to a child from both parents, they inherently require a complete trio. Subsequently, the non-transmitted sample was much smaller than the transmitted sample. Although the results in Paper 3 do not provide evidence of genetic nurture, it may be that non-transmitted ADHD-PGS are still influential in the relationship between ADHD genetic liability and children's physical health. Future research, with higher statistical power, should explore whether non-transmitted PGS may have a moderating effect.

As previously discussed, measured environmental factors could not be included in the genetic analyses due to passive rGE. As parents provide both genetic material and the rearing environment, the individual contribution of each factor is hard to disentangle. A lower household income for example may result from multiple different factors, both genetic and environmental. Meaningful analyses would not be possible if it were necessary to separate income from any possible related factor. The Biopsychosocial Model (Engel, 1977) acknowledges this complexity by promoting the need to consider the overlap between the biological, psychological and societal factors influencing an association. The results from all three papers in this thesis show that the relationship between ADHD and physical health does not exist within a bubble. Every child with ADHD is subject to influences spanning every aspect of their biology and environment across the whole of their development and into

adulthood. As well as overlapping factors within the individual, this thesis demonstrates how genetic and environmental factors overlap across generations. Food insecurity is increasingly prevalent in low income households (Loopstra et al., 2019) and poor nutrition may have long lasting consequences for both mother and child. The Thrifty Phenotype Hypothesis (Hales & Barker, 2001) describes how poor nutrition during the antenatal period increases the risk of negative, and permanent, changes to a child's metabolism. A mother's sociological risk factor may become a child's biological one. Research which isolates and adjusts for individual confounders should acknowledge this complexity and consider risk through a biopsychosocial lens.

5.4 Millennium Cohort Study Considerations

When investigating associations across multiple stages of development, cohort studies are invaluable. The Millennium Cohort Study provides a wealth of information about a large number of cohort members and their families. In addition, the MCS sample is representative of the UK population with purposeful oversampling of children in disadvantaged areas (Plewis, 2007) as well as survey weights along with stratification and cluster variables to include in analyses. Seven data sweeps over 17 years have provided information about countless areas of cohort members' lives including genetic, cognitive, behavioural, physical, and environmental data. The rich quantity of data enabled numerous physical health conditions to be included in Paper 1. Multiple waves of data collection meant that the association between ADHD and weight could be explored from birth to emerging adulthood in Paper 2, both at individual time points and in path analyses. The role of genetic liability in the relationship between ADHD and physical comorbidities was possible due to the MCS collecting DNA samples from cohort members and their biological parents when children were 14 years old. When interpreting results of analyses which use MCS data, several limitations should be considered alongside its strengths. The varying gaps between data sweeps prevent more sensitive analysis of age. Between wave 4 (age 7) and wave 5 (age 11) there is a gap of 4 years, compared to a gap of only 2 years between other waves. Although each wave provides a vast amount of data, this is not always consistent. Some questions regarding physical health in particular were either not asked at each wave or were phrased differently. Consequently, this limited the number of physical health conditions which could be included in analyses. Additionally, the number of cohort members reporting

certain conditions did not reflect prevalences within the general population. In the whole MCS cohort, 4.4% of cohort members had received an ADHD diagnosis by age 14 (Pearce et al., 2024). This is below reported prevalence ranges (Ayano et al., 2023; Cortese et al., 2023) and after exclusions due to missing outcome data, prevalence dropped even lower to 2.2% in Paper 1 and 3.6% in Paper 2. There are several hypothesised reasons for this. A study exploring ADHD prevalence in the MCS reported that families of children with ADHD were more likely to withdraw from the study between waves (G. Russell, Rodgers, et al., 2014). The study also suggested that clinical and social attitudes towards ADHD in the UK may in part explain lower diagnostic numbers. Conversely, eczema was reported by 42.3% of the sample in Paper 1. Eczema prevalence estimates vary considerably between country and age group, but a large scale survey of nearly 160,000 children and adolescents found that even in areas with the highest prevalences, only 35.7% had ever experienced eczema (García-Marcos et al., 2022). Across the whole sample, estimates were much lower at 13.4% in children and 10.6% in adolescents. It seems likely that at least some eczema cases in the MCS sample were inaccurately reported, and results should therefore be interpreted with this in mind. Future research in this area should consider using clinically confirmed data instead of, or as well as, parent reports.

Although parents were interviewed at each wave and asked questions about numerous areas of their lives, there were some notable omissions. The MCS provides no information about parents' neurodevelopmental diagnoses or any measure of ADHD symptoms they may experience. However, these limitations should be considered with reasonable expectations of feasibility in mind. It would be impossible for a cohort study to collect data on every conceivable variable required by research so the strengths and limitations should be weighed accordingly. Future research into ADHD and physical comorbidities in childhood, both cross-sectional and longitudinal should aim to include data from children and parents about their physical health and ADHD history.

5.5 Implications and Future Directions

5.5.1 A Stepped Care and Multifaceted approach

This thesis demonstrates that there are significant key time points across development for different associations between ADHD and physical health. This highlights

the importance of a stepped care approach in clinical practice and policy implementation in order to offer support or introduce preventative measures at the most beneficial times. Each paper contributes towards an overall picture which shows that genetic and environmental influences have long-lasting consequences. In line with the BPS model, the results from the three papers support the need for research and clinical practice to adopt a nuanced and holistic approach. Biological and psychosocial factors cannot be considered in isolation due to their overlap and support for children with ADHD should recognise the complicated and interconnected facets of family history and current experiences. Comprehensive support for children with ADHD will also involve support for parents and successful intervention may also benefit future generations. Children who inherit higher genetic ADHD liability from their parents are more likely to experience various health issues throughout their childhood and beyond. Combined with the increased risk arising from prenatal factors, it appears crucial that support should begin in the antenatal period. Current NICE guidelines provide comprehensive information for clinicians about nutrition and weight management in pregnancy (NICE, 2025) and expectant parents should be directed to NHS guidance on healthy eating in pregnancy (National Health Service [NHS], 2020). However, this guidance is only beneficial if it is able to be accessed by those most at risk. Future policy changes should include additional funding and resources to enable clinicians to provide optimal care. Health care professionals involved in antenatal care should ensure that information is given in a sensitive yet accessible way with an emphasis on promoting a healthy lifestyle for the whole family. This should continue once the baby is born and support should remain consistent throughout the postnatal and pre-school period. It will not always be apparent who is most at risk so support should not only be given once an issue is identified. Providing information about nutrition and weight trajectories to all families will benefit all children, including those with a genetic predisposition for ADHD. Ensuring this guidance is implemented as standard practice, for every family, should aid in the reduction of stigma surrounding the topic of weight.

As ADHD genetic liability is associated with earlier onset of epilepsy and asthma, it would be beneficial to make all parents aware of the key signs and symptoms of both ADHD and comorbid physical health conditions in order to enable prompt diagnosis and management. In addition, factors delaying or preventing access to ADHD assessments (see

section 1.1.2) should be addressed and improving equal and timely access to diagnostic assessments should be a priority for future policy implementation. Once a child has received an ADHD diagnosis, it is important that they are monitored for any physical comorbidities to allow support to be provided at the earliest opportunity. The diagnostic process itself requires symptoms to impact multiple areas of life for a substantial period of time (American Psychiatric Association, 2013). It is logical that this acknowledgment should extend to ADHD's many comorbidities, not just the core traits of the condition.

In addition to the increased risk of multiple comorbidities, the association between ADHD and physical health may impact treatment pathways. Children and adolescents with ADHD often struggle with medication adherence, both for ADHD (Ferrin et al., 2025) and other conditions such as asthma (Silverstein et al., 2023). Health care professionals should be aware of and consider possible complications resulting from comorbid conditions, not only at the point of diagnosis but as an ongoing concern. As well as having implications across multiple periods of development, the complex relationship between ADHD and physical health requires a comprehensive approach which considers all biological, psychological, and sociological influences. The results of Paper 3 underline the role of genetic liability for ADHD. ADHD Polygenic scores are associated with ADHD diagnosis and symptoms (Green et al., 2022), and ADHD is highly heritable (Faraone & Larsson, 2019). However, a high polygenic score does not mean that developing ADHD is a certainty. Clinicians involved in the care of a young person with ADHD should endeavour to gather as much information as possible about family ADHD history and past and current environmental factors as well as current symptomology.

5.5.2 Research Implications and Future Priorities

5.5.2.1 Confirming and expanding findings

The papers in this thesis describe several novel findings in the field of ADHD and physical health. They offer insight into the impact of cumulative comorbidities, notable time points for key associations and provide further evidence of the interaction between genetic and environmental factors. The findings also give rise to several future lines of enquiry. As discussed above (see 5.4), the Millennium Cohort Study contains a wealth of valuable

information, but some analyses would benefit from more comprehensive data. Future research should aim to replicate these findings in a dataset with richer physical health data.

Environmental variables in papers 1 and 2 were measured at one time point only. Investigating fluctuations in psychosocial factors over time would be a valuable next step to determine the impact of environmental influences on the association between ADHD and physical health at different developmental stages. As it was beyond the scope of this thesis to separate the effects of genetic and environmental measures, future research should aim to explore this with the use of adoption or twin studies.

Future research may also consider using alternative methods to determine healthy weight status. BMI is used extensively within research but is also subject to widespread criticism. BMI often lacks the reliability of other measures, such as waist circumference measurement, and may not always accurately reflect true obesity levels within a sample (Marković-Jovanović et al., 2015). To further increase knowledge and understanding of the relationship between ADHD and weight, research should employ a variety of methods to ensure sensitivity and specificity is high.

5.5.2.2 Inclusion of new variables

Figure 5.

A summary of Results Relating to Key Aspects of the Relationship Between ADHD and Physical Health..

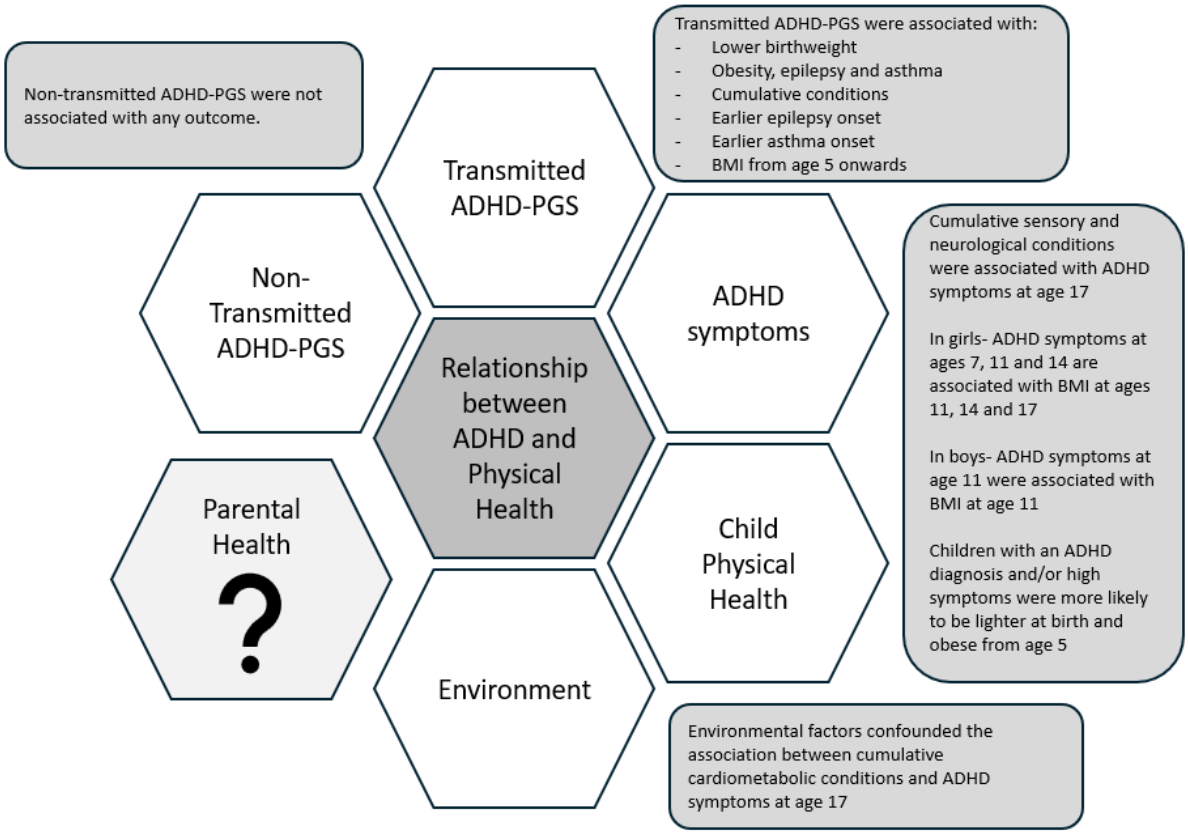


Figure 5 shows a number of key areas involved in the association between ADHD and physical health. This thesis addresses all but one of these aspects and a brief summary of how the results relate to each is included in the figure. Unfortunately, it was not possible to include any sufficient measure of parent health within the analyses. Future research should consider it a high priority to explore how parental physical health influences the relationship between ADHD and physical health in children. Although Paper 3 explored parental ADHD genetic liability, parents' ADHD symptoms or diagnosis status could not be examined. In order to better understand the complex interplay of multiple factors, Future research should consider the genetic liability and parents' phenotypic presentation of both ADHD and physical health conditions as well as their children's.

5.6 Conclusion

The papers in this thesis identify several new pieces of the ADHD and physical comorbidity puzzle. The results highlight the increased risk associated with having multiple conditions, identify key developmental milestones and show that inherited genetic liability drives many associations. The world of ADHD and physical comorbidity is messy and complex and current research often seeks to rectify this by identifying linear causes. The three papers presented in this thesis show that this is not always the best approach. There will never be one single answer which explains why ADHD is associated with so many physical health outcomes and the findings in this thesis, along with the vast body of ADHD literature, show that there are countless overlapping and interacting factors spanning all areas and stages of life. This thesis proposes that instead of seeking to reduce complexity, research should instead acknowledge that all people are inherently complex. Studies investigating ADHD and physical health comorbidity should use developmentally informed frameworks and give careful consideration to the use of environmental confounders. In order to help and support people who have ADHD and comorbid health conditions, research and clinical practice needs to be aware of the many genetic, biological, environmental, and societal factors which make up the larger picture.

Appendix A Standardised Model Statistics for the Weighted RI-CLPM- Females only

	Estimate	95% CI	SE	*p*
Age 5 SDQ score on age 3 SDQ score	0.340	[0.29, 0.39]	0.024	**<.001**
Age 5 SDQ score on age 3 BMI z-score	-0.028	[-0.08, 0.03]	0.028	.33
Age 5 BMI z-score on age 3 SDQ score	0.024	[-0.03, 0.08]	0.027	.36
Age 5 BMI z-score on age 3 BMI z-score	0.480	[0.38, 0.58]	0.049	**<.001**
Age 7 SDQ score on age 5 SDQ score	0.470	[0.42, 0.52]	0.024	**<.001**
Age 7 SDQ score on age 5 BMI z-score	-0.041	[-0.09, 0.01]	0.026	.11
Age 7 BMI z-score on age 5 SDQ score	0.008	[-0.03, 0.05]	0.020	.67
Age 7 BMI z-score on age 5 BMI z-score	0.613	[0.53, 0.70]	0.045	**<.001**
Age 11 SDQ score on age 7 SDQ score	0.455	[0.41, 0.50]	0.024	**<.001**
Age 11 SDQ score on age 7 BMI z-score	-0.036	[-0.09, 0.01]	0.026	.16
Age 11 BMI z-score on age 7 SDQ score	0.048	[0.02, 0.08]	0.016	**.002**
Age 11 BMI z-score on age 7 BMI z-score	0.638	[0.57, 0.70]	0.034	**<.001**
Age 14 SDQ score on age 11 SDQ score	0.403	[0.35, 0.46]	0.027	**<.001**
Age 14 SDQ score on age 11 BMI z-score	-0.016	[-0.06, 0.03]	0.024	.51
Age 14 BMI z-score on age 11 SDQ score	0.066	[0.03, 0.10]	0.017	**<.001**
Age 14 BMI z-score on age 11 BMI z-score	0.714	[0.67, 0.75]	0.021	**<.001**
Age 17 SDQ score on age 14 SDQ score	0.373	[0.31, 0.42]	0.031	**<.001**
Age 17 SDQ score on age 14 BMI z-score	0.007	[-0.04, 0.05]	0.023	.75
Age 17 BMI z-score on age 14 SDQ score	0.044	[0.01, 0.07]	0.015	**.005**
Age 17 BMI z-score on age 14 BMI z-score	0.750	[0.72, 0.78]	0.015	**<.001**

Appendix B Standardised Model Statistics for the Weighted RI-CLPM- Males only

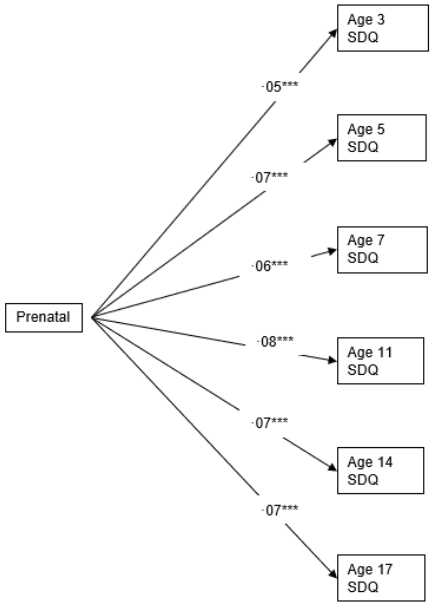
	Estimate	95% CI	SE	*p*
Age 5 SDQ score on age 3 SDQ score	0.319	[0.27, 0.37]	0.024	**<.001**
Age 5 SDQ score on age 3 BMI z-score	0.052	[-0.02, 0.12]	0.034	.13
Age 5 BMI z-score on age 3 SDQ score	0.005	[-0.05, 0.06]	0.026	.85
Age 5 BMI z-score on age 3 BMI z-score	0.527	[0.39, 0.66]	0.068	**<.001**
Age 7 SDQ score on age 5 SDQ score	0.459	[0.41, 0.51]	0.024	**<.001**
Age 7 SDQ score on age 5 BMI z-score	-0.060	[-0.12, -0.00]	0.031	.05
Age 7 BMI z-score on age 5 SDQ score	0.022	[-0.02, 0.06]	0.020	.25
Age 7 BMI z-score on age 5 BMI z-score	0.663	[0.56, 0.77]	0.052	**<.001**
Age 11 SDQ score on age 7 SDQ score	0.429	[0.38, 0.48]	0.027	**<.001**
Age 11 SDQ score on age 7 BMI z-score	-0.005	[-0.07, 0.06]	0.031	.88
Age 11 BMI z-score on age 7 SDQ score	0.002	[-0.04, 0.04]	0.019	.94
Age 11 BMI z-score on age 7 BMI z-score	0.668	[0.60, 0.74]	0.037	**<.001**
Age 14 SDQ score on age 11 SDQ score	0.471	[0.42, 0.52]	0.026	**<.001**
Age 14 SDQ score on age 11 BMI z-score	-0.031	[-0.07, 0.01]	0.022	.16
Age 14 BMI z-score on age 11 SDQ score	0.067	[0.04, 0.10]	0.014	**<.001**
Age 14 BMI z-score on age 11 BMI z-score	0.791	[0.76, 0.83]	0.018	**<.001**
Age 17 SDQ score on age 14 SDQ score	0.462	[0.41, 0.51]	0.026	**<.001**
Age 17 SDQ score on age 14 BMI z-score	0.004	[-0.04, 0.05]	0.022	.86
Age 17 BMI z-score on age 14 SDQ score	0.005	[-0.02, 0.03]	0.013	.70
Age 17 BMI z-score on age 14 BMI z-score	0.788	[0.76, 0.82]	0.015	<.001

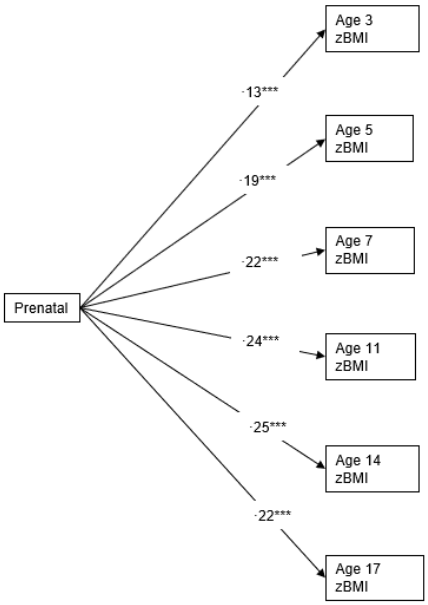
Appendix C Standardised Model Statistics for the Combined Sex Weighted RI-CLPM

	Est	95% CI	SE	*p*
Age 5 SDQ score on age 3 SDQ score	0.327	[0.29, 0.36]	0.017	**<.001**
Age 5 SDQ score on age 3 BMI z-score	0.012	[-0.03, 0.06]	0.023	.60
Age 5 BMI z-score on age 3 SDQ score	0.013	[-0.02, 0.05]	0.018	.46
Age 5 BMI z-score on age 3 BMI z-score	0.499	[0.42, 0.58]	0.042	**<.001**
Age 7 SDQ score on age 5 SDQ score	0.462	[0.43, 0.50]	0.017	**<.001**
Age 7 SDQ score on age 5 BMI z-score	-0.052	[-0.09, -0.01]	0.020	**.009**
Age 7 BMI z-score on age 5 SDQ score	0.014	[-0.02, 0.04]	0.015	.34
Age 7 BMI z-score on age 5 BMI z-score	0.638	[0.57 0.71]	0.035	**<.001**
Age 11 SDQ score on age 7 SDQ score	0.441	[0.40, 0.48]	0.019	**<.001**
Age 11 SDQ score on age 7 BMI z-score	-0.021	[-0.06, 0.02]	0.020	.30
Age 11 BMI z-score on age 7 SDQ score	0.024	[-0.00, 0.05]	0.012	**.047**
Age 11 BMI z-score on age 7 BMI z-score	0.652	[0.60, 0.70]	0.025	**<.001**
Age 14 SDQ score on age 11 SDQ score	0.441	[0.40, 0.48]	0.020	**<.001**
Age 14 SDQ score on age 11 BMI z-score	-0.023	[-0.06, 0.01]	0.016	.15
Age 14 BMI z-score on age 11 SDQ score	0.067	[0.05, 0.09]	0.011	**<.001**
Age 14 BMI z-score on age 11 BMI z-score	0.756	[0.73, 0.78]	0.014	**<.001**
Age 17 SDQ score on age 14 SDQ score	0.424	[0.39, 0.46]	0.020	**<.001**
Age 17 SDQ score on age 14 BMI z-score	0.004	[-0.03, 0.04]	0.017	.81
Age 17 BMI z-score on age 14 SDQ score	0.021	[-0.00, 0.04]	0.010	**.030**
Age 17 BMI z-score on age 14 BMI z-score	0.770	[0.75, 0.79]	0.011	**<.001**

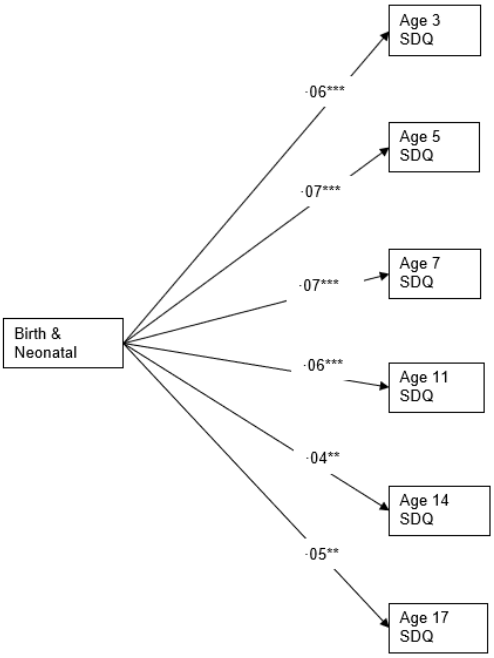
Appendix D Beta Statistics for Covariates in the Combined Sex RI-CLPM

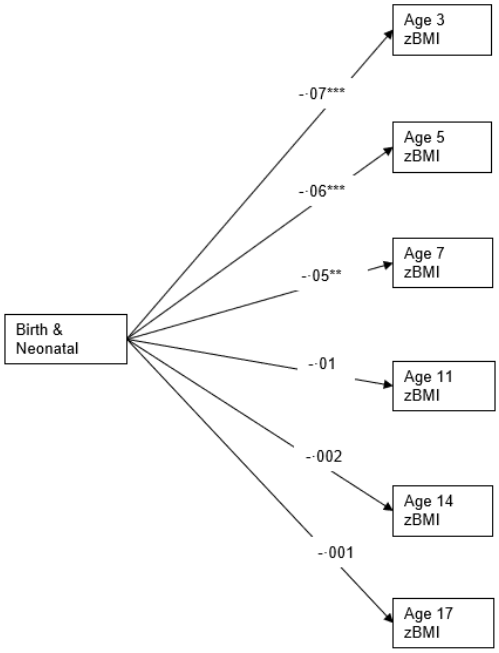
* $p < .05$, ** $p < .01$, *** $p < .001$



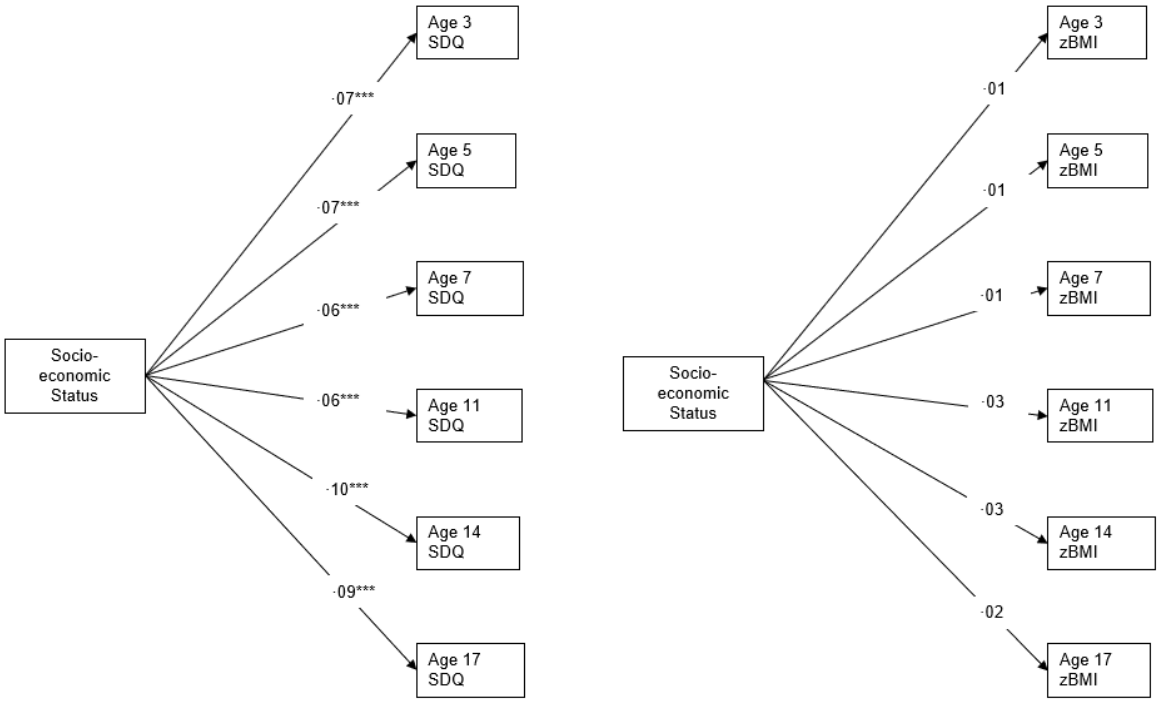


D1:Prenatal Risk Factors.

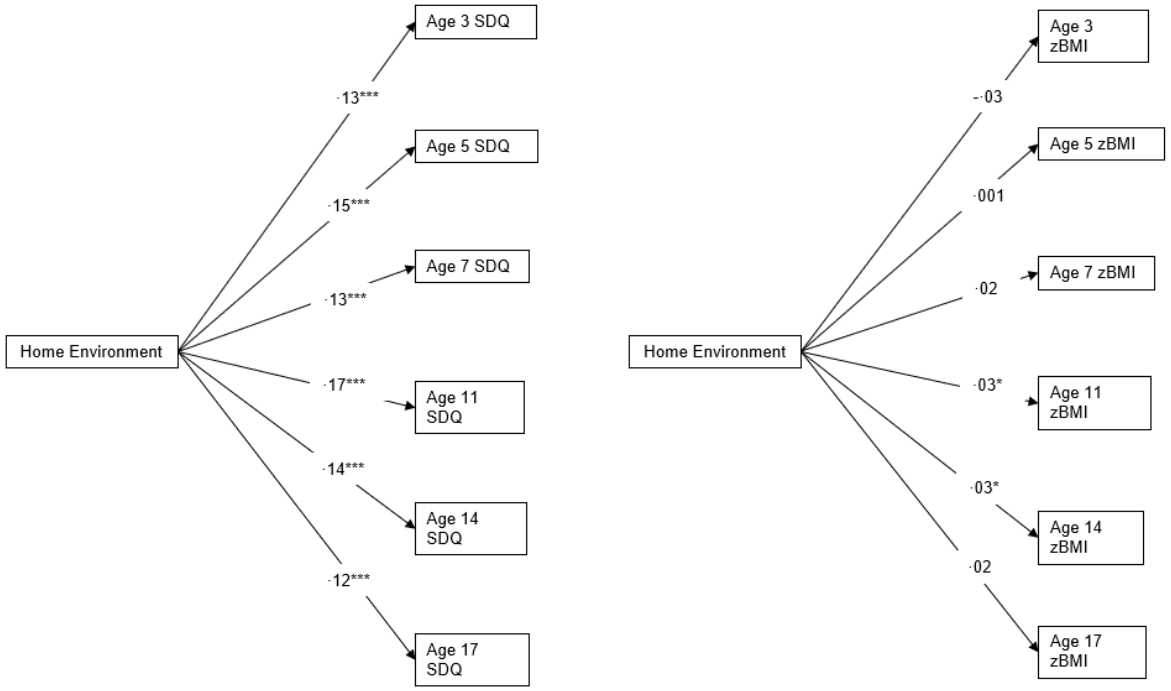




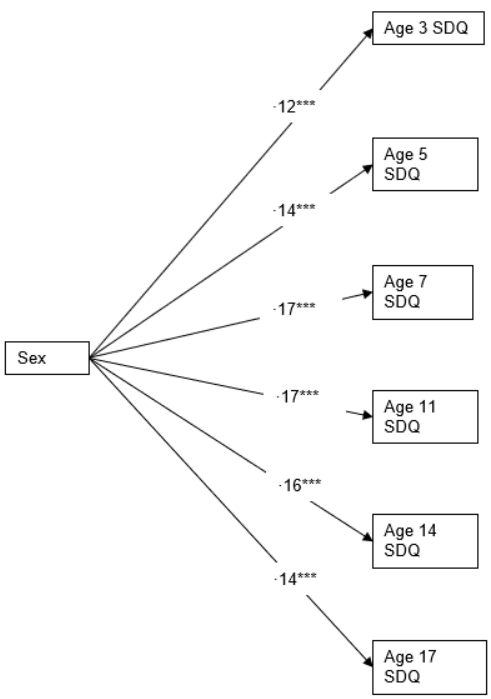
D2:Birth and Neonatal Risk Factors.

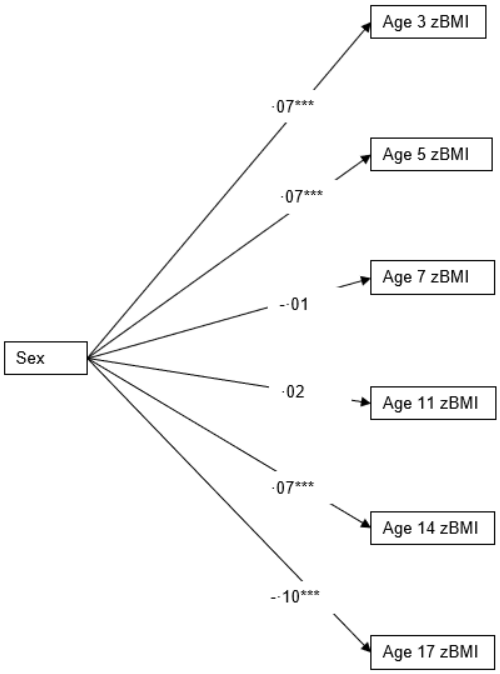


D3:Socioeconomic Status Risk Factors.

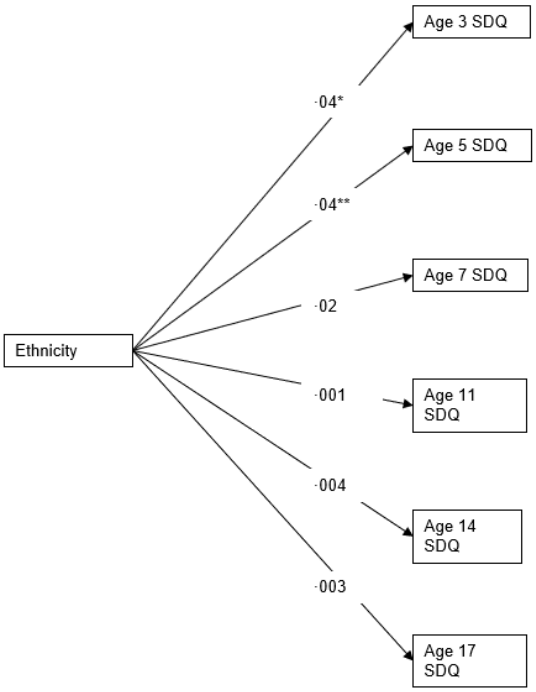


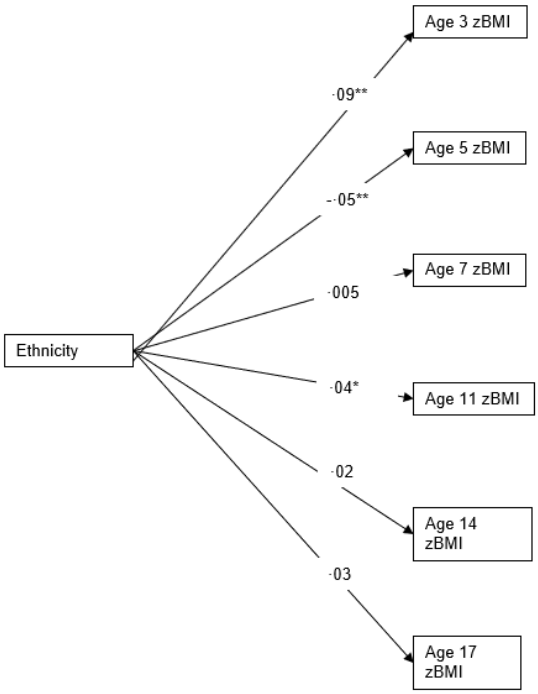
D4. Home Environment Risk Factors.



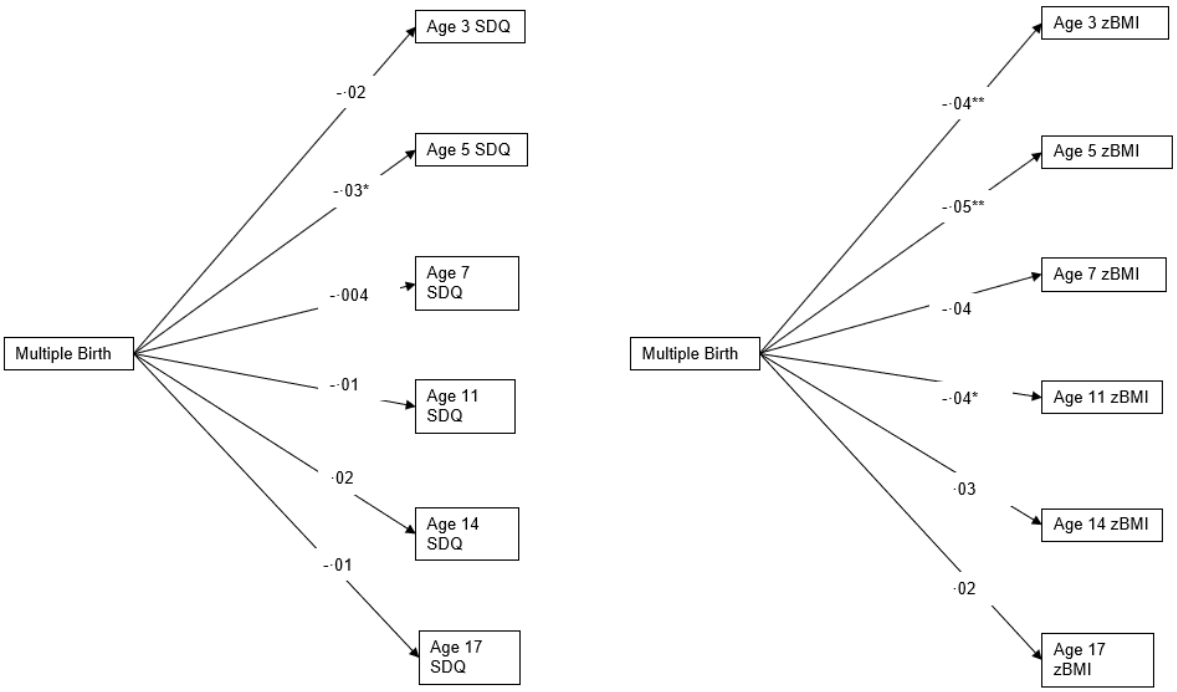


D5:Sex entered as Time Invariant Predictor.

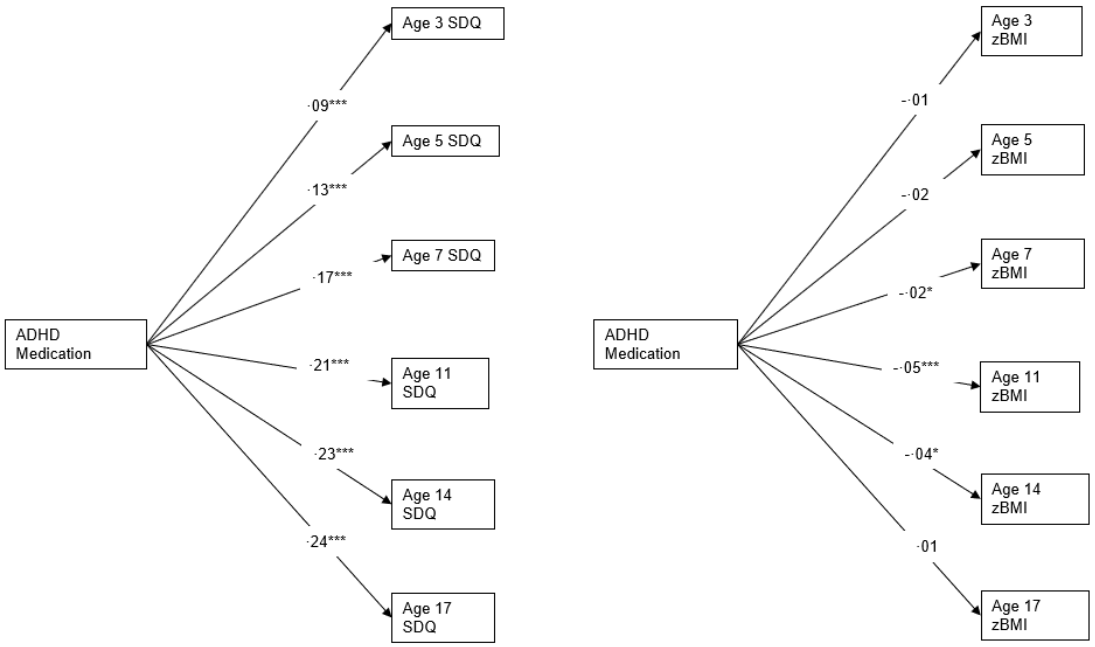




D6:Ethnicity entered as Time Invariant Predictor.



D7:Multiple Birth Status entered as Time Invariant Predictor.



D8:ADHD Medication Status entered as Time Invariant Predictor

Appendix E MPlus Syntax for Path Analyses

```
TITLE: ZBMI RI_CLPM
DATA: FILE IS {REDACTED}

VARIABLE:
NAMES ARE
MCSID
CNum
Ethnicity
Multiples
W7_WGHT
W2_SDQ
W3_SDQ
W4_SDQ
W5_SDQ
W6_SDQ
W7_SDQ
W2_BMI
W3_BMI
W4_BMI
W5_BMI
W6_BMI
W7_BMI
W2_zbmi
W3_zbmi
W4_zbmi
W5_zbmi
W6_zbmi
W7_zbmi
ADHD_Med
Prenatal
BirthNeo
SES
HomeEnv
PTTYPE2
SPTN00;

USEVARIABLES ARE

Ethnicity
Multiples
W7_WGHT
W2_SDQ
W3_SDQ
W4_SDQ
W5_SDQ
```

```
W6_SDQ
W7_SDQ
W2_zbmi
W3_zbmi
W4_zbmi
W5_zbmi
W6_zbmi
W7_zbmi
ADHD_Med
Prenatal
BirthNeo
SES
HomeEnv
PTTYPE2
SPTN00;

MISSING ARE ALL (-999);
WEIGHT = W7_WGHT;
STRATIFICATION IS PTTYPE2;
CLUSTER IS SPTN00;

ANALYSIS:
TYPE = COMPLEX;
ESTIMATOR = MLR;
MODEL = NOCOV;

MODEL:
! Create between components (random intercepts)
RISDQ BY W2_SDQ@1 W3_SDQ@1 W4_SDQ@1 W5_SDQ@1 W6_SDQ@1 W7_SDQ@1;
RIBMI BY W2_zbmi@1 W3_zbmi@1 W4_zbmi@1 W5_zbmi@1 W6_zbmi@1 W7_zbmi;

! Estimate covariance between random intercepts
RISDQ WITH RIBMI;

! Create within-person centered variables
wW2_SDQ BY W2_SDQ@1;
wW3_SDQ BY W3_SDQ@1;
wW4_SDQ BY W4_SDQ@1;
wW5_SDQ BY W5_SDQ@1;
wW6_SDQ BY W6_SDQ@1;
wW7_SDQ BY W7_SDQ@1;
wW2_zbmi BY W2_zbmi@1;
wW3_zbmi BY W3_zbmi@1;
wW4_zbmi BY W4_zbmi@1;
wW5_zbmi BY W5_zbmi@1;
wW6_zbmi BY W6_zbmi@1;
wW7_zbmi BY W7_zbmi@1;
```

```
! Constrain measurement error variances to 0
W2_SDQ-W7_zbmi@0;

! Regression of observed variables on covariates
W2_SDQ ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W3_SDQ ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W4_SDQ ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W5_SDQ ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W6_SDQ ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W7_SDQ ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;

W2_zbmi ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W3_zbmi ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W4_zbmi ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W5_zbmi ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W6_zbmi ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;
W7_zbmi ON Sex Ethnicity Multiples ADHD_Med Prenatal BirthNeo SES HomeEnv;

! Estimate lagged effects between within-person centered variables
wW3_SDQ wW3_zbmi ON wW2_SDQ wW2_zbmi;
wW4_SDQ wW4_zbmi ON wW3_SDQ wW3_zbmi;
wW5_SDQ wW5_zbmi ON wW4_SDQ wW4_zbmi;
wW6_SDQ wW6_zbmi ON wW5_SDQ wW5_zbmi;
wW7_SDQ wW7_zbmi ON wW6_SDQ wW6_zbmi;

! Estimate covariance between within-person components at first wave
wW2_SDQ WITH wW2_zbmi;

! Estimate covariances between residuals of within-person component

wW3_SDQ WITH wW3_zbmi;
wW4_SDQ WITH wW4_zbmi;
wW5_SDQ WITH wW5_zbmi;
wW6_SDQ WITH wW6_zbmi;
wW7_SDQ WITH wW7_zbmi;

OUTPUT:     TECH1 STDYX SAMPSTAT CINTERVAL;
```

Appendix F Sensitivity Analysis- t/ χ^2 Coefficients for Analyses with ADHD Group only Consisting of Cohort Members with a Diagnosis

	ADHD group (n=392)	Control group (n=5398)				
	M (SD)		t	*p*	Cohen's d	
Birth weight	3.27 (0.70)	3.38 (0.65)	3.18	**.002**	0.17	
9 months weight	8.38 (3.10)	8.53 (8.38)	1.10	.270	-0.06	
Number of cohort members with obesity	N (% of valid data)		χ^2	*p*	**Odds Ratio (95% CI)**	**Relative Risk (95% CI)**
Age 3	14 (4.76)	227 (4.52)	0.04	.848	1.06 (0.61, 1.84)	1.05 (0.62, 1.78)
Age 5	25 (7.27)	217 (4.06)	8.18	**.004**	1.85 (1.21, 2.85)	1.79 (1.20, 2.67)
Age 7	25 (7.72)	265 (4.94)	4.85	**.028**	1.61 (1.05, 2.46)	1.56 (1.05, 2.32)
Age 11	38 (11.84)	277 (5.25)	24.7	**<.001**	2.42 (1.69, 3.47)	2.25 (1.64, 3.10)
Age 14	27 (11.25)	303 (5.83)	11.8	**<.001**	2.05 (1.35, 3.11)	1.93 (1.33, 2.80)
Age 17	23 (12.9)	446 (8.87)	3.45	.063	1.52 (0.97, 2.39)	1.46 (0.99, 2.16)

Appendix G Additional Analyses for Transmitted ADHD Polygenic Scores

Transmitted ADHD-PGS predicting a) birthweight, and b) BMI at each time point adjusted for ADHD symptoms at age 3.

	β	95% CI	*p-value*
Birthweight			
ADHD-PGS$_T$	-0.04	-0.06, -0.01	**.002**
BMI age 3			
ADHD-PGS$_T$	0.01	-0.01, 0.04	.320
SDQ Age 3	0.02	-0.01, 0.04	.235
BMI age 5			
ADHD-PGS$_T$	0.04	0.01, 0.06	**.014**
SDQ Age 3	0.03	0.01, 0.06	**.017**
BMI age 7			
ADHD-PGS$_T$	0.05	0.02, 0.07	**< .001**
SDQ Age 3	0.03	0.00, 0.05	.057
BMI age 11			
ADHD-PGS$_T$	0.06	0.03, 0.09	**< .001**
SDQ Age 3	0.06	0.03, 0.08	**< .001**
BMI age 14			
ADHD-PGS$_T$	0.06	0.04, 0.09	**< .001**
SDQ Age 3	0.07	0.04, 0.10	**< .001**
BMI age 17			
ADHD-PGS$_T$	0.07	0.04, 0.10	**< .001**
SDQ Age 3	0.07	0.04, 0.10	**< .001**

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