GROWING UP WITH ADHD

A study into long-term outcomes and their predictors



NOA VAN DER PLAS

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Growing up with ADHD

A study into long-term outcomes and their predictors

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CHAPTER 1

General introduction

Prologue

Attention-deficit/hyperactivity disorder (ADHD) is a predominantly childhood-onset neurodevelopmental disorder [1, 2]. However, ADHD is not limited to childhood. The disorder has a highly heterogeneous developmental trajectory from childhood into adulthood [3], ranging from full remission to persistence of ADHD with adverse sequelae [4]. The aim of this thesis is to get more insight into the long-term trajectories of ADHD. To meet that aim, it is important to study a broad set of outcomes and identify both risk and protective factors. As a result, knowledge on long-term outcomes can support a good prognosis for adulthood functioning of children with ADHD, and knowledge on risk and protective factors can suggest possible targets for early prevention and intervention strategies. This knowledge may inform targeted support and alleviate negative outcomes.

ADHD diagnosis

ADHD is defined by persistent and impairing symptoms of inattention and/or hyperactivity/impulsivity. In the general population, the prevalence of ADHD is 5.3% in school-aged children, and approximately 2.5% in early adulthood [1]. Notably, in childhood the prevalence rates of ADHD are three to sixteen times higher in boys compared to girls [5], while this gap attenuates during adulthood to a male to female ratio between 2:1 and 1:1 [6].

Standard diagnostic criteria are based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) [2]. For children up to and including age 16, the DSM-5 requires at least 6 symptoms of inattention and/or hyperactivity-impulsivity to be present for at least 6 months. Inattentive symptoms include problems with attention, concentration, and organization, such as having difficulty sustaining focus, being easily distracted, or forgetting daily tasks, whereas hyperactive-impulsive symptoms include problems with self-control, such as the display of excessive movements and restlessness, interrupting others, and acting without thinking. For people aged 17 years and above, the DSM-5 requires at least 5 symptoms of inattention and/or hyperactivity-impulsivity to be present for at least 6 months. To receive a diagnosis these symptoms should be present before age 12 years, apparent in two or more settings (home, school, or social settings), and clearly interfere with (quality of) functioning at home, in school or other settings. Several combinations of symptoms are possible, and can result in one of the three main presentations of ADHD: the predominantly inattentive presentation (≥ 6 inattentive symptoms and < 6 hyperactive-impulsive symptoms), the predominantly hyperactive-impulsive presentation (≥ 6 hyperactive-impulsive symptoms and < 6 inattentive symptoms), and the combined presentation (≥ 6 inattentive symptoms and ≥ 6 hyperactive-impulsive symptoms), or with thresholds at 5 symptoms for people aged 17 and above. The combined presentation is most common in childhood, whereas a predominantly

inattentive presentation is most common in adulthood, likely as the mean age at diagnosis is usually higher for the predominantly inattentive presentation [7, 8]. Females are more likely to be diagnosed with a predominantly inattentive presentation and often receive a diagnosis later compared to males [9, 10].

ADHD persistence

ADHD typically begins in childhood and often continues into adulthood, though its course varies widely between individuals. Some experience complete remission of symptoms, others have persistent symptoms throughout life, and for many, symptoms fluctuate over time [11]. Although meta-analyzed point estimations of ADHD persistence rates range between 3.3% and 25.7%, up to two-thirds of adults with childhood ADHD still experience impairing symptoms either at clinical or subthreshold levels [1, 2, 12]. In cohort studies with clinical samples, the ADHD persistence rates reported are often higher, up to 77% [13].

Long-term outcomes of ADHD

Negative long-term outcomes

Childhood ADHD seems to be associated with many negative long-term outcomes, across several domains, including psychiatric problems, behavioral and emotional problems, academic and professional functioning, adaptive functioning, neurocognitive functioning, and physical health, which adversely impact quality of life and daily functioning. Besides children with ADHD, their siblings might also be at risk for negative long-term outcomes, but thus far no prospective cohort study has investigated long-term outcomes of siblings of children with ADHD without an ADHD diagnosis themselves. These siblings share half of their genetic material as well as part of their childhood environment with the sibling with an ADHD diagnosis and show more ADHD-related traits compared to children without a sibling with an ADHD diagnosis [14, 15]. A design including children with ADHD, their siblings, and controls can investigate whether these siblings are indeed at an increased risk of negative long-term outcomes and hint towards the potential contribution of shared genetics and childhood environment to long-term outcomes.

Despite a limited scope and generalizability of current studies, prospective cohort studies reported several negative long-term outcomes of childhood ADHD. More specifically, prospective cohort studies showed that adults with childhood ADHD are 1.5 to 4.3 times more often diagnosed with a mental disorder, including major depressive disorder (MDD), anxiety disorder, substance use disorder (SUD), and/or antisocial personality/conduct disorder [16]. Furthermore, behavioral and emotional difficulties not qualifying for a full mental diagnosis are also seen in adults with a childhood diagnosis of ADHD, such as increased levels of emotional

dysregulation and the presence of autistic traits [17]. Also, childhood ADHD is associated with lower academic and professional achievement, as these adults were 3.7 times more likely to not finish high school, and 1.5 times more likely to receive public assistance [16, 18, 19]. Further, 65% of adults with ADHD in childhood face functional impairments, for example, worse social functioning, and reduced quality of life compared to adults without childhood ADHD [4, 18]. Notably, although these negative long-term outcomes are likely worse for adults with persistent childhood ADHD, they also seem to be experienced by adults with remitted childhood ADHD [20, 21].

Furthermore, few studies have investigated domains such as neurocognitive and physical health outcomes. However, the few prospective studies on neurocognitive functioning in adults with childhood-diagnosed ADHD suggest poorer executive functioning (e.g., verbal reasoning, perceptual skills, memory, and processing speed) [22, 23]. Moreover, growing evidence suggests childhood ADHD is linked to poorer physical health, with increased risk for injury, obesity, and other somatic conditions [24-26]. In line with the latter finding, adults with childhood ADHD have a higher healthcare utilization in adulthood, including more inpatient hospitalization days, outpatient visits, and medication use [27].

While these outcomes have been reported by previous prospective studies, additional work is required. Most importantly, the available studies target only a limited set of outcomes of childhood ADHD per study and do not provide a comprehensive understanding of the full range of long-term outcomes [28]. Indeed, the majority of the studies investigate psychiatric outcomes and/or antisocial behaviors in adulthood, thereby disregarding many other domains relevant for daily life functioning. Mapping a broad range of long-term outcomes of childhood ADHD is necessary to inform children with ADHD, their parents, and potentially their siblings, on prospective outcomes. Therefore, **Chapter 2** and **Chapter 3** of this thesis provide a comprehensive overview of long-term outcomes of childhood ADHD in both children with ADHD and their siblings.

Furthermore, generalizability of previous results is restricted, as most of the studies included mainly males and were conducted in the USA [28]. Long-term outcomes should be studied in a sample including both males and females to increase generalizability of the findings. Similarly, inclusion of both males and females allows for an investigation of sex and gender-related differences in the long-term outcomes, a topic which has received little attention until now.

Differences between males and females

As there seemingly are differences between boys and girls with ADHD in childhood, there might also be differences in the long-term outcomes of males and females with childhood ADHD. In childhood, there are clear differences in the prevalence of

ADHD, with the prevalence rates of ADHD being 3 to 16 times higher in boys compared to girls [5], but this gap attenuates during adulthood to a male to female ratio between 2:1 and 1:1 [6]. This attenuation suggests there are different factors in play in the manifestation and/or recognition of ADHD between males and females, potentially also influencing differences in long-term outcomes.

Although the literature on this subject is sparse, some differences between adult males and females with ADHD have been suggested. Therefore, there might potentially also be differences in the long-term outcomes of males and females with childhood ADHD. Most likely, both sex, reflecting biological sex-related factors, and gender, defined as the socially constructed roles, behaviors, expression, and identities that a given society considers appropriate for males and females, contribute to differences between males and females with ADHD [29]. Some previously reported sex differences in adults with ADHD include that males with ADHD have more difficulties with complex attention and show higher levels of antisocial behaviors compared to females with ADHD, while females with ADHD report more symptoms of mood disorders and higher levels of stress compared to males with ADHD [5, 6, 30, 31]. However, it remains understudied whether the identified sex differences are evident in long-term outcomes of ADHD. Also, it remains poorly understood whether the potential sex differences are more pronounced in individuals with ADHD or if they are comparable to the sex differences observed in the general population, while effects of gender have not yet been explored at all.

The previously identified differences between males and females with ADHD seem to follow similar patterns as in the general population, but they may be more pronounced in ADHD. For instance, females with ADHD engage in more risky sexual behavior than males with ADHD and females without ADHD, increasing the risk of sexually transmitted infections and unplanned parenthood [10, 32]. This potentially reflects a more pronounced sex difference in ADHD. Furthermore, a gender-related difference may also be present, where, specifically for females, the social stigma around risky sexual behavior can cause social and relational problems (e.g., bullying or abuse) [10]. Currently, hardly any study has investigated the moderating effects of sex and gender on long-term outcomes of childhood ADHD. To that end, in **Chapter 4** of this thesis, we investigated differences between males and females in long-term outcomes of ADHD by testing the moderation of sex and exploring potential moderating effects of gender-expression. Importantly, knowledge on these differences can support a good prognosis and guide more effective monitoring and prevention strategies.

Predictors long-term outcomes

Predicting ADHD persistence

A substantial number of studies have addressed predictors specifically for adult psychiatric outcomes of childhood ADHD, but the ability to accurately predict the course and outcomes of childhood ADHD remains a challenge. Notably, studies on predictors for long-term outcomes of ADHD have been limited in study design and results.

At the time of the start of this thesis, there was only one review on predictors of one single long-term outcome of ADHD: ADHD (symptom) persistence [33]. No other review or meta-analysis was available for any other long-term outcome of ADHD, such as psychiatric outcomes other than ADHD persistence or overall functioning. The single available review on predictors of ADHD (symptom) persistence aggregated the results of 16 studies and was able to identify some predictors. These were higher ADHD severity, having received pharmacological treatment for ADHD, comorbid conduct disorder (CD), and comorbid MDD. Consequently, many other predictors, including genetic, prenatal, perinatal, neuroimaging, neurocognitive, environmental, psychological, and social factors, have either not been investigated at all or only examined in isolated studies, which is insufficient for inclusion in systematic reviews.

Further, despite a broad range of negative long-term outcomes, including mental, physical, and social health, information on reliable predictors for these other long-term outcomes of childhood ADHD remains scarce. Importantly, identification of such (childhood) predictors can alleviate the burden of negative long-term outcomes by guiding timely monitoring, prevention, and intervention. Psychiatric long-term outcomes are additionally associated with functional impairments, and, consequently, likely among the most impairing long-term outcomes. Therefore, **Chapter 5** of this thesis provides a systematic review and meta-analysis of all currently known predictors of prevalent psychiatric outcomes of ADHD, including ADHD persistence, SUD, CD, antisocial personality disorder, MDD, and anxiety disorders.

Stimulant treatment use as possible predictor

One potentially relevant predictor influencing long-term outcomes of ADHD is childhood stimulant treatment. This potential predictor is important to investigate, as stimulant treatment is the first-line pharmacological treatment option for ADHD and between 0.76 to 3.13% of all children use stimulant medication worldwide, with a sustained annual increase in stimulant use observed among both children and adults [34-36]. It is the first-line pharmacological treatment option as it is highly efficacious in reducing ADHD symptoms [37]. Besides the reduction of ADHD symptoms, short-term effects in youth with ADHD

include reduction of oppositional behavior, conduct problems, and aggression [38], anxiety [39], and suicide risk [40]. While short-term effects are often studied, long-term (>10 years) effects remain ambiguous [41].

Several potential long(er)-term outcomes of stimulant use have been suggested, including a mitigating risk of childhood stimulant treatment for mood or depression problems, anxiety, suicidal behavior, and SUD, and a potential increased risk of childhood stimulant treatment for psychosis and tics [42]. However, the previous findings have been hampered by relatively weak and heterogeneous study designs, issues regarding generalizability due to a limited scope, and questionable definitions of 'long-term' outcomes in terms of follow-up interval. Most studies used a follow-up interval of one year after start of stimulant treatment, which is a questionable definition of a long-term outcome, while studies should investigate adult outcomes with a long follow-up period (e.g., >10 years) to effectively inform treatment plans and monitor long-term risks and beneficial effects.

In one large naturalistic follow-up study, the Multimodal Treatment Study (MTA), short-term effects of medication use on symptom severity disappeared at follow-up 16 years later, as different childhood stimulant treatment groups showed no differences in adult ADHD symptom severity. Groups of childhood stimulant treatment were based on a threshold of at least 10 mg/day for at least 50% of days in between the six assessment intervals over a 10-year interval, and included consistent use (above the threshold in all intervals), inconsistent use (above the threshold in some but not all intervals), and negligible use (below the threshold in all intervals). The only difference observed was for adult height, where the group which was consistently treated with stimulants had shorter length compared to the groups with inconsistent and negligible stimulant treatment [43]. Therefore, findings from the MTA suggest that childhood stimulant treatment generally does not have long-term effects.

Nonetheless, stimulant treatment has been identified as a predictor for one long-term outcome: ADHD persistence [33]. Although this specific finding may reflect an association between childhood ADHD severity and ADHD persistence, as the most affected children may receive stimulant treatment, it is important to note that children treated with stimulant medication may represent a subgroup at heightened risk for different long-term outcomes compared to children with ADHD who did not use stimulant treatment in childhood. This may explain why stimulant treatment was not identified as a predictor in the MTA, as the different childhood medication groups did not significantly differ in childhood symptom severity (except for the negligible medication group with slightly lower parent-rated symptom severity, but no difference on teacher-rated symptom severity).

Ideally, long-term effects of stimulant treatment are investigated using a placebo-controlled design, but this is not a feasible approach. Therefore, a suitable approach to investigate the long-term outcomes of medication use in a clinically informative manner is to take several aspects of medication use into account. Notably, there is variation in stimulant treatment use, such as age at initiation, dose, and duration. Possibly, not necessarily stimulant treatment use (yes/no) is associated with long-term outcomes, but rather a combination of characteristics of medication use. For example, children with ADHD using a high dose of stimulant treatment at a young age were at a lower risk of developing SUD in adolescence, where individuals initiating stimulant treatment at a later age with a lower dose were not [44]. Therefore, multiple aspects of stimulant treatment should be considered when investigating its effects in contrast to use (yes/no; e.g., as in the MTA). A design including subgroups based on several aspects of stimulant treatment can investigate the joint effects on long-term outcomes, something which has not been done so far in previous studies. Accordingly, in **Chapter 6** of this thesis, adults with childhood ADHD were categorized in groups of stimulant treatment trajectories based on their stimulant treatment in childhood (i.e., start age, treatment duration, total dose, maximum dose, variability, and stop age) to investigate the long-term (> 10 years) effects of stimulant treatment, thereby investigating potential prediction profiles for the long-term outcomes of ADHD.

Machine learning techniques

In previous studies into predictors of long-term outcomes of ADHD, predictors have often been investigated in isolation, disregarding the additive effects of multiple predictors. Furthermore, most studies have used conventional statistical models assuming linearity between predictors and outcome, while it is probable that outcomes in ADHD are difficult to predict due to both complex relationships between predictors and outcome and interactions between predictors. For example, the risk for comorbid disruptive disorders in ADHD depends on the presence of autism-associated genetic variants which interact with environmental exposures, highlighting the importance of investigating several predictors and their interactions [45]. In contrast to conventional statistical models, machine learning models seem a promising approach to predict long-term outcomes of ADHD, as these can appropriately deal with non-linear relationships and interactions between predictors rather than investigating predictors in isolation [46]. Promising machine learning models with high predictive accuracy have been developed in several healthcare fields [47-49]. Although results from such models are not yet widely implemented in clinical practice, partly as many of those models are not yet tested in external samples, the promising results on predictive accuracy allude towards future clinical utility of prediction models. These models show promise for guidance of a personalized approach to care, including a good prognosis and prevention and treatment strategies, to reduce negative long-term outcomes [50].

In ADHD research, promising prediction models have been developed, although not yet clinically implemented, for diagnosing ADHD [51], decreasing time needed for screening [52], and for predicting methylphenidate treatment response [53]. Despite these promising results so far, hardly any models have been developed investigating early life predictors of adult outcomes in ADHD samples. Currently, this has only been attempted for the prediction of an adulthood SUD diagnosis using a random forest approach (AUC = .73), and for the prediction of adulthood methylphenidate related psychiatric symptoms using a logistic regression approach (AUC = .75), based on childhood and adolescent predictors for both models [54, 55]. This is a striking gap in the literature on ADHD, where prediction models for many long-term outcomes are missing [56]. Furthermore, given the availability of numerous different machine learning approaches, it is not immediately clear which is most suitable for a specific research question, and comparison of several established algorithms (such as ridge regression, support vector machine, random forest, and extreme gradient boosting) is desirable [57]. Thus, in **Chapter 7** of this thesis, a large set of childhood predictors was used to develop several machine learning models, to assess which could most adequately predict ADHD persistence and functioning (based on 41 outcome measures tapping into 7 domains of functioning) in adulthood.

Study design

With one single exception (**Chapter 5**), all chapters in this thesis are based on an 18-year follow-up of a cohort study initiated as part of the Dutch branch of the International Multicenter ADHD Genetics (IMAGE) study [58]. After enrolment in the cohort (wave I, 2003-2005), previous follow-ups took place in 2009-2012 (wave II, NeuroIMAGE) and 2015-2016 (wave III, NeuroIMAGE2). Originally, both ADHD and control families were recruited. ADHD families had at least one child with ADHD combined type, while control families had at least one child without ADHD and did not have any first-degree family members diagnosed with ADHD. Inclusion criteria at wave I were: aged 5-19 years, Caucasian descent, IQ ≥ 70, and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, or known genetic disorders [58]. In contrast to the inclusion criteria of wave I, the follow-up waves allowed any ADHD subtype for newly recruited participants with ADHD [59], see Figure 1.1 for an overview of all follow-up waves.

Each wave involved extensive data collection. Wave I included a psychiatric diagnostic interview, behavioral questionnaires, neurocognitive assessment, and genetic phenotyping. Similar measures were collected in wave II and III, in addition to pharmacological data and magnetic resonance imaging (MRI) data. Pharmacological data collected at wave II were used to identify medication subgroups in **Chapter 6**, and measures collected at wave I were used as childhood predictors in **Chapter 7.**

For the current 18-year follow-up (2022-2024), all participants who took part in any of the previous waves were re-invited. During the extensive follow-up, data was collected via online questionnaires (self-report and other report) and two online video calls, including a psychiatric diagnostic interview and neurocognitive tests. Furthermore, pharmacy dispensing records were requested from the pharmacies. In most chapters of this thesis (**Chapter 2-4** and **Chapter 6-7**) the data from the 18-year follow-up were used to reflect adult outcomes.

In this thesis, participants belonged to one of three groups based on their diagnostic status and family at study entry. The childhood ADHD group consisted of children with an ADHD diagnosis at study entry, whereas the sibling group consisted of children without an ADHD diagnosis at study entry with a sibling with an ADHD diagnosis at study entry. Participants in the control group did not have an ADHD diagnosis at study entry nor any siblings with an ADHD diagnosis.

Thesis outline

The aims of this thesis are to map the nature and severity of the long-term outcomes of an ADHD diagnosis in childhood (**Part I**) and to identify predictors for the course of ADHD (**Part II**).

In **Part I**, the long-term outcomes in adulthood of childhood ADHD are investigated. First, **Chapter 2** provides a comprehensive overview of long-term outcomes, comparing outcomes of adults with childhood-diagnosed ADHD, their siblings without childhood-diagnosed ADHD, and controls without childhood-diagnosed ADHD. Specifically, in **Chapter 3**, we focus on differences in adult medication use (psychotropic and somatic medication) between adults with childhood ADHD, their siblings, and controls. Following this, in **Chapter 4**, we investigate differences between males and females in long-term outcomes of ADHD by testing the moderation of sex, and exploring the moderating of gender-expression.

Subsequently, **Part 2** describes predictors of long-term outcomes of childhood ADHD. **Chapter 5** includes a meta-analysis and systematic review of all currently known predictors of prevalent psychiatric outcomes of ADHD, including ADHD persistence, SUD, CD, antisocial personality disorder, MDD, and anxiety disorders. Thereafter, in **Chapter 6**, adults with childhood ADHD are categorized in groups of stimulant treatment trajectories based on their stimulant treatment in childhood (i.e., age at initiation, treatment duration, total dose, maximum dose, variability, and stop age) as potential prediction profiles for long-term outcomes, and the observed trajectory groups are compared on the long-term outcomes of ADHD. Finally, in **Chapter 7**, we compare several machine learning techniques to a conventional statistical approach to explore the added value of using a machine learning approach in predicting ADHD persistence and functioning in adulthood using childhood characteristics.

PART 1

Long-term outcomes of childhood ADHD



CHAPTER 2

Growing up with ADHD: findings from an 18-year longitudinal follow-up study of adults with childhood ADHD, their siblings, and controls

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Abstract

Background. The prevalent childhood-onset disorder attention-deficit/hyperactivity disorder (ADHD) (5-7%) poses risks for adult functioning, which should be identified with long-term prospective follow-up studies including a broad range of outcomes.

Methods. Differences in outcomes (measures of psychiatric status, behavioral/emotional problems, academic/professional functioning, adaptive functioning, neurocognition, physical health, healthcare service use) were investigated in an 18-year follow-up study of adults with childhood ADHD (n = 154, $M\pm SD$ age = 27.4±3.7, 68% males), their siblings without childhood ADHD (n = 138, $M\pm SD$ age = 29.6±4.4, 35% males), and controls (n = 129, $M\pm SD$ age = 28.2±3.5, 40% males). Post-hoc tests investigated whether observed differences between the ADHD group and controls may be driven by a current ADHD diagnosis, by comparing persistent ADHD, remitted ADHD, and control groups.

Results. Childhood ADHD was related to worse functioning in adulthood on >60% of outcomes across all domains with small to large-sized effects (e.g., moderate/large differences in increased rates of ADHD and depression, externalizing problems, autistic traits, and worse neurocognitive outcomes). Siblings showed comparable functioning to controls. Persistent ADHD showed worse functioning on specific outcomes in the psychiatric, behavioral/emotional, adaptive, and physical health domains, as compared to remitted ADHD. Both ADHD groups had worse functioning compared to controls.

Conclusions. Childhood ADHD increased the risk of worse functioning in adulthood. Siblings of the childhood ADHD group were not at risk for adverse outcomes. The current study identifies childhood ADHD as a risk condition for poorer long-term functioning, although substantial heterogeneity in outcomes across groups was noted. Heterogeneity within the childhood ADHD group seemed partly attributable to a current ADHD diagnosis.

Key words: ADHD, longitudinal, adults, children, real-world functioning, siblings

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by hyperactive-impulsive and/or inattentive behaviors, with prevalence estimate rates ranging between 3% to 14%, depending on the definition used [60]. The developmental trajectory of ADHD from childhood into adulthood is highly heterogeneous [3], ranging from full remission to persistence of ADHD with adverse sequelae of which psychiatric outcomes are most intensively studied [4].

Currently, prospective cohort studies show that adults with childhood ADHD are 1.48 to 4.32 times more often diagnosed with other mental disorders, including major depressive disorder (MDD), anxiety disorder, substance use disorder (SUD), and/or antisocial personality/conduct disorder [16]. Behavioral and emotional difficulties not qualifying for a full mental diagnosis are also seen in adults with a childhood diagnosis of ADHD, such as increased levels of emotional dysregulation and the presence of autistic traits [17]. Furthermore, childhood ADHD is associated with lower academic and professional achievement, as these adults were 3.7 times more likely to not finish high school, and 1.5 times more likely to receive public assistance [16, 18, 19]. Further, 65% of adults with ADHD in childhood face functional impairments, for example, worse social functioning and reduced quality of life compared to non-ADHD controls [4, 18]. The few prospective studies on neurocognitive functioning in adults with childhood-diagnosed ADHD show persistent poorer executive functioning [22, 23]. Finally, growing evidence suggests childhood ADHD is linked to poorer physical health, with increased risk for injury, obesity, and somatic conditions [24-26]. Overall, a childhood diagnosis of ADHD increases risk for poor long-term outcomes.

Although a substantial number of prospective cohort studies have identified impairments in adulthood, additional work is required for three reasons. First, thus far no prospective cohort studies have investigated long-term outcomes of siblings of children with ADHD without an ADHD diagnosis. These siblings are an important group, sharing half of their genetic material as well as part of their environment with the affected siblings. This is notable as ADHD shows strong familial clustering, which is driven by genetic factors (heritability ~80%) and shared environmental factors [1, 61]. Therefore, the siblings of children with ADHD are at an increased risk for the development of ADHD, and potentially also for (some of) the negative long-term outcomes of ADHD. Indeed, they show more ADHD-related traits compared to children without a sibling with an ADHD diagnosis and an intermediate neurocognitive profile which falls between the profile of siblings with ADHD and unrelated peers without ADHD [15, 62]. A design including children with ADHD, their siblings, and controls can indicate differences in diagnosis specific outcomes that are not attributable to familial vulnerability, and hint towards the potential contribution of shared genetics and childhood

environment to long-term outcomes. Second, the available studies do not provide a comprehensive understanding of the full range of long-term outcomes, targeting a limited set of outcomes, often disregarding many domains relevant for daily life functioning [28, 63]. Finally, generalizability of previous results is restricted, as most of the studies were conducted in the USA [28]. Non-USA studies may shed light on the possible impact that cultural and healthcare differences may have on the long-terms outcomes of ADHD [34, 64].

The aim of this 18-year follow-up of a large, well-defined sample of adults with childhood-diagnosed ADHD, their siblings (without childhood-diagnosed ADHD), and controls (without childhood-diagnosed ADHD) was to investigate a broad range of long-term outcomes of childhood ADHD, including measures of psychiatric status, behavioral and emotional problems, academic and professional functioning, adaptive functioning, neurocognition, physical health, and healthcare service use. Our first hypothesis was that children with an ADHD diagnosis, as compared to controls, would show worse results on the adulthood outcomes. Furthermore, our second hypothesis was that functioning of the siblings would fall between functioning of their brothers and sisters with a childhood ADHD diagnosis and controls. Finally, the current study examined whether functioning of adults with a childhood ADHD diagnosis was related to a current ADHD diagnosis by comparing outcomes of adults with persistent ADHD, those remitted from ADHD, and non-childhood ADHD controls.

Methods

Sample

In total, 421 participants were recruited from a longitudinal cohort study initiated as part of the Dutch branch of the International Multicenter ADHD Genetics (IMAGE) study [58], of which the current study is an 18-year follow-up. In previous follow-ups (wave II and wave III, see below), the cohort was enriched by recruiting additional families, mainly targeting girls with an ADHD diagnosis and control boys without an ADHD diagnosis, along with siblings from already participating families. After enrolment in the cohort (wave I, 2003-2005), follow-ups took place in 2009-2012 (wave II, NeuroIMAGE) and 2015-2016 (wave III, NeuroIMAGE2). Inclusion criteria at wave I were: aged 5-19 years, Caucasian descent, IQ ≥ 70, and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders or known genetic disorders [58]. Both ADHD and control families were recruited. ADHD families had at least one child with ADHD combined type, while control families had at least one child without ADHD and did not have any first-degree family members diagnosed with ADHD. In contrast to the inclusion criteria of wave I, the follow-up waves allowed any ADHD subtype for newly recruited participants with ADHD [59]. In the current follow-up (wave IV,

2021-2024), all participants who participated in any of the previous waves were invited [58, 59].

Outcomes at Follow-Up (wave IV)

The assessments targeted the following outcome domains: 1) psychiatric status, 2) behavioral and emotional problems, 3) academic and professional functioning, 4) adaptive functioning, 5) neurocognitive functioning, 6) physical health, and 7) healthcare service use. All domains were assessed using several measures. Table S1 provides a description of the instruments used, selected based on strong psychometric characteristics, and the derived dependent variables. Also, two custom-made questionnaires were used to assess: 1) diet (domain physical health), using a visual analogue scale to assess diet health and adherence to diet advice of the Netherlands Nutrition Centre; and 2) number of visits to healthcare institutions in the last year (domain healthcare service use), using an extensive list of all healthcare institutions, including all medical specialists. See the study's registration on the Open Science Framework (OSF) for further details https://doi.org/10.17605/OSF.IO/5Y29Q.

Demographic information was assessed through self-report, including 1) current living situation and 2) information on the participant's offspring, if applicable including number of children, their birth date, sex, and any diagnoses. Medication use (domain healthcare service use) of one full year (the most recent full year available) was assessed using pharmacy dispending records. The year preceding study participation was chosen. However, if the most recent full year overlapped more than a month with the period of the COVID pandemic with health-care related restrictions (February 2020 until February 2022) [65-67], the year before the start of the COVID pandemic was chosen (January 2019 to January 2020) to obtain generalizable information on medication use. Current use of ADHD medication (yes/no) was based on the presence of at least one prescription of amphetamines, methylphenidate, or atomoxetine, using anatomical therapeutic chemical codes. Current general medication use was captured by the total number of different anatomical therapeutic chemical (ATC) codes prescribed.

Procedure

Before assessment took place, all participants signed informed consent. Assessments comprised self-reported online questionnaires (110-118 minutes), other-reported online questionnaires (20 minutes), and two (secured) video calls (30-100 and 76 minutes, respectively), see Table S2.1 for included measures at each assessment part.

The assessments started with the participant's completion of the self-reported online questionnaires. The participants forwarded the link for the other-reported questionnaires to, preferably, their significant other, otherwise their parents or

someone else closest to them. Before assessments by video call took place, participants completed online screening questions of the Structured Clinical Interview for DSM-5 Disorders (SCID-5) modules MDD, anxiety disorders, and antisocial personality disorder (ASPD) [68], as these psychiatric disorders are most prevalent in adults with childhood ADHD [28]. The SCID-5 module SUD was screened using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-Lite) [69], administered during the first video call assessment. The ASSIST-Lite provides a reliable indication of problematic substance use. If the screening questions (SCID-5 or ASSIST-Lite) yielded scores indicative of any diagnosis, the corresponding full SCID-5 module (i.e., MDD, anxiety disorder, ASPD, SUD) was assessed via an interview. The diagnostic interview included the SCID-5 ADHD module for all participants. This interview was administered only by researchers certified and trained in SCID-5 administration with at least a master's degree in a relevant field.

During the second video call, assessment of the cognitive tests took place. Trained researchers administered tests according to a standardized protocol and using standardized instructions. Participants were instructed to call from a laptop/computer (or tablet if no laptop/computer was available), with a webcam and proper internet connection, and be alone in a room without any distractions. Finally, pharmacy dispensing records were requested from the pharmacies of participants who gave permission to do so.

The study procedure was similar for all participants. However, if participants were unwilling to participate in the video calls, they were allowed to only complete the online questionnaires to increase participant retention. The study was approved by the local medical ethics committee of the Amsterdam Universities Medical Center (ABR NL77520.029.21). Participants provided informed consent, all data was pseudo anonymized, and participants received 25 euros after completion.

Imputation

Multiple imputation, including parcel summary scores of online questionnaires and video call measures, was used to impute missing outcome variables with a maximum of 10% missing data using the mice package in R (v3.19.0) [70]. The imputation model included all individual items used to construct all outcome variables used in the analyses (see Table S2.1). In addition to the parcel summary scores, family and sex were included as auxiliary variables to support imputation. Generally, predictive mean matching was used as imputation method, except for the outcome variables derived from the diagnostic interview (ADHD, MDD, anxiety disorders, ASPD, SUD; including binary data) for which logistic regression was used and the Pittsburgh Sleep Quality Index (PSQI; including time and date data) for which classification and regression trees were used. A maximum of 10

iterations were used. Imputation was evaluated by trace plots and density plots to check for convergence and realistic distributions.

Percentage of missing data across all outcomes of the online questionnaires and video calls varied between 0-10% for the childhood ADHD group, 0-9% for the siblings, and 0-9% for the controls. Pharmacy data were not imputed as the percentage of missing data exceeded 10%, with 32 participants (8%) not providing consent to obtain their pharmacy records, and pharmacies failing to provide the required information of another 55 participants (13%) despite three reminders being sent out. Even though the average fraction of missing data was 6% across outcome variables used in the analysis, we did not choose to impute 6 different datasets but based on the recommendation to impute as many datasets as the percentage of participants with any missing data (max 10%), 10 imputed datasets were created [71, 72]. The analyses were rerun 10 times using each imputed dataset and subsequently the summary statistics of each analysis were pooled according to Rubin's rules [73]. Specifically, to obtain pooled main effects, the testModels() function was used from the mitml package (v0.4-5) [74]. To obtain the pooled contrasts, the pool() function was used from the mice package (v3.19.0) [70]. P-values were calculated after pooling.

Statistical analyses

All statistical analyses were run using Generalizing Estimating Equation (GEE) from the geepack package in R (v1.3.13) [75]. GEE is a suitable approach to account for the familial dependency in the data caused by the inclusion of siblings (i.e., possible siblings in the same group or across groups). However, to determine the most suitable correlation structure we tested several correlation structures (independence, exchangeable, autoregressive, and unstructured) and compared Quasi-likelihood Information Criterion's (QIC), which was averaged across differently imputed datasets. The correlation structure with the lowest QIC values across outcomes was selected as correlation structure. Within the GEE the selected method reflected the distribution of the outcome data, where continuous outcomes were analyzed using a gaussian distribution (with identity link) and binary outcomes were analyzed using a binomial distribution (with logit link). All GEE models were checked for convergence by the absence of convergence warnings after running geeglm().

Attrition analyses were run to test representativeness of the retained sample compared to the initial sample at the earliest inclusion (IMAGE, wave I). The attrition analyses were run on data collected in wave I using GEE. Groups were compared on sex, age, estimated total intelligence quotient (TIQ; estimated by the Vocabulary, Similarities, Block Design and Picture Completion subtests of the Wechsler Intelligence Scale for Children [WISC-III] or WAIS-III) [76, 77], average educational level of both parents (or one parent, if only information on one parent

was available), parent-reported severity of symptoms of ADHD, oppositional defiant disorder, anxious/shy behavior (using scale N, A, and D of the Conners' ADHD rating scale long version [78], respectively), and behavioral and emotional difficulties (using the Strengths and Difficulties Questionnaire [79]; not assessed in controls). Parental educational level was based on the Dutch Verhage scale [80], based on the assessment in wave II as this was not assessed at wave I, assuming these levels did not differ between waves I and II.

Outcomes were compared across the three groups based on diagnostic status at study entry (mostly wave I): childhood ADHD, including all siblings of a family with an ADHD diagnosis at study entry, 2) siblings, including siblings of participants with a childhood ADHD diagnosis who themselves did not have an ADHD diagnosis at study entry, and 3) individuals from a control family. All numerical outcomes were log-transformed for the GEE analyses to reduce skewness and approximate normality. Outcomes with no variation or (quasi-)complete separation, where the outcome was predicted perfectly within any group (indicated by model termination or extreme odds ratios), were precluded from statistical testing [81]. Multicollinearity was not tested, as the models only included one predictor (diagnostic status at study entry) without covariates. Potential influential observations were checked by index plots of residuals to check for outliers and further explored by investigating the main effects of diagnostic status at study entry on outcomes while excluding the outliers (residuals > 3 SD from the mean of residuals). Using the pooled effect sizes (across 10 imputed datasets), the main effects of group were adjusted for multiple testing using false discovery rate correction (FDR) [82], applied within the 7 outcome domains, and only the FDR-corrected *p*-values are provided for the main effects of diagnostic group. For significant main effects of group, the pair-wise group comparisons (childhood ADHD group, siblings, and controls) were investigated. The pairwise group comparisons were not subjected to the FDR correction. Only the significant pairwise group comparisons of significant main effects are described in the results. Effect sizes were quantified by calculating odds ratios (OR) for categorical outcomes, and standardized betas for continuous outcomes. The magnitude of the standardized beta's was interpreted as group difference using similar threshold levels as used to interpret Cohen's *d* (small = 0.2 to 0.5, moderate = 0.5 to 0.8, large ≥ 0.8) [83].

Additional analysis tested whether differences in long-term outcomes between those with a childhood ADHD diagnosis and controls (at study entry) were related to their current ADHD status (at follow-up), by comparing participants with persistent ADHD (childhood ADHD group with current ADHD), remitted ADHD (childhood ADHD group without current ADHD), and controls without current ADHD. These group differences were tested using the same GEE analyses described previously. As only the outcomes with significant main effects of group (ADHD, sibling, control) were included in the post hoc analyses, the post hoc analyses were

not additionally subjected to FDR correction. All analyses were performed in R (v4.3.0) [84].

Results

In order to determine the correct correlation structure, several correlation structures were tested (i.e., independence, exchangeable, autoregressive, and unstructured). The unstructured correlation structure did not converge. The independent correlation structure (which assumes no correlation within clusters) showed the lowest average QIC across all outcomes. Therefore, the GEE models were run with an independent correlation structure.

Attrition analysis

The current follow-up successfully included 26% of participants of the childhood ADHD group (*n* = 154), 34% of the sibling group (*n* = 138), and 38% of the control group (*n* = 129) of wave I. The mean follow-up period was 17.6 years (*SD* = 0.8) from wave I to the current follow-up. The most important reasons for drop out were outdated contact information (30%), no interest in participating (13%), unresponsiveness (13%), no time (12%), and personal problems (6%).

Table S2.2 shows the characteristics of the initial groups at wave I and retained groups, along with the attrition analyses testing representativeness of the retained sample. The retained childhood ADHD group (wave IV) did not differ from the initial childhood ADHD group in wave I in terms of sex, age, estimated TIQ, parental education level, ODD symptoms, anxious/shy symptoms, and behavioral and emotional difficulties, except for ADHD symptom severity, where the retained childhood ADHD group showed higher ADHD symptom severity at wave I than the initial childhood ADHD group (Wald χ^2 = 4.36, p = .037; initial *M*±*SD* = 75.3±9.8; retained *M*±*SD* = 77.3±9.3). Retained siblings (wave IV) were similar to the initial sibling group on any of the wave I measures except for TIQ, where average estimated TIQ was higher in the retained sibling group than in the initial sibling group (Wald χ^2 = 5.66, p = .017; initial *M*±*SD* = 102.1±11.3; retained *M*±*SD* = 105.2±10.7). Retained controls (wave IV) were similar to the initial control group in wave I on all measures.

Group characteristics

The final successfully retained sample included 154 participants with childhood ADHD (*M*±*SD* age = 28.7±3.7, 68% males), 138 siblings (*M*±*SD* age = 29.6±4.4, 35% males), and 129 controls (*M*±*SD* age = 28.2±3.5, 40% males). The siblings were older than the controls (small difference; Table 2.1). Also, similarly to the rates at baseline, there were more males in the childhood ADHD group compared to the control and sibling group (OR = 3.08 [95% CI 1.89-5.01] and OR = 3.90 [95% CI 2.39-6.36, respectively). See Table S2.3 for a description of all follow-up outcomes

of the three groups. Across all outcomes, no collinearity was present (r <.9). Table 2.1 shows the main effects of group and the results of the pair-wise group comparisons obtained from the GGE analysis.

Individuals in the childhood ADHD group (33%) were more often single compared to those in the sibling group (17%; OR = 2.37 [95% CI 1.35-4.17]). Also, controls (28%) were more often single than siblings (OR = 1.84 [95% CI 1.03-3.30]). Furthermore, the childhood ADHD group (19%) had children less frequently compared to their siblings (43%; OR = 0.45 [95% CI 0.26-0.77]). Groups did not differ on the remaining demographic measures.

Group differences in long-term outcomes

A sensitivity power analysis in G*Power showed we were able to detect small to moderate effects (power = 0.80) based on our sample size (n = 421) with an estimated correlation of 0.6 between study entry and follow-up. Imputation seemed valid based on the trace and distribution plots and plausibility checks.

Psychiatric status

At follow-up, the childhood ADHD group, compared to the control and sibling group, was more often diagnosed with ADHD (childhood ADHD = 45%, controls = 9%, siblings = 11%; OR = 8.21 [95% CI 4.11-16.37] and OR = 6.73 [95% CI 3.66-12.38], respectively) and MDD (childhood ADHD = 18%, controls = 8%, siblings = 6%; OR = 2.91 [95% CI 1.31-6.42] and OR = 4.71 [95% CI 1.99-11.16], respectively). No other group differences were observed for psychiatric status.

Behavioral and emotional problems

The childhood ADHD group showed, compared to controls, more severe self- and other-reported ADHD symptoms, externalizing symptoms, and autistic traits (large differences); mood dysregulation, physical and social aggression (moderate differences); internalizing problems, callous-unemotional traits, rule-breaking behavior, tobacco use, and gaming addiction symptoms (small differences).

The comparison between the childhood ADHD group and their siblings revealed highly similar differences as the comparison with controls. Compared to their siblings, the childhood ADHD group reported more severe self- and other-reported ADHD symptoms, externalizing symptoms, and autistic traits (large differences); physical aggression, gaming addiction symptoms (moderate differences); internalizing problems, mood dysregulation, callous-unemotional traits, rule-breaking behavior, social aggression, and tobacco (small differences).

The only group difference between siblings and controls was that siblings had more severe self- and other-reported ADHD symptoms, and autistic traits (small

differences). No other group differences were observed on the behavioral and emotional problems measures.

Academic and professional functioning

The childhood ADHD group completed a lower educational level compared to the control and sibling group (moderate differences). No other group differences were found for academic and professional functioning.

Adaptive functioning

The childhood ADHD group, compared to controls and siblings, showed more self-perceived stress, took more risks, had worse social functioning, emotional wellbeing, and lower quality of life (outlook and relationships) (small differences). No other group differences were observed on the adaptive functioning measures.

Neurocognitive functioning

The childhood ADHD group differed from both controls and siblings on assessed estimated TIQ, verbal short-term memory, verbal long-term memory, working memory, and letter fluency, with the childhood ADHD group scoring lower on all measures. Observed group differences were small, except for moderate differences for working memory and letter fluency compared to controls, and verbal short-term memory and long-term memory compared to siblings.

Physical health

The childhood ADHD group, compared to controls, reported worse general health perceptions, higher body mass index (BMI), and eating a less healthy diet (small differences). Also, the childhood ADHD group showed a worse adherence to the Dutch recommended diet compared to controls (moderate difference) and compared to their siblings (small differences). Finally, the childhood ADHD group showed more severe sleep problems compared to the control and sibling group (small differences).

The sibling group had a higher BMI, worse adherence to the Dutch recommended diet, and ate a less healthy diet compared to controls (small differences). No other group differences were found for physical health.

Healthcare service use

The childhood ADHD group was more likely to use ADHD medication compared to controls (OR = 8.35 [95% CI 2.83-24.63]) and their siblings (OR = 5.89 [95% CI 2.36-14.68]). No other group differences were observed on the measures of healthcare service use.

Comparing significant outcomes at follow-up in relation to current ADHD status

Additionally, we tested whether a current ADHD diagnosis drove the significant differences between childhood ADHD and controls. See Table S2.4 for a description of the demographics, baseline and follow-up measures for participants with persistent ADHD, remitted ADHD, and controls without a current ADHD diagnosis. For a wide range of outcomes, results were not driven by current ADHD status, as outcomes of participants with persistent ADHD and those with remitted ADHD did not differ, and both the persistent and remitted group had worse outcomes compared to controls, though the effect sizes of the differences were larger for the persistent ADHD group (Table 2.1). However, a few exceptions were noted: the group with persistent ADHD showed worse long-term outcomes compared to the remitted group and controls without a current ADHD diagnosis for MDD, internalizing problems, perceived stress, sleep quality and general health perceptions. Also, compared to the remitted group and controls, the persistent ADHD group was more often male compared to controls.

Sensitivity analyses excluding outliers

Index plots of residuals identified some outliers (mean proportion of outliers = 0.02), which may potentially influence GEE model performance. Therefore, sensitivity analyses excluded all observations with residuals > 3 SD from the mean of residuals. Generally, findings remained robust, except the main effect of diagnostic status at study entry became significant for some outcomes (i.e., risk taking and being employed), and the main effect of diagnostic status at study entry of life outlook (quality of life) became non-significant.

Table 2.1. *Pairwise group comparisons of outcome measures for participants diagnosed with ADHD in childhood, their siblings, and controls*

	Wald χ^2 of group effect[a]	Pairwise group comparisons childhood ADHD (A), siblings (S) and controls (C)	Post-hoc pairwise group comparisons persistent ADHD (PA), remitted ADHD (RA) and controls without ADHD (TDC)[b]	ß TDC vs CA	ß SB vs CA	ß TDC vs SB
Demographics						
Age	Wald χ^2=4.20*	S > C	N/A	0.14	-0.22	0.36
Male	Wald χ^2=17.28***	A > S, C	PA, RA > TDC	3.08 (OR)	3.90 (OR)	0.79 (OR)
Family status						
Single	Wald χ^2=4.57*	A, C > S	N/A	1.29 (OR)	2.37 (OR)	0.54 (OR)
Cohabitation	Wald χ^2=0.13			0.94 (OR)	0.88 (OR)	1.07 (OR)
Married	Wald χ^2=5.93*	S > A, C	N/A	0.88 (OR)	0.43 (OR)	2.08 (OR)
Children at home[c]	Wald χ^2=0.76			0.53 (OR)	0.65 (OR)	0.81 (OR)
Co-parenting[c]	Wald χ^2=0.41			0.58 (OR)	1.77 (OR)	0.33 (OR)
Living at home with parents/caregivers	Wald χ^2=1.36			0.88 (OR)	1.77 (OR)	0.50 (OR)
Children (yes/no)	Wald χ^2=4.36*	S > A	N/A	0.70 (OR)	0.45 (OR)	1.58 (OR)
Number of children[c]	Wald χ^2=0.62			0.24	0.02	0.22
Children with an ADHD-diagnosis[d]	NA[d]	-	-	-	-	-
Children with any diagnosis other than ADHD[d]	Wald χ^2=2.27			2.06 (OR)	4.08 (OR)	0.50 (OR)

	Wald χ^2 of group effect[a]	Pairwise group comparisons childhood ADHD (A), siblings (S) and controls (C)	Post-hoc pairwise group comparisons persistent ADHD (PA), remitted ADHD (RA) and controls without ADHD (TDC)[b]	ß TDC vs CA	ß SB vs CA	ß TDC vs SB
Psychiatric status (SCID-5)						
DSM-5 ADHD	Wald χ^2=29.22***	A > S, C	PA > RA, TDC	8.21 (OR)	6.73 (OR)	1.22 (OR)
DSM-5 MDD	Wald χ^2=7.89**	A > S, C	PA > RA, TDC	2.91 (OR)	4.71 (OR)	0.62 (OR)
DSM-5 any anxiety disorder	Wald χ^2=2.26			1.44 (OR)	2.17 (OR)	0.66 (OR)
DSM-5 ASPD	NA[d]	-	-	-	-	-
DSM-5 any SUD	Wald χ^2=0.76			1.60 (OR)	1.53 (OR)	1.05 (OR)
Behavioral and emotional problems						
ADHD index, Self-reported (CAARS)	Wald χ^2=34.20***	A > S > C	PA > RA > TDC	0.91	0.61	0.3
ADHD index, Other-reported (CAARS)	Wald χ^2=44.63***	A > S > C	PA > RA > TDC	1.03	0.78	0.25
Externalizing problems (ASEBA-ASR)	Wald χ^2=28.84***	A > S, C	PA > RA > TDC	0.81	0.70	0.10
Internalizing problems (ASEBA-ASR)	Wald χ^2=5.18**	A > S, C	PA > RA, TDC	0.33	0.35	-0.02
Autistic traits (ASBQ)	Wald χ^2=44.51***	A > S > C	PA > RA > TDC	1.06	0.78	0.28
Mood dysregulation (ARI)	Wald χ^2=10.55***	A > S, C	PA > RA > TDC	0.53	0.46	0.07
Callous-unemotional traits (ICU)	Wald χ^2=7.05**	A > S, C	PA, RA > TDC	0.44	0.27	0.17
Rule-breaking behavior (STAB)	Wald χ^2=5.76**	A > S, C	PA, RA > TDC	0.33	0.38	-0.06
Physical aggression (STAB)	Wald χ^2=18.90***	A > S, C	PA, RA > TDC	0.71	0.62	0.1

	Wald χ^2 of group effect[a]	Pairwise group comparisons childhood ADHD (A), siblings (S) and controls (C)	Post-hoc pairwise group comparisons persistent ADHD (PA), remitted ADHD (RA) and controls without ADHD (TDC)[b]	ß TDC vs CA	ß SB vs CA	ß TDC vs SB
Social aggression (STAB)	Wald χ^2=10.06***	A > S, C	PA, RA > TDC	0.53	0.34	0.19
Tobacco use (ASSIST-Lite)	Wald χ^2=3.99*	A > S, C	PA, RA > TDC	0.31	0.31	0.00
Alcohol use (ASSIST-Lite)	Wald χ^2=2.99			0.22	0.28	-0.06
Drug use (ASSIST-Lite)	Wald χ^2=1.11			0.12	0.19	-0.07
Gaming addiction symptoms (GAS)	Wald χ^2=9.52***	A > S, C	PA, RA > TDC	0.47	0.53	-0.05
Academic and professional functioning						
Education Verhage	Wald χ^2=21.08***	C, S > A	TDC > RA, PA	-0.75	-0.59	-0.16
Repeated grade (primary and secondary education)	Wald χ^2=2.92			1.82 (OR)	1.13 (OR)	1.61 (OR)
Employed	Wald χ^2=1.61			0.60 (OR)	0.5 (OR)	1.19 (OR)
Number of times switched jobs	Wald χ^2=1.22			0.17	0.15	0.02
Adaptive functioning						
Perceived stress (PSS)	Wald χ^2=7.83**	A > S, C	PA > RA, TDC	0.45	0.33	0.12
Risk-taking (DOSPERT)	Wald χ^2=3.05			0.26	0.03	0.23
Risk perception (DOSPERT)	Wald χ^2=1.63			-0.22	-0.22	0.00

	Wald χ^2 of group effect[a]	Pairwise group comparisons childhood ADHD (A), siblings (S) and controls (C)	Post-hoc pairwise group comparisons persistent ADHD (PA), remitted ADHD (RA) and controls without ADHD (TDC)[b]	ß TDC vs CA	ß SB vs CA	ß TDC vs SB
Social functioning (SF36)	Wald χ^2=6.52**	C, S > A	TDC > RA, PA	-0.39	-0.35	-0.04
Emotional wellbeing (SF36)	Wald χ^2=6.13**	C, S > A	TDC > RA > PA	-0.42	-0.25	-0.17
Quality of life – Outlook (AAQoL)	Wald χ^2=4.01*	C, S > A	TDC > RA > PA	-0.32	-0.27	-0.05
Quality of life – Relationships (AAQoL)	Wald χ^2=5.42*	C, S > A	TDC > RA, PA	-0.38	-0.30	-0.08
Significant life events (after age 16) (LTE)	Wald χ^2=1.56			0.05	-0.15	0.20
Creative achievement (CAQ)	Wald χ^2=2.00			-0.06	0.16	-0.22
Neurocognitive functioning						
Estimated TIQ (WAIS)	Wald χ^2=9.25***	C, S > A	TDC > RA, PA	-0.5	-0.36	-0.15
Short-term memory – digits (WAIS)	Wald χ^2=4.94**	C, S > A	TDC > RA	-0.36	-0.28	-0.07
Short-term memory – verbal (15WT)	Wald χ^2=14.89***	C, S > A	TDC > RA, PA	-0.48	-0.61	0.13
Long-term memory (15WT)	Wald χ^2=12.11***	C, S > A	TDC > RA, PA	-0.47	-0.56	0.09
Working memory (WAIS)	Wald χ^2=14.86***	C, S > A	TDC > RA, PA	-0.63	-0.43	-0.20
Letter fluency score (COWAT)	Wald χ^2=8.55***	C, S > A	TDC > RA, PA	-0.51	-0.27	-0.24
Physical health						
BMI	Wald χ^2=7.98**	A, S > C	PA, RA > TDC	0.44	0.16	0.28

	Wald χ^2 of group effect[a]	Pairwise group comparisons childhood ADHD (A), siblings (S) and controls (C)	Post-hoc pairwise group comparisons persistent ADHD (PA), remitted ADHD (RA) and controls without ADHD (TDC)[b]	ß TDC vs CA	ß SB vs CA	ß TDC vs SB
MET minutes per week (IPAQ)	Wald χ^2=2.26			0.21	0.26	-0.05
General health perceptions (SF36)	Wald χ^2=3.54			-0.32	-0.17	-0.15
Physical functioning (SF36)	Wald χ^2=0.61			-0.10	-0.12	0.02
Pain (SF36)	Wald χ^2=2.13			-0.24	-0.19	-0.04
Energy/vitality (SF36)	Wald χ^2=1.84			-0.21	-0.04	-0.17
Role limitations due to physical health (SF36)	NA[d]	-	-	-	-	-
Role limitations due to emotional problems (SF36)	NA[d]	-	-	-	-	-
Sleep quality (PSQI)	Wald χ^2=4.51*	A > S, C	PA > RA, TDC	0.30	0.34	-0.04
Healthy diet	Wald χ^2=4.19*	C > S, A	TDC > PA	-0.33	-0.09	-0.24
Diet adherence	Wald χ^2=14.08***	C > S > A	TDC > RA, PA	-0.61	-0.31	-0.3
Healthcare service use						
Number of visits to health and safety doctors and/or the employee insurance agency last year	Wald χ^2=0.46			0.05	0.1	-0.05
Number of visits to mental healthcare institutes last year	Wald χ^2=2.33			0.28	0.26	0.02

	Wald χ^2 of group effect[a]	Pairwise group comparisons childhood ADHD (A), siblings (S) and controls (C)	Post-hoc pairwise group comparisons persistent ADHD (PA), remitted ADHD (RA) and controls without ADHD (TDC)[b]	ß TDC vs CA	ß SB vs CA	ß TDC vs SB
Number of visits to physical healthcare institutes last year	Wald χ^2=1.30			0.17	0.2	-0.03
Current ADHD medication use	Wald χ^2=12.63***	A > S, C	PA, RA > TDC	8.34 (OR)	5.91 (OR)	1.41 (OR)
Current general medication use	Wald χ^2=2.93			0.32	0.15	0.17

Note. Non-significant group comparisons are not reported.
A = childhood ADHD group, AAQoL = adult ADHD quality of life questionnaire, ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, C = control group, CAARS = Conners' Adult ADHD Rating Scales, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LTE = long-term difficulties questionnaire, MDD = major depressive disorder, MET = metabolic equivalent, PA = ADHD-persistent group, PSS = perceived stress scale, PSQI = Pittsburgh sleep quality index, RA = ADHD-remittent group, S = sibling group, SF36 = short form health survey, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TDC = controls without ADHD at follow-up (typically developing controls), TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.
[a] FDR-corrected significance per domain, $^{*}p < .05$ $^{**}p < .01$ $^{***}p < .001$.
[b] For significant main effects of group (childhood ADHD and controls), post-hoc analyses were conducted using pair-wise group comparison between ADHD-persistent, ADHD-remittent, and typically developing control groups without an ADHD diagnosis at follow-up.

[c] Assessed only for participants with a child/children (n = 107).
[d] Due to insufficient variation or complete separation, no formal statistical testing was conducted for this outcome represented by N/A in the table.

Discussion

This 18-year follow-up of adults with childhood-diagnosed ADHD, their siblings, and controls investigated a broad range of long-term outcomes of ADHD across seven domains encompassing adult functioning. Compared to their siblings and controls, adults with childhood-diagnosed ADHD showed worse long-term outcomes on more than 60% of the outcomes with these differences translating into small to large-sized effects, while their other outcomes were similar. The siblings were similar to controls on long-term outcomes, except for worse outcomes compared to controls in terms of some behavioral and emotional problems (i.e., symptoms of ADHD, autism) and physical outcomes (i.e., higher BMI, worse diet). Furthermore, both adults with remittent and persistent childhood ADHD were at an increased risk of negative long-term outcomes, with the persistent ADHD group showing worse outcomes with larger effect sizes on the long-term outcomes for three out of seven domains.

Outcomes childhood ADHD

A childhood ADHD diagnosis was related to worse long-term outcomes compared to their siblings and controls across outcome domains with effect sizes ranging from small to large. Specifically, adults with childhood ADHD show the largest differences in outcomes compared to their siblings and controls in terms of psychiatric outcomes/symptoms, where large-sized group differences were observed for the risk for a DSM-5 diagnosis of ADHD or MDD, ADHD symptoms, externalizing problems, autistic traits, and treatment with ADHD medication, and moderate-sized group differences were observed for mood dysregulation, physical and social aggression, and a lower educational level. Compared to controls, moderate effects were found for neurocognitive outcomes (i.e., reduced letter fluency and worse working memory), and health outcomes (i.e., worse adherence to the Dutch recommended diet) [85, 86]. These results strengthen the findings of previous prospective cohort studies identifying childhood ADHD as risk condition for lower adult functioning [16, 17, 23, 28].

Importantly, despite significant differences in group averages on more than 60% of all outcomes, there was substantial overlap in the distributions of all outcome scores between the childhood ADHD, sibling and control groups (see Figures S2.1-S2.6). Notably, many differences between adults with childhood ADHD and controls comprised small effects. Also, several group averages of the childhood ADHD group were similar to means reported in normative studies or scores of the childhood ADHD group fell below clinical thresholds indicative of problem levels, which indicates that the majority of adults with childhood ADHD exhibit functioning comparable to controls. These findings may suggest that the majority of the adults with childhood ADHD has (partly) recovered from ADHD, been able to adapt by developing compensatory skills, such as self-regulatory skills, and/or

benefited from supportive environments [87, 88]. This contrasts with previous studies into long-term outcomes of ADHD reporting substantial long-term impairments of childhood ADHD [16, 17, 23, 28]. These inconsistent findings may partly reflect differences in the interpretation of results (whether or not emphasis is put on results reflecting poorer functioning), whether effect sizes of significant differences have been considered, and the range of functional outcomes assessed.

Our findings suggest that there is a subset of adults with childhood ADHD who show impairment in adulthood. The heterogeneity within the childhood ADHD group seems partly attributable to ADHD persistence, as the persistent ADHD group seems to carry the highest risk for adverse outcomes with larger effect sizes compared to controls and the remittent ADHD group. Specifically, the persistent ADHD group showed the most prominent differences (large effects) on the outcomes compared to the remitted ADHD group and controls on a MDD diagnosis, ADHD symptoms, externalizing and internalizing problems, and perceived stress, and additionally compared only to controls on autistic traits and direct aggression. Our prevalence of persistence (45%) matches the prevalences previously reported (33-64%; [28]), and our findings agree with previous studies linking ADHD persistence to impairments in adulthood [28, 63, 89]. Nonetheless, our finding that adults with remitted ADHD also showed an increased risk of negative long-term outcomes compared to controls, suggests that childhood ADHD acts as a risk factor for difficulties in adult functioning, even when diagnostic criteria are not met (see also Faraone et al. [4]), and developmental difficulties continue to affect adult functioning. Previous attempts to identify predictors for the negative long-term outcomes of ADHD that may identify factors underlying the heterogeneity in adult outcomes of childhood ADHD have not been very fruitful, with interpretation of existing research being hampered by clinical and methodological heterogeneity between studies [33, 63].

The role of siblings

The current study's familial design, including participants with ADHD in childhood and their siblings without an ADHD diagnosis in childhood, showed higher levels of functioning in siblings without an ADHD diagnosis in childhood with outcomes of this group being comparable to controls. Previous studies on siblings of children with ADHD primarily focused on psychiatric disorders, showing siblings of children with ADHD having an increased risk for adverse outcomes, such as ADHD and ODD [90]. The current results extend these findings into other outcome domains (i.e., behavioral and emotional problems, physical health), showing some differences with small effects compared to controls, including increased symptoms of ADHD and autism, higher BMI, and worse diet. Thus, the present findings show unaffected siblings (as assessed at inclusion) of adults with childhood ADHD are not at risk of negative long-term outcomes of ADHD other than some psychiatric symptoms and obesity. It should be mentioned however,

that the siblings included in our follow-up had higher IQ and less anxiety symptoms compared to the initial sample of siblings at study entry, leaving the possibility that some siblings with the highest risk of negative long-term outcomes have been lost to follow-up. Nonetheless, our findings of overall negligible negative long-term outcomes in siblings suggest that the negative long-term outcomes observed in those with ADHD in childhood are primarily diagnosis specific impairments, rather than impairments related to shared familial factors.

Beyond shared familial factors, adult functioning is likely influenced by unique genetic, environmental, and behavioral characteristics, as well as unique gene-environment interplays [91]. Potentially the same (shared) childhood environment may have different effects on the expression of ADHD behaviors, and therefore also on long-term outcomes, for siblings with different genetic predispositions for ADHD (e.g., adults diagnosed with childhood ADHD and their siblings not diagnosed with childhood ADHD) [92, 93]. It is likely that gene-environment interplays contribute to the differences in outcomes between participants with and without ADHD in childhood, where unaffected siblings may be less susceptible to impairment due to lower genetic predispositions and/or exposure to more unique (environmental) protective factors [94]. The role of both unique environmental factors and gene–environment interplay, as suggested by our results, are supported by twin studies [95, 96]. For example, evocative gene–environment correlations were found, where higher ADHD polygenic risk scores predicted more ADHD symptoms, which in turn predicted worse parenting behaviors, while siblings with less ADHD symptoms may be less likely to evoke these parenting behaviors [92]. This reciprocity between child and parental behavior may result in a negative spiral that can influence future behavioral expressions, unique environment, and functioning. Importantly, gene-environment interplay remains largely underexplored with respect to long-term outcomes of childhood ADHD, underscoring the need for future research.

Strengths and limitations

Some limitations are important to note. First, the sample included Caucasians only, limiting generalizability. Nonetheless, the results extend the findings from US-based studies. Second, most of the initial cohort was lost to follow-up. The retained childhood ADHD group had worse childhood ADHD severity compared to the initial ADHD group, suggesting the current outcomes bear particular relevance for children with more severe ADHD. Still, selective attrition seems limited, as the retained groups were similar to the initial cohort in important demographic and behavioral characteristics, implying the results are mostly generalizable to the initial cohort. Third, all assessments were done online via video calls rather than in controlled settings, so participants might have been more distracted. However, a standardized protocol was used, and remote neurocognitive testing seems valid

[97, 98]. Importantly, the current study has several strengths, including the long follow-up period and unique extensive coverage of outcome domains. Specifically, this study is among few studies looking at long-term neurocognitive and physical outcomes. Including both siblings and controls allowed for the investigation of potential effects of a shared genetic and childhood environment on long-term outcomes.

Conclusions

In conclusion, individuals in the childhood ADHD group showed worse outcomes as adults across several domains, although many differences translated into small effects. The siblings typically showed functioning similar to controls. The long-term outcomes of childhood ADHD include substantial heterogeneity, with some individuals showing comparable functioning to the adult general population, and others showing difficulties in daily life functioning. Future studies should investigate the risk and protective factors that may cascade into this heterogeneity and identify individuals most at risk. While this heterogeneity seems partly attributable to a current ADHD status, both remitted and persistent ADHD groups had an increased risk for long-term negative outcomes of childhood ADHD, suggesting that factors other than a current ADHD status may also explain heterogeneity in adult functioning, including childhood differences, genetic risk shared with the outcomes studied, sex, socioeconomic status, and history of stimulant treatment [63]. In sum, this long-term follow-up provides valuable insights and highlights the long-term impact of childhood ADHD into adulthood.

Table S2.1. *Description of outcomes, measures, and dependent variables derived*

Outcome	Measure and key reference	Dependent variable and range of scores	Description[a]	Assessment part	Figure 8.1[c]
Outcome domain: Psychiatric status					
DSM-5 ADHD	ADHD module of SCID-5 Disorders [99, 100]	Presence of DSM-5 ADHD	Structured interview assessing number of symptoms and presence of DSM-5 ADHD	Video call 1	
DSM-5 MDD	Depression module of SCID-5 Disorders [99, 100]	Presence of DSM-5 depression	Structured interview assessing number of symptoms and presence of DSM-5 depression	Video call 1	1
DSM-5 anxiety disorders	Anxiety module of SCID-5 Disorders [99, 100]	Presence of any of the DSM-5 anxiety disorders (i.e., either panic disorder, agoraphobia, social anxiety disorder, specific disorder, and/or GAD)	Structured interview assessing number of symptoms and presence of any of the DSM-5 anxiety disorders (i.e., either panic disorder, agoraphobia, social anxiety disorder, specific disorder, and/or GAD)	Video call 1	2
DSM-5 ASPD	ASPD module of SCID-5 Disorders [99, 100]	Presence of DSM-5 ASPD	Structured interview assessing number of symptoms and presence of DSM-5 ASPD	Video call 1	3
DSM-5 any SUD	SUD module of SCID-5 Disorders [99, 100]	Presence of any of the DSM-5 AUD and/or drug use disorders	Structured interview assessing number of symptoms and presence of any of the DSM-5 AUD and/or drug use disorders	Video call 1	4
Outcome domain: Behavioral and emotional problems					

Outcome	Measure and key reference	Dependent variable and range of scores	Description[a]	Assessment part	Figure 8.1[c]
ADHD symptoms	CAARS [78]	ADHD index score (range = 0 – 36)	Self-report questionnaire assessing DSM-related ADHD symptoms	Online questionnaire	5
ADHD symptoms - other report[b]	CAARS [78]	Other-reported ADHD index score (range = 0 – 36)	Other-report questionnaire assessing DSM-related ADHD symptoms	Online questionnaire	6
Externalizing problems	Externalizing problems subscale of ASEBA-ASR [101]	Externalizing problems score (range = 0 – 70)	Self-report questionnaire assessing aggressive, rule-breaking behavior, and intrusive behavior/problems	Online questionnaire	7
Internalizing problems	Internalizing problems subscale of ASBEA-ASR [101]	Internalizing problems score (range = 0 – 78)	Self-report questionnaire assessing somatic complaints, anxious/depressed and withdrawn behavior/problems	Online questionnaire	8
Autistic traits - other report[b]	ASBQ [85]	Other-reported autistic traits total score (range = 0 – 98)	Other-report questionnaire assessing autistic traits	Online questionnaire	9
Mood dysregulation	ARI [102]	Mood dysregulation total score (range = 0 – 12)	Self-report questionnaire assessing irritability as a measure of mood dysregulation	Online questionnaire	10
Callous and unemotional traits	ICU [103]	Callous and unemotional traits total score (range = 0 – 72)	Self-report questionnaire assessing callous and unemotional traits	Online questionnaire	11
Rule-breaking	Rule-breaking subscale of STAB [104]	Rule-breaking score (range = 0 – 44)	Self-report questionnaire assessing rule breaking behavior	Online questionnaire	12
Physical aggression	Physical aggression subscale of STAB [104]	Physical aggression score (range = 0 – 40)	Self-report questionnaire assessing direct/physical aggressive behavior	Online questionnaire	13
Social aggression	Social aggression subscale of STAB [104]	Social aggression score (range = 0 – 44)	Self-report questionnaire assessing indirect/social aggressive behavior	Online questionnaire	14

Outcome	Measure and key reference	Dependent variable and range of scores	Description[a]	Assessment part	Figure 8.1[c]
Tobacco use	Tobacco use subscale of ASSIST-Lite [69]	Tobacco use score (range = 0 – 30)	Self-report questionnaire assessing tobacco use problems	Video call 2	15
Alcohol use	Alcohol use subscale of ASSIST-Lite [69]	Alcohol use score (range = 0 – 36)	Self-report questionnaire assessing alcohol use problems	Video call 2	16
Drug use	Drug use subscale of ASSIST-Lite [69]	Drug use score (range = 0 – 36)	Self-report questionnaire assessing drug use problems	Video call 2	17
Game addiction	GAS [105]	Game addiction scale total score (range = 0 – 21)	Self-report questionnaire assessing addictive game use	Video call 2	18
Outcome domain: Academic and professional functioning					
Educational level	Dutch Verhage scale [80]	Dutch Verhage score (range = 1 – 7)	Classification of highest level of completed education level based on the Dutch Verhage categories. Higher scores indicate a higher level of completed education	Online questionnaire	19
Repeated grade	Custom made question	Ever repeated a grade (yes/no)	Self-report question assessing if a school year ever was repeated	Online questionnaire	
Employed	Custom made question	Currently employed (yes/no)	Self-report question assessing current (un)employment	Online questionnaire	20
Number of times switched jobs	Custom made question	Number of times switched jobs	Self-report question assessing how often jobs were switched	Online questionnaire	21
Outcome domain: Adaptive functioning					
Perceived stress	PSS [106]	Perceived stress total score (range 0 – 40)	Self-report questionnaire assessing perception of stress during the last month	Video call 2	22

Outcome	Measure and key reference	Dependent variable and range of scores	Description[a]	Assessment part	Figure 8.1[c]
Risk-taking	Risk-taking subscale of DOSPERT [107, 108]	Risk-taking total score (range = 30 – 210)	Self-report questionnaire assessing general and domain-specific risk preference	Online questionnaire	23
Risk perception	Risk-perception subscale of DOSPERT [107, 108]	Risk perception total score (range = 30 – 210)	Self-report questionnaire assessing perception of general and domain-specific risk	Online questionnaire	24
Social functioning	Social functioning subscale of SF-36 [109, 110]	Social functioning scale score (range = 0 – 100)	Self-report questionnaire assessing limitations in social activities because of physical or emotional problems. Higher scores indicate a more favorable health state	Online questionnaire	25
Emotional wellbeing	Emotional wellbeing subscale of SF-36 [109, 110]	Emotional wellbeing scale score (range = 0 – 100)	Self-report questionnaire assessing general mental health. Higher scores indicate a more favorable health state	Online questionnaire	26
Quality of life - life outlook	Life outlook subscale of AAQoL [111]	Quality of life - life outlook scale score (range = 0 – 100)	Self-report questionnaire assessing quality of life regarding life outlook. Higher scores indicate a more favorable level of quality of life	Online questionnaire	27
Quality of life - relationships	Relationships subscale of AAQoL [111]	Quality of life - relationships scale score (range = 0 – 100)	Self-report questionnaire assessing quality of life regarding relationships. Higher scores indicate a more favorable level of quality of life	Online questionnaire	28
Number of significant life events after age 16	Long-term Difficulties Questionnaire [112]	Total number of significant life events	Self-report questionnaire assessing number of significant life events after age 16	Online questionnaire	

Outcome	Measure and key reference	Dependent variable and range of scores	Description[a]	Assessment part	Figure 8.1[c]
		after age 16 (range = 0 – 21)			
Creative achievement	CAQ [113]	Creative achievement total score (range = 0 – 70)	Self-report questionnaire assessing presence of 10 domains of creative achievements. Higher scores indicate more creative achievements	Online questionnaire	
Outcome domain: Neurocognitive functioning					
Estimated Total IQ	Matrix Reasoning and Verbal module of WAIS-IV [114, 116]	Estimated Total IQ (range = 50 – 247)	Two-subtest short form to estimate total IQ. Higher scores indicate a higher total IQ	Video call 2	38
Short-term memory – digits	Digits Span module of WAIS-IV [114, 116]	Short-term memory score – digits (WAIS) (range = 0 – 8)	Total score of the Digit Span Forwards subtask from the Digit Span module. Higher scores indicate better short-term memory	Video call 2	
Short-term memory – verbal	First part of 15WT [117]	Short-term memory score – verbal (15WT) (range = 0 – 75)	Test assessing short-term memory, based on total number of correct short-term retention of 5 times auditory presentation of 15 words. Higher scores indicate better short-term memory	Video call 2	
Long-term memory	Second part of 15WT [117]	Long-term memory score (15WT) (range = 0 – 15)	Test assessing long-term memory, based on total number of correct words retained after 20 minutes.	Video call 2	

Outcome	Measure and key reference	Dependent variable and range of scores	Description[a]	Assessment part	Figure 8.1[c]
			Higher scores indicate better long-term memory		
Working memory	Digits Span module of WAIS-IV [114, 118]	Working memory score (WAIS) (range = 0 – 16)	Total score of the Digit Backwards and Digit Span Sequencing subtasks from the Digit Span module. Higher scores indicate better working memory	Video call 2	
Cognitive fluency	Dutch version of the COWAT [83]	Letter fluency score (COWAT) (range = 0 – ∞)	Test assessing letter fluency, based on total number of correct words produced across 3 letters (D, A, T). Higher scores indicate better letter fluency	Video call 2	
Outcome domain: Physical health					
BMI	Height and weight	BMI (range = 0 – ∞)	Height (in cm) and weight (in kg) based calculation of BMI	Online questionnaire	29
MET minutes per week	IPAQ [86]	MET minutes per week (range = 0 – 19278)	Self-report questionnaire assessing physical activity of the last week based on length, frequency, and intensity of physical activity. Higher scores indicate more physical activity	Video call 2	30
General health perceptions	General health perceptions subscale of SF-36 [109, 110]	General health perceptions scale score (range = 0 – 100)	Self-report questionnaire assessing general health perceptions. Higher scores indicate a more favorable health state	Online questionnaire	31

Outcome	Measure and key reference	Dependent variable and range of scores	Description[a]	Assessment part	Figure 8.1[c]
Physical functioning	Physical functioning subscale of SF-36 [109, 110]	Physical functioning scale score (range = 0 – 100)	Self-report questionnaire assessing limitations in physical activities because of health problems. Higher scores indicate a more favorable health state	Online questionnaire	32
Pain	Pain subscale of SF-36 [109, 110]	Pain scale score (range = 0 – 100)	Self-report questionnaire assessing bodily pain. Higher scores indicate a more favorable health state	Online questionnaire	33
Energy/vitality	Energy/vitality subscale of SF-36 [109, 110]	Energy/vitality scale score (range = 0 – 100)	Self-report questionnaire assessing vitality, energy, and fatigue. Higher scores indicate a more favorable health state	Online questionnaire	34
Role limitation due to physical problems	Role limitation due to physical problems subscale of SF-36 [109, 110]	Role limitation due to physical problems scale score (range = 0 – 100)	Self-report questionnaire assessing limitations in usual role activities because of physical health problems. Higher scores indicate a more favorable health state	Online questionnaire	
Role limitation due to emotional problems	Role limitation due to emotional problems subscale of SF-36 [109, 110]	Role limitation due to emotional problems scale score (range = 0 – 100)	Self-report questionnaire assessing limitations in usual role activities because of emotional problems. Higher scores indicate a more favorable health state	Online questionnaire	
Sleep quality	PSQI [120]	Sleep quality score (range = 0 – 21)	Self-report questionnaire assessing sleep quality during the last month	Video call 2	35
Healthy diet	Custom made question	Healthy diet score (range = 0 – 10)	Self-report question assessing diet healthiness on a visual analogue	Online questionnaire	36

Outcome	Measure and key reference	Dependent variable and range of scores	Description[a]	Assessment part	Figure 8.1[c]
			scale. Higher scores indicate a healthier diet		
Diet adherence	Custom made question	Diet adherence score (range = 1 – 10)	Self-report question assessing diet adherence based on the recommendations of The Netherlands Nutrition Centre on a visual analogue scale. Higher scores indicate a better adherence	Online questionnaire	37
Outcome domain: Healthcare service use					
Healthcare service use - health and safety doctors and/or the employee insurance agency	Number of visits to health and safety doctors and/or the employee insurance agency last year	Number of visits to health and safety doctors and/or the employee insurance agency last year (range = 0 - ∞)	Questionnaire assessing number of visits to health and safety service and/or employee insurance agency institutes during the last year	Online questionnaire	39
Healthcare service use - mental healthcare institutes	Number of visits to mental health institutes last year	Number of visits to mental healthcare institutes last year (range = 0 - ∞)	Questionnaire assessing number of visits to mental healthcare institutes	Online questionnaire	40
Healthcare service use - physical healthcare institutes	Number of visits to physical healthcare institutes last year	Number of visits to physical healthcare institutes last year (range = 0 - ∞)	Questionnaire assessing number of visits to 41 various physical health institutes	Online questionnaire	41

Outcome	Measure and key reference	Dependent variable and range of scores	Description[a]	Assessment part	Figure 8.1[c]
Current ADHD medication use	Pharmacy dispensing records	Current ADHD medication use	Based on the presence of at least one prescription of dexamphetamine, methylphenidate, or atomoxetine in the previous year	Pharmacy dispensing records	
Current general medication use	Pharmacy dispensing records	Current general medication use (range = 0 - ∞)	Based on summing the total number of different ATC codes prescribed in the previous year	Pharmacy dispensing records	

Note. All measures were self-report, unless otherwise specified, and based on raw scores, with the single exception of estimated TIQ. AAQoL = adult ADHD quality of life questionnaire, ADHD = attention-deficit/hyperactivity disorder, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self report, ASPD = antisocial personality disorder, ARI = affective reactivity index, ASSIST-Lite = alcohol, smoking and substance involvement screening tool – lite, ATC = anatomical therapeutic chemical, AUD = alcohol use disorder, BMI = body mass index, CAARS = Conners' adult ADHD rating scale, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, DSM-5 = diagnostic and statistical manual of mental disorders fifth edition, GAD = generalized anxiety disorder, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, TIQ = total intelligence quotient, MDD = major depressive disorder, MET = metabolic equivalent, PSS = perceived stress scale, PSQI = Pittsburgh sleep quality index, SCID-5 = structured clinical interview for dsm-5, SF-36 = short form health survey, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.

[a] The description includes score interpretation only if higher scores do not reflect worse functioning.

[b] Other reporter preferably was their significant other, and otherwise their parents or someone else close to them.

[c] The 41 measures corresponding to the x-axis in Figure 8.1.

Table S2.2. *Characteristics at wave I (IMAGE) of participants successfully retained and initial cohort tabulated according to diagnostic status at cohort entry*

	Childhood ADHD			Siblings			Controls		
M (SD)	Retained (*n* = 133)	Initial sample (*n* = 510)	Retained versus initial sample	Retained (*n* = 123)	Initial sample (*n* = 361)	Retained versus initial sample	Retained (*n* = 106)	Initial sample (*n* = 281)	Retained versus initial sample
Male, *n* (%)	100 (75%)	400 (78%)	Wald χ^2=0.62	46 (37%)	158 (44%)	Wald χ^2=1.70	39 (37%)	117 (42%)	Wald χ^2=0.71
Age	11.1 (2.8)	11.0 (2.8)	Wald χ^2=0.24	10.8 (3.5)	10.8 (3.6)	Wald χ^2=0.01	11.1 (3.3)	11.2 (3.3)	Wald χ^2=0.04
Estimated TIQ	100.7 (12.4)	98.9 (12.0)	Wald χ^2=1.81	105.2 (10.7)	102.1 (11.3)	Wald χ^2=5.66*	107.6 (10.4)	106.2 (10.4)	Wald χ^2=0.99
Parental education level[a]	5.2 (0.8)	5.2 (0.7)	Wald χ^2=0.26	5.1 (0.4)	5.2 (0.8)	Wald χ^2=0.05	5.3 (0.5)	5.3 (0.6)	Wald χ^2=0.13
Severity of ADHD symptoms	77.3 (9.3)	75.3 (9.8)	Wald χ^2=4.36*	50.4 (9.7)	51.0 (9.8)	Wald χ^2=0.28	46.6 (4.5)	46.6 (4.6)	Wald χ^2=0.01
ODD symptoms	66.1 (12.3)	66.1 (12.4)	Wald χ^2=0.00	49.2 (9.1)	51.0 (10.2)	Wald χ^2=3.30	47.2 (6.5)	47.1 (6.7)	Wald χ^2=0.01
Anxious/shy behavior	57.1 (13.4)	58.0 (13.7)	Wald χ^2=0.44	49.1 (8.7)	50.6 (10.3)	Wald χ^2=2.27	48.6 (8.4)	48.8 (7.9)	Wald χ^2=0.02
Behavioral and emotional difficulties[b]	18.9 (5.7)	18.9 (6.2)	Wald χ^2=0.01	6.7 (5.9)	7.2 (5.8)	Wald χ^2=0.42	N/A	N/A	N/A

Note. Differences in characteristics were tested only for participants included in wave I.
ADHD = attention-deficit/hyperactivity disorder, ODD = oppositional defiant disorder, TIQ = total intelligence quotient.
[a] Assessed in wave II (see main text).
[b] Not assessed for controls.
Significance levels denoted as $^*p < .05$

Table S2.3. *Outcomes of the three groups tabulated according to diagnostic status at cohort entry*

	Childhood ADHD (*n* = 154)	Sibling (*n* = 138)	Control (*n* = 129)
Demographics, *n* (%)			
Age, years (*SD*)	28.7 (3.7)	29.6 (4.4)	28.2 (3.5)
Male	104 (68%)	48 (35%)	52 (40%)
Family status			
Single	51 (33%)	24 (17%)	36 (28%)
Cohabitation	56 (36%)	54 (39%)	49 (38%)
Married	30 (19%)	50 (36%)	28 (22%)
Children at home[a]	12 (8%)	27 (20%)	24 (19%)
Co-parenting[a]	1 (3%)	1 (2%)	2 (6%)
Living at home with parents/caregivers	17 (11%)	9 (7%)	16 (12%)
Children (yes/no)	29 (19%)	47 (43%)	32 (25%)
Number of children, *M* (*SD*)[a]	1.8 (0.9)	1.7 (0.8)	1.6 (0.8)
Children with an ADHD-diagnosis[a]	3 (10%)	3 (6%)	0 (0%)
Children with any diagnosis other than ADHD[a]	8 (28%)	4 (9%)	5 (16%)
Psychiatric status, *n* (%)			
DSM-5 ADHD	70 (45%)	15 (11%)	11 (9%)
DSM-5 MDD	28 (18%)	8 (6%)	10 (8%)
DSM-5 any anxiety disorder	21 (14%)	14 (10%)	12 (9%)
DSM-5 ASPD	4 (3%)	0 (0%)	1 (1%)
DSM-5 any SUD	11 (7%)	9 (7%)	5 (4%)
Behavioral and emotional problems, *M* (*SD*)			
ADHD index (CAARS)	17.6 (5.8)	13.8 (5.2)	11.94 (6.2)
ADHD index, Other-reported (CAARS)	12.2 (7.1)	7.2 (5.2)	5.28 (5.2)
Externalizing problems (ASEBA-ASR)	13.3 (8.4)	7.9 (6.5)	6.65 (6.3)
Internalizing problems (ASEBA-ASR)	16.0 (13.0)	12.1 (10.1)	11.86 (10.4)
Autistic traits, Other-reported (ASBQ)	26.4 (14.4)	15.8 (11.9)	11.39 (11.1)
Mood dysregulation (ARI)	2.3 (2.5)	1.3 (1.6)	1.15 (1.6)
Callous-unemotional traits (ICU)	19.8 (6.6)	17.9 (6.3)	16.92 (6.2)
Rule-breaking behavior (STAB)	1.4 (2.5)	0.6 (1.6)	0.74 (2.0)
Physical aggression (STAB)	6.7 (5.5)	3.9 (3.2)	3.47 (3.7)
Social aggression (STAB)	7.2 (5.1)	5.6 (4.2)	4.69 (4.5)
Tobacco use (ASSIST-Lite)	4.5 (7.2)	2.7 (5.6)	2.74 (5.9)
Alcohol use (ASSIST-Lite)	4.6 (3.6)	3.7 (3.0)	3.96 (3.2)
Drug use (ASSIST-Lite)	2.1 (5.7)	1.2 (4.9)	1.55 (3.7)
Gaming addiction symptoms (GAS)	1.8 (3.1)	0.5 (1.5)	0.65 (1.9)
Academic and professional functioning			
Education Verhage, *M* (*SD*)	5.3 (1.2)	5.9 (0.8)	6.1 (0.8)
Repeated grade (primary and secondary education), *n* (%)	65 (42%)	54 (39%)	37 (29%)
Employed, *n* (%)	135 (88%)	128 (93%)	119 (92%)

	Childhood ADHD (*n* = 154)	Sibling (*n* = 138)	Control (*n* = 129)
Number of times switched jobs, *M* (*SD*)	2.7 (3.3)	2.2 (2.5)	2.1 (2.5)
Adaptive functioning, *M* (*SD*)			
Perceived stress (PSS)	12.8 (5.9)	10.8 (5.4)	10.2 (5.4)
Risk-taking (DOSPERT)	18.9 (4.9)	18.6 (4.4)	17.5 (4.0)
Risk perception (DOSPERT)	29.7 (4.9)	30.4 (3.2)	30.3 (3.3)
Social functioning (SF36)	61.4 (21.0)	68.9 (20.7)	69.8 (20.9)
Emotional wellbeing (SF36)	67.2 (18.9)	71.4 (15.5)	73.9 (14.6)
Quality of life – Outlook (AAQoL)	60.8 (19.8)	65.6 (16.3)	67.3 (15.8)
Quality of life – Relationships (AAQoL)	64.0 (21.6)	67.0 (18.1)	72.1 (16.8)
Significant life events (after age 16) (LTE)	2.6 (2.7)	2.4 (2.4)	2.6 (2.7)
Creative achievements	4.6 (8.2)	3.3 (6.6)	5.1 (8.5)
Neurocognitive functioning, *M* (*SD*)			
Estimated TIQ (WAIS)	90.0 (13.3)	94.9 (11.9)	97.4 (11.3)
Short-term memory – digits (WAIS)	8.8 (2.1)	9.5 (2.2)	9.6 (2.0)
Short-term memory – verbal (15WT)	46.5 (9.9)	52.7 (8.5)	51.5 (8.8)
Long-term memory (15WT)	9.7 (3.1)	11.3 (2.4)	11.0 (2.4)
Working memory (WAIS)	18.0 (4.1)	19.8 (3.9)	20.6 (3.9)
Letter fluency score (COWAT)	30.9 (9.8)	33.9 (9.2)	36.3 (10.5)
Physical health, *M* (*SD*)			
BMI	26.3 (4.9)	25.5 (4.8)	24.2 (3.9)
MET minutes per week (IPAQ)	4742.3 (4713.1)	3547.7 (3978.3)	3745.2 (3511.9)
General health perceptions (SF36)	66.8 (20.2)	69.8 (18.43	72.5 (17.9)
Physical functioning (SF36)	84.0 (11.8)	85.2 (9.4)	85.0 (11.0)
Pain (SF36)	84.4 (20.4)	87.9 (17.2)	88.6 (16.9)
Energy/vitality (SF36)	57.9 (20.4)	58.7 (17.9)	61.6 (17.0)
Role limitations due to physical health (SF36)	100 (0)	100 (0)	100 (0)
Role limitations due to emotional problems (SF36)	100 (0)	100 (0)	100 (0)
Sleep quality (PSQI)	5.6 (3.7)	4.5 (3.0)	4.6 (2.9)
Healthy diet	6.2 (1.7)	6.4 (1.5)	6.7 (1.4)
Diet adherence	5.6 (2.2)	6.2 (1.8)	6.8 (1.6)
Healthcare service use			
Number of visits to health and safety doctors and/or the employee insurance agency last year, *M* (*SD*)	0.2 (0.8)	0.1 (0.6)	0.2 (0.8)
Number of visits to mental healthcare institutes last year, *M* (*SD*)	6.3 (27.1)	2.1 (5.3)	1.7 (4.2)
Number of visits to physical healthcare institutes last year, *M* (*SD*)	11.4 (33.1)	6.8 (11.8)	7.5 (13.5)
Current ADHD medication use, *n* (%)	32 (21%)	6 (4%)	4 (3%)
Current general medication use, *n* (%)	1.8 (2.2)	1.5 (1.9)	1.2 (1.7)

Note. AAQoL = adult ADHD quality of life questionnaire, ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self-report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, CAARS = Conners' adult ADHD rating scales, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LTE = long-term difficulties questionnaire, MET = metabolic equivalent, PSS = perceived stress scale, PSQI = Pittsburg sleep quality index, SF36 = short form health survey, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.
[a] Assessed only for participants with a child/children (*n* =107).

Table S2.4. *Outcomes of participants with childhood ADHD with current ADHD, remitted ADHD and controls without a current diagnosis of ADHD*

	Persistent ADHD (*n* = 70)	Remittent ADHD (*n* = 72)	Controls without current ADHD (*n* = 110)
Demographics			
Age, years (*SD*)	28.8 (3.4)	28.8 (3.7)	28.3 (3.4)
Male, *n* (%)	46 (66%)	52 (72%)	44 (40%)
Family status, *n* (%)			
Single	25 (36%)	21 (29%)	31 (28%)
Cohabitation	25 (36%)	29 (40%)	40 (36%)
Married	13 (19%)	14 (19%)	24 (22%)
Children at home[a]	3 (8%)	3 (9%)	7 (12%)
Co-parenting[a]	0 (0%)	0 (0%)	0 (0%)
Living at home with parents/caregivers	5 (7%)	11 (15%)	15 (14%)
Children (yes/no)	15 (21%)	10 (14%)	27 (25%)
Number of children, *M* (*SD*)[c]	0.4 (0.8)	0.2 (0.5)	0.4 (0.8)
Children with an ADHD-diagnosis, *n* (%)[a]	0 (0%)	0 (0%)	0 (0%)
Children with any diagnosis other than ADHD, *n* (%)[a]	4 (10%)	1 (3%)	1 (2%)
Psychiatric status, *n* (%)			
DSM-5 ADHD	70 (100%)	0 (0%)	0 (0%)
DSM-5 MDD	23 (33%)	5 (7%)	8 (7%)
DSM-5 any anxiety disorder	13 (19%)	4 (6%)	6 (5%)
DSM-5 ASPD	4 (6%)	0 (0%)	1 (1%)
DSM-5 any SUD	6 (9%)	5 (7%)	3 (3%)
Behavioral and emotional problems, *M* (*SD*)			
ADHD index (CAARS)	20.8 (5.0)	14.5 (4.7)	10.9 (5.9)
ADHD index, Other-reported (CAARS)	14.0 (7.1)	10.1 (6.2)	4.4 (4.2)
Externalizing problems (ASEBA-ASR)	17.1 (8.6)	9.6 (6.7)	5.7 (5.7)

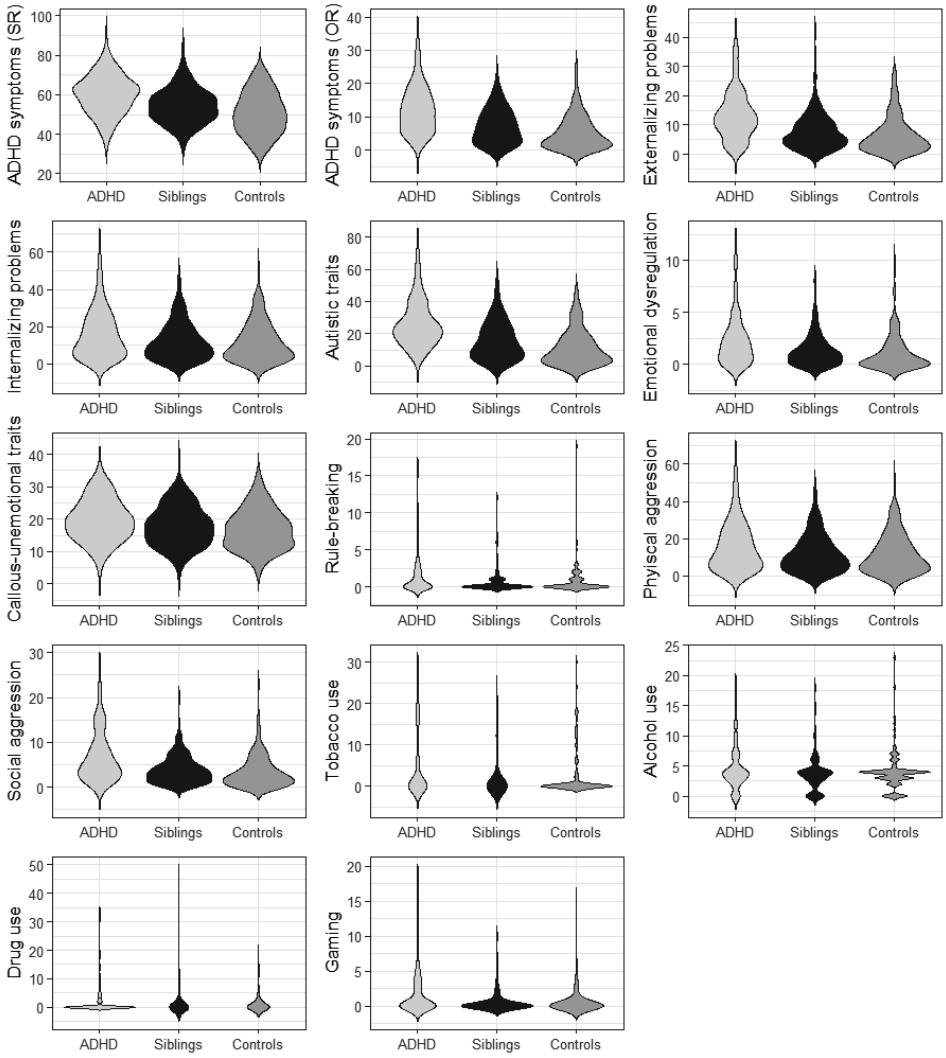
	Persistent ADHD (*n* = 70)	Remittent ADHD (*n* = 72)	Controls without current ADHD (*n* = 110)
Internalizing problems (ASEBA-ASR)	22.2 (13.8)	9.3 (7.0)	10.4 (9.4)
Autistic traits, Other-reported (ASBQ)	29.7 (14.2)	21.8 (12.2)	10.4 (10.5)
Mood dysregulation (ARI)	2.8 (2.6)	1.8 (2.3)	1.1 (1.9)
Callous-unemotional traits (ICU)	19.7 (7.2)	20.2 (5.7)	16.5 (6.3)
Rule-breaking behavior (STAB)	1.8 (2.8)	1.1 (2.2)	0.6 (1.2)
Physical aggression (STAB)	7.4 (5.9)	5.9 (5.2)	3.0 (3.1)
Social aggression (STAB)	7.9 (5.4)	6.9 (4.9)	4.1 (3.7)
Tobacco use (ASSIST-Lite)	5.1 (7.7)	4.0 (6.7)	2.3 (5.0)
Alcohol use (ASSIST-Lite)	4.4 (3.7)	4.8 (3.6)	3.6 (2.2)
Drug use (ASSIST-Lite)	3.3 (7.5)	1.0 (2.6)	1.3 (3.4)
Gaming addiction symptoms (GAS)	2.0 (3.3)	1.6 (2.9)	0.6 (1.8)
Academic and professional functioning			
Education Verhage, *M* (*SD*)	5.3 (1.3)	5.4 (1.2)	6.1 (0.8)
Repeated grade (primary and secondary education), *n* (%)	33 (47%)	28 (39%)	28 (25%)
Employed, *n* (%)	57 (81%)	68 (94%)	104 (95%)
Number of times switched jobs, *M* (*SD*)	2.5 (2.3)	3.0 (4.1)	2.2 (2.7)
Adaptive functioning, *M* (*SD*)			
Perceived stress (PSS)	15.5 (5.8)	10.2 (4.6)	9.6 (5.0)
Risk-taking (DOSPERT)	19.6 (5.2)	18.7 (4.3)	17.2 (3.9)
Risk perception (DOSPERT)	29.7 (5.1)	30.1 (3.2)	30.4 (3.3)
Social functioning (SF36)	60.5 (20.0)	62.8 (20.0)	69.6 (21.4)
Emotional wellbeing (SF36)	58.3 (18.0)	76.7 (13.8)	75.9 (13.9)
Quality of life – Outlook (AAQoL)	54.4 (20.3)	68.5 (15.5)	69.1 (15.6)
Quality of life – Relationships (AAQoL)	53.6 (21.4)	74.9 (15.1)	73.8 (16.5)
Significant life events (after age 16) (LTE)	3.0 (2.9)	2.2 (2.3)	2.4 (2.6)
Creative achievements	5.7 (10.2)	4.0 (6.3)	5.0 (8.6)
Neurocognitive functioning, *M* (*SD*)			
Estimated TIQ (WAIS)	92.0 (12.2)	88.4 (13.9)	97.1 (11.5)
Short-term memory – digits (WAIS)	9.0 (2.1)	8.7 (2.1)	9.6 (2.0)
Short-term memory – verbal (15WT)	46.6 (9.4)	46.5 (10.6)	51.1 (8.7)
Long-term memory (15WT)	9.9 (2.8)	9.5 (3.3)	10.9 (2.5)
Working memory (WAIS)	18.3 (3.9)	17.8 (4.1)	20.7 (4.0)
Letter fluency score (COWAT)	31.4 (9.6)	30.3 (10.1)	36.1 (10.8)
Physical health, *M* (*SD*)			
MET minutes per week (IPAQ)	26.7 (5.7)	25.6 (3.9)	24.2 (3.8)
General health perceptions (SF36)	4024.2 (3850.6)	5544.5 (5377.3)	3889.1 (3610.5)
Physical functioning (SF36)	60.4 (20.5)	73.9 (17.5)	74.2 (17.2)
Pain (SF36)	81.6 (12.9)	86.1 (11.0)	85.7 (10.1)
Energy/vitality (SF36)	77.6 (21.4)	92.1 (15.3)	90.0 (15.6)

	Persistent ADHD (*n* = 70)	Remittent ADHD (*n* = 72)	Controls without current ADHD (*n* = 110)
Role limitations due to physical health (SF36)	51.5 (19.6)	65.0 (18.4)	63.3 (16.2)
Role limitations due to emotional problems (SF36)	100 (0)	100 (0)	100 (0)
Sleep quality (PSQI)	100 (0)	100 (0)	100 (0)
Healthy diet	6.9 (4.1)	4.4 (2.8)	4.5 (2.7)
Diet adherence	6.1 (1.8)	6.5 (1.6)	6.8 (1.4)
	5.3 (2.2)	5.9 (2.1)	6.9 (1.6)
Healthcare service use			
Number of visits to health and safety doctors and/or the employee insurance agency last year, *M* (*SD*)	0.3 (1.1)	0.1 (0.4)	0.2 (0.8)
Number of visits to mental healthcare institutes last year, *M* (*SD*)	6.7 (12.6)	6.9 (37.4)	1.7 (4.4)
Number of visits to physical healthcare institutes last year, *M* (*SD*)	10.8 (16.1)	12.3 (45.3)	6.6 (11.3)
Current ADHD medication use, *n* (%)	16 (23%)	13 (18%)	1 (1%)
Current general medication use, *n* (%)	2.2 (2.6)	1.3 (1.7)	1.2 (1.7)

Note. AAQoL = adult ADHD quality of life questionnaire, ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self-report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, CAARS = Conners' adult ADHD rating scales, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LTE = long-term difficulties questionnaire, MET = metabolic equivalent, PSS = perceived stress scale, PSQI = Pittsburg sleep quality index, SF36 = short form health survey, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.

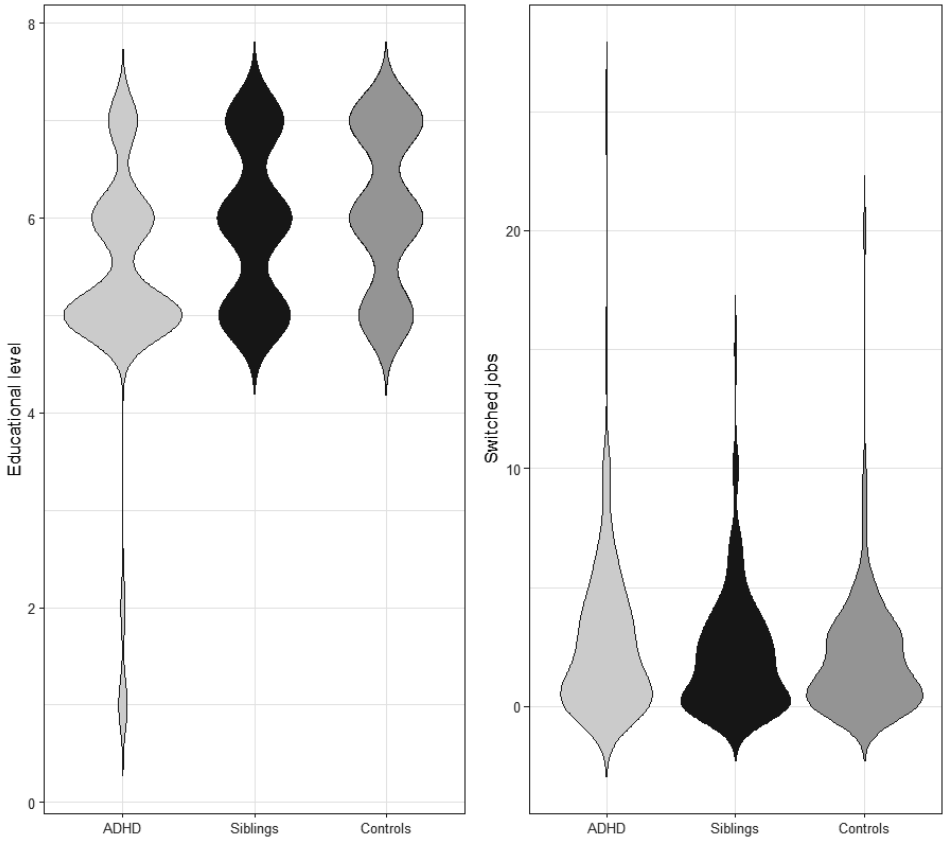
[a] Assessed only for participants with a child/children (*n* = 52).

Figure S2.1. *Violin plots showing the distribution of the behavioral and emotional functioning outcome measures for participants diagnosed with ADHD in childhood, their siblings, and controls*



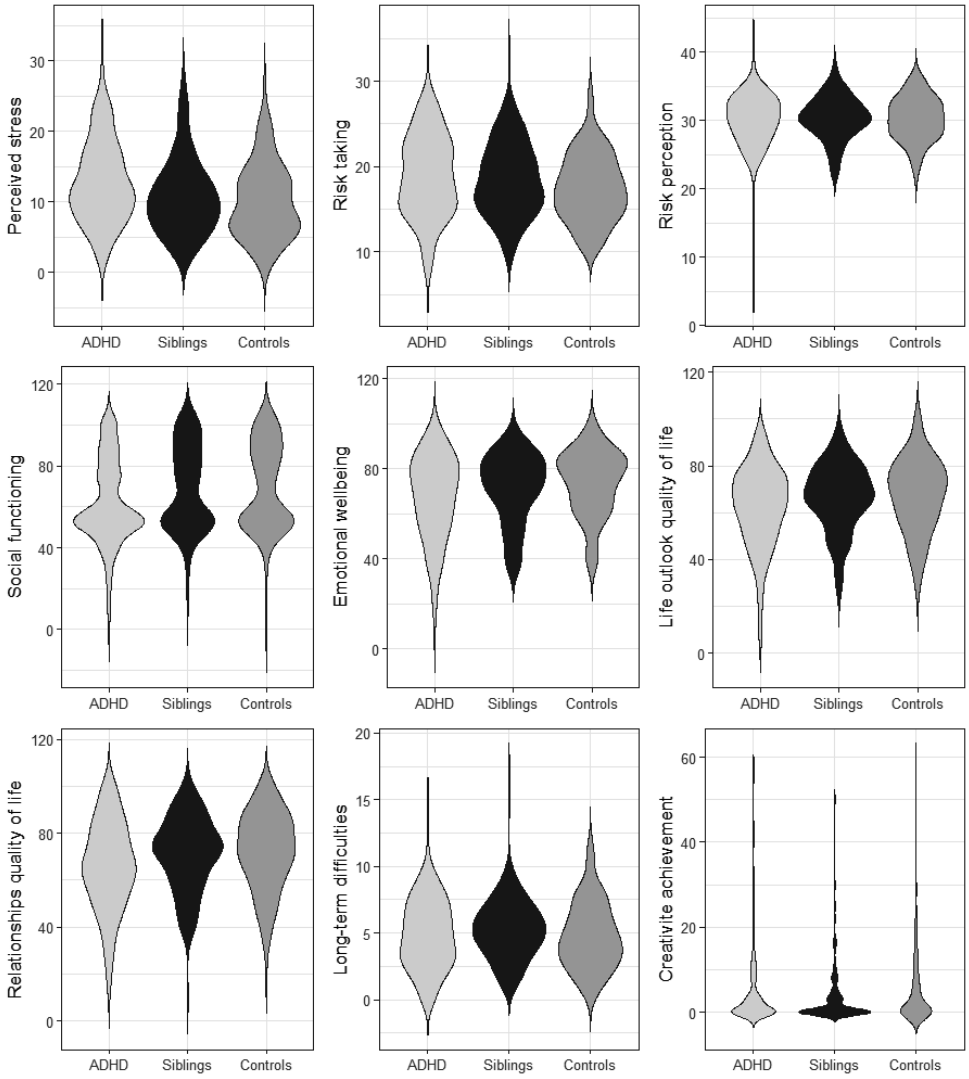
Note. ADHD = attention-deficit hyperactivity disorder, OR = other-report, SR = self-report.

Figure S2.2. *Violin plots showing the distribution of the academic and professional functioning outcome measures for participants diagnosed with ADHD in childhood, their siblings, and controls*



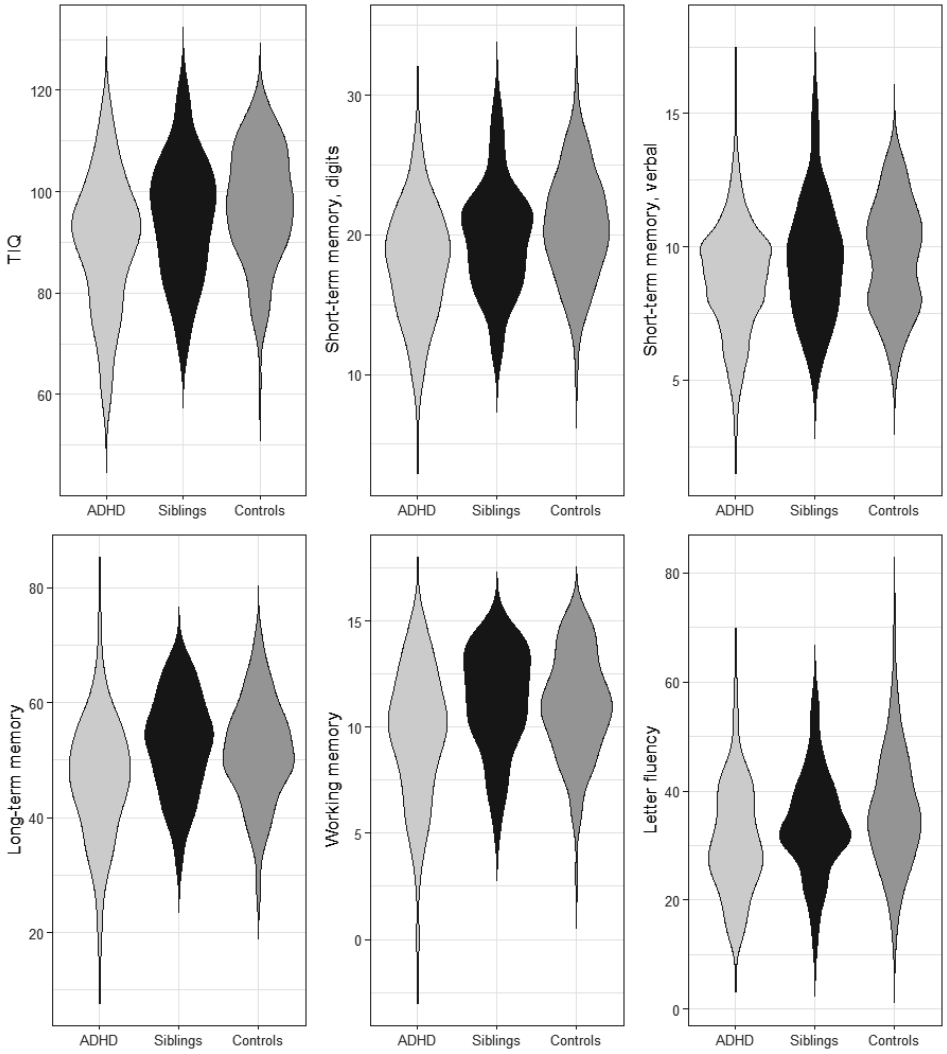
Note. Educational level was measured categorically. Two outcome measures were left out, as they were measured on a two-point scale (yes/no; i.e., repeated a grade, employed).
ADHD = attention-deficit hyperactivity disorder.

Figure S2.3. *Violin plots showing the distribution of the adaptive functioning outcome measures for participants diagnosed with ADHD in childhood, their siblings, and controls*



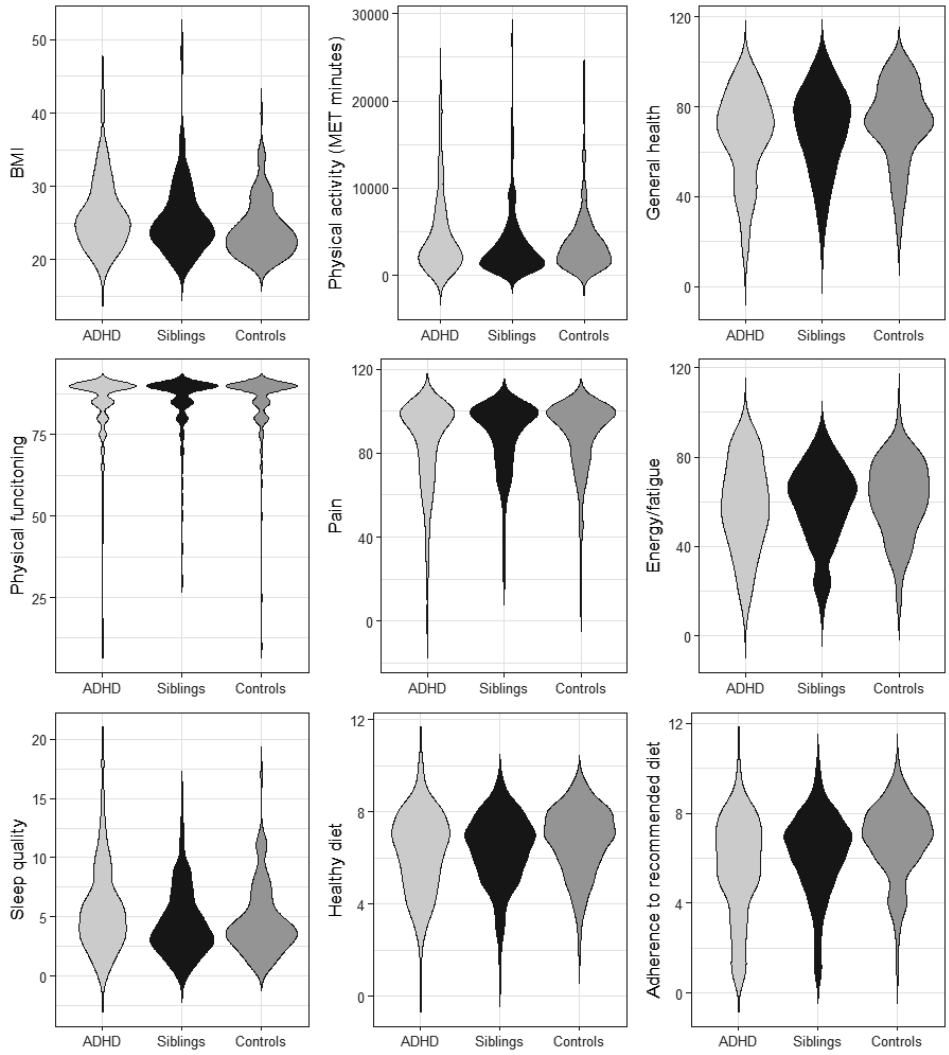
Note. ADHD = attention-deficit hyperactivity disorder.

Figure S2.4. *Violin plots showing the distribution of the neurocognitive functioning outcome measures for participants diagnosed with ADHD in childhood, their siblings, and controls*



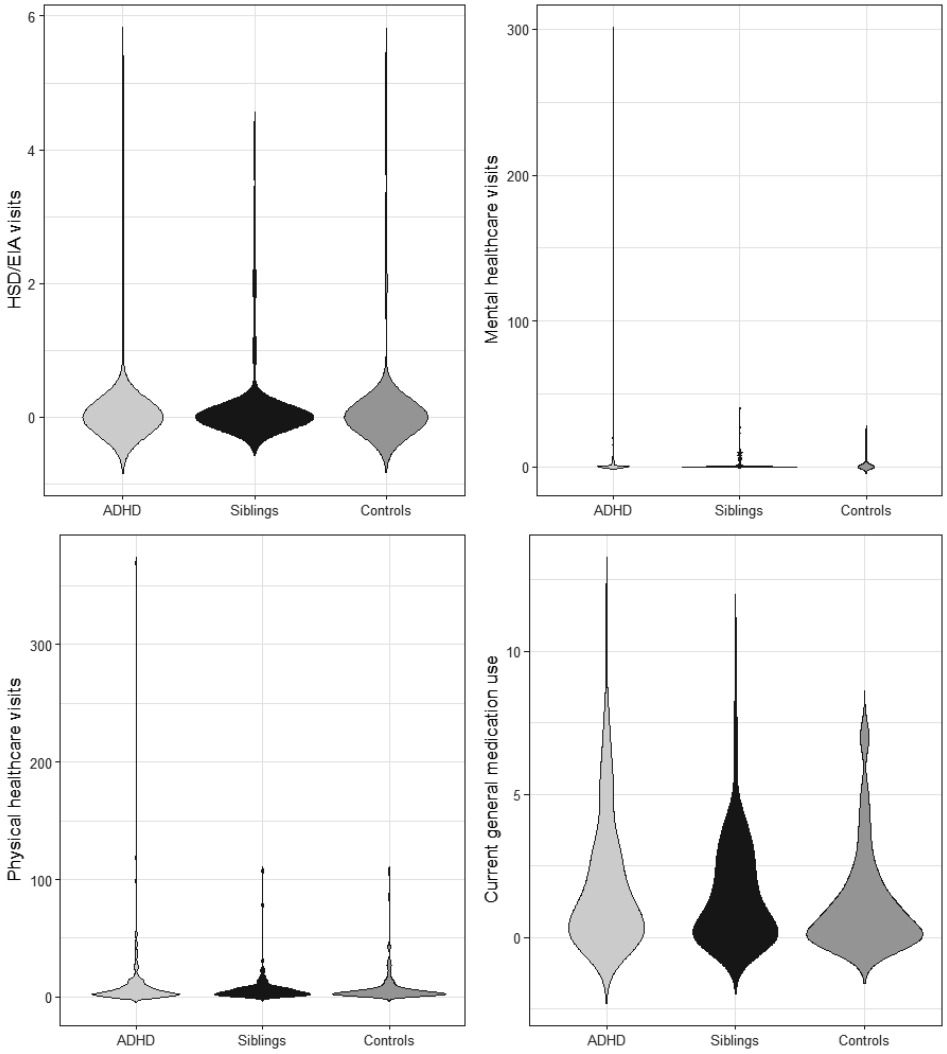
Note. ADHD = attention-deficit hyperactivity disorder, TIQ = total intelligence quotient (estimated using two subtests, see main text).

Figure S2.5. *Violin plots showing the distribution of the physical health outcome measures for participants diagnosed with ADHD in childhood, their siblings, and controls*



Note. ADHD = attention-deficit hyperactivity disorder, BMI = body mass index, MET = metabolic equivalent.

Figure S2.6. *Violin plots showing the distribution of the healthcare service use outcome measures for participants diagnosed with ADHD in childhood, their siblings, and controls*



Note. Current ADHD medication use was left out, as it was measured on a two-point scale (yes/no).
ADHD = attention-deficit hyperactivity disorder, HSD/EIA = health and safety doctors and/or the employee insurance agency.



CHAPTER 3

Psychotropic and somatic medication use in adults with childhood ADHD, their siblings, and controls: a prospective long-term longitudinal study

Under review as:
van der Plas, N. E., Noordermeer, S. D. S., Franke, B., Hartman, C. A., Hoekstra, P. J., Rommelse, N. N. J., Sprooten, E., Bet, P. M., Luman, M., & Oosterlaan, J. Psychotropic and Somatic Medication Use in Adults with Childhood ADHD, their Siblings, and Controls: A Prospective Long-Term Longitudinal Study.

Abstract

Background. Adults with attention-deficit/hyperactivity disorder (ADHD) diagnosed in childhood show higher healthcare utilization, but their medication use remains understudied while this can clarify the long-term health burden of childhood ADHD.

Methods. In this 18-year prospective cohort study, pharmacy dispensing records of ADHD, other psychotropic, and somatic medication of the last year were compared between adults with childhood ADHD (n = 125, M_{age} = 29, 68% males), their siblings (n = 109, M_{age} = 28, 35% males) and controls (n = 101, M_{age} = 30, 42% males) without childhood ADHD at study entry. Group differences in demographics and psychiatric status were included as covariates (sensitivity analyses).

Results. The childhood ADHD group was more likely to be prescribed ADHD medication, more different ADHD medications, non-steroidal anti-inflammatory drugs (NSAIDs), and neurological medications (specifically analgesics) compared to their siblings and controls (OR range = 3.25-8.35, β range = 0.61-0.65). Compared to controls, the childhood ADHD group was also more likely to be prescribed other psychotropic medication (OR = 3.82) and used more different types of psychotropic medication (β = 0.38). Siblings and controls did not differ. Findings remained after controlling for demographic differences, except that the childhood ADHD group no longer differed from controls on analgesics. After controlling for psychiatric status differences (ADHD, major depressive disorder), the childhood ADHD group still differed on ADHD medication use, more different ADHD medications, and NSAIDs, and from controls on more different psychotropic medications.

Conclusions. Adults with childhood ADHD, but not their siblings, show elevated long-term medication use. The elevated medication use is not merely explained by shared familial factors but is partly attributable to current psychiatric status.

Key words: childhood ADHD, adult medication use, health, follow-up, outcome

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by impairing symptoms of inattention and/or hyperactivity-impulsivity, and is often diagnosed in childhood [2]. The diagnosis of childhood ADHD persists into adulthood in up to 77% of individuals, and up to 90% still experience symptoms when reaching adulthood [11, 13]. Adults with childhood ADHD not only suffer from impairment due to symptoms of ADHD, but also are more likely to be diagnosed with another mental disorder, including mood, antisocial/disruptive, and substance use disorders (SUDs) [16]. Additionally, cross-sectional and prospective studies show that adults with childhood ADHD are at a higher risk of developing somatic disorders, such as an increased risk for a neurological condition, sleep disorder, metabolic and endocrine condition, and autoimmune disorder [121, 122]. This increased risk for both mental and somatic disorders likely drives the association between childhood ADHD and higher healthcare utilization in adulthood, including medication use [27].

To date, medication use of adults with a childhood ADHD diagnosis remains understudied, especially in prospective cohort studies. Such studies are important because they provide more insight into the long-term health burden of ADHD and may inform early prevention of mental and somatic problems. Children with ADHD are often prescribed ADHD medication, particularly stimulants [123], but the number of adults with childhood ADHD using stimulants has not yet been investigated in prospective studies. Furthermore, very little is known about other psychotropic and somatic medication use in individuals with ADHD, although two Swedish registry studies provided important insights [27, 124]. One of these studies reported that adults using ADHD medication used more additional psychotropic as well as somatic medications compared to controls (OR range = 4.1–21.7) [124]. Subgroup analysis showed that ADHD medication users had elevated use of all types of medication. However, these results are not generalizable to all adults with a childhood ADHD diagnosis, as this study included only participants who still had ADHD and used ADHD medication. The second registry study showed elevated use of both psychotropic and somatic medication in a sample of adults with childhood ADHD [27]. Yet, this study did not explore specific types of medication. Therefore, research remains sparse on associations between childhood ADHD and adult medication use which up till now has never been investigated in much detail in a prospective cohort study. Additionally, adult medication use of siblings of individuals with childhood ADHD has not been investigated, while medication use of these siblings might also be elevated due to a higher familial risk based on shared environmental and genetic factors [15]. Childhood environmental factors might influence adult medication use, such as socioeconomic status [125] or parental mental health [126], and investigating siblings can provide information on the extent of that influence.

In the present study, we aimed to investigate current medication use, including ADHD, other psychotropic, and somatic medication use, in adults with a childhood ADHD diagnosis, their siblings and controls without an ADHD diagnosis at study entry. This study adds to the limited literature on medication use in adults with childhood ADHD, and in particular the scarcity of prospective cohort studies and studies providing a detailed analysis in terms of the types of medication used. We are the first to include siblings to inform on the influence on familial versus individual factors. Participants were selected from an 18-year prospective cohort study. We expected adults with childhood ADHD to use more medication compared to their siblings and controls. Further, we expected the siblings to use more medication compared to controls, as familial factors were expected to contribute to elevated medication use [90].

Methods

Participants

This study included three groups based on diagnostic status at entry in the current prospective cohort study: individuals with a diagnosis of ADHD in childhood, their siblings without childhood ADHD ("unaffected siblings", hereafter referred to as "siblings"), and controls without childhood ADHD. These participants came from an 18-year follow-up of a longitudinal cohort study that was initiated as part of the Dutch branch of the International Multicenter ADHD Genetics (IMAGE) study [58]. Enrollment in this cohort took place between 2003-2005 (wave I). Both ADHD and control families were recruited. Families with ADHD had at least one child with a diagnosis of ADHD combined type. Included control families had at least one child without ADHD without first-degree family members diagnosed with ADHD. From these families children were recruited that met the following inclusion criteria: aged 5-19 years, Caucasian descent, IQ ≥ 70, and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, or known genetic disorders [58]. Participants were previously followed up in 2009-2012 (wave II, NeuroIMAGE) and 2015-2016 (wave III, NeuroIMAGE2). In contrast to the inclusion criteria of wave I, the follow-up waves included newly recruited participants who could be diagnosed with any ADHD type [59]. The current 18-year follow-up study (wave IV, 2021-2024) included all participants who had participated in any of the previous waves and of whom pharmacy dispensing records could be obtained [58, 59]. Further details on the wave IV follow-up are available in van der Plas, et al. [127].

Demographics (wave IV)

Demographics included sex, age at follow-up, and educational level. Educational level was defined as the highest completed educational level based on the Dutch Verhage scale [80].

Psychiatric status (wave IV)

Psychiatric status was assessed by the Structured Clinical Interview for DSM-5 Disorders (SCID-5) using DSM-5 criteria [100]. The SCID-5 is a structured diagnostic interview and was administered by certified researchers based on present symptoms. For all participants, DSM-5 ADHD was assessed using the ADHD module. Other psychiatric outcomes, including major depressive disorder (MDD), antisocial personality disorder (ASPD), anxiety disorders, and SUDs were only assessed with the SCID-5 if participants screened positive on the SCID-5 screening questions for these outcomes or in case of SUDs, on the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-Lite) [69]. All anxiety disorders and SUDs were united into the measures "any anxiety" disorder and "any SUD", respectively.

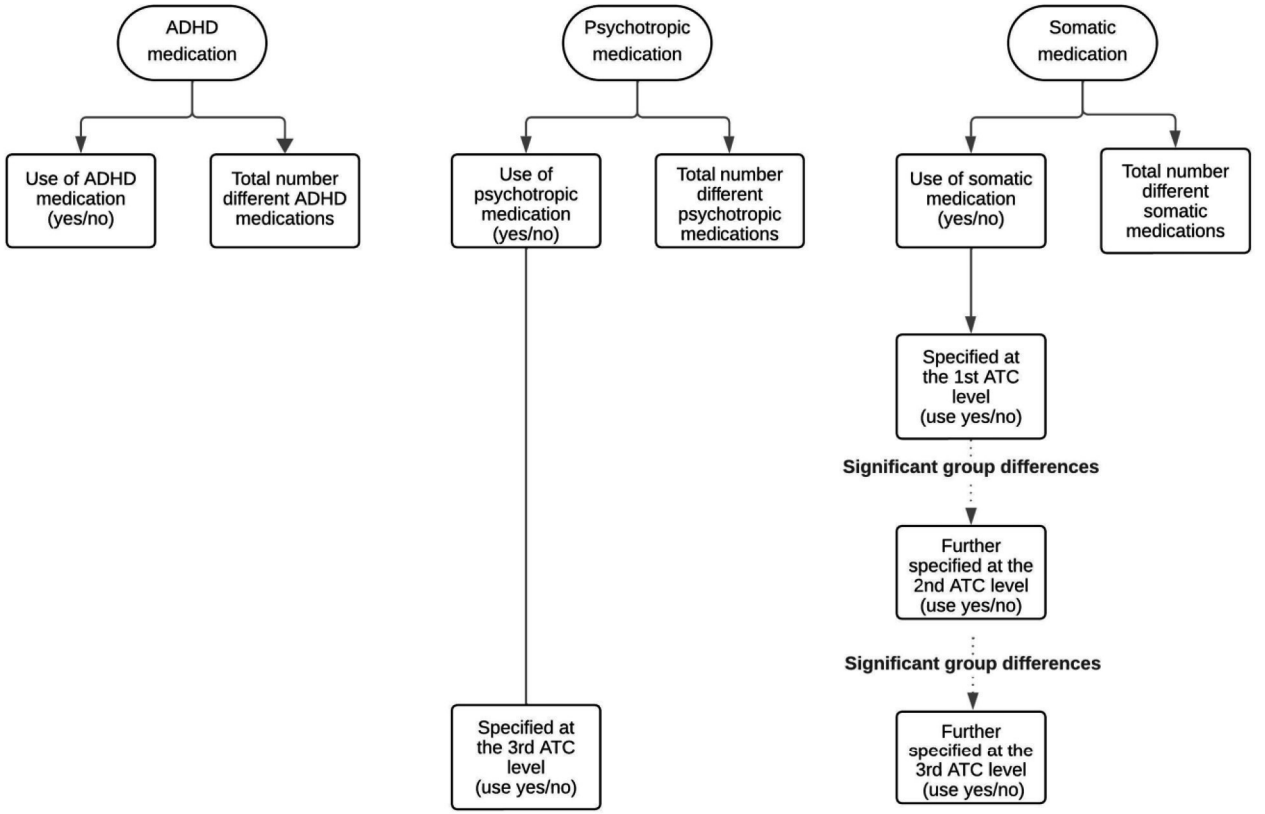
Medication use (wave IV)

Medication use of one full year was assessed using pharmacy dispensing records that were obtained from the participant's pharmacy. The records included the following details on the dispensed medication: delivery date, pharmacological substance name, ATC code, strength, quantity, and dosing information. If possible, the most recent 12-month period covered by the available pharmacy dispensing records was chosen. However, if the most recent full year overlapped more than a month with the period of the COVID pandemic with health-care related restrictions (February 2020 until February 2022) [66, 67], the year before the start of the COVID pandemic was chosen (January 2019 to January 2020) to rule out the impact of the COVID pandemic on medication use.

Several measures were constructed to reflect ADHD, psychotropic, and somatic medication use in the last year, see Figure 3.1 for an overview of the outcomes. Use of ADHD medication (yes/no) was based on the presence of at least one prescription of amphetamines, methylphenidate, or atomoxetine, and the total number of different ADHD medications was based on the number of different pharmacological substances prescribed (5th ATC level of code N06B). Psychotropic medication usage, excluding ADHD medication, was captured by 1) use of psychotropic medication (yes/no), 2) the total number of different psychotropic medications, and 3) use of subgroups of psychotropic medication (yes/no) (specified at the 3rd ATC level, N05A, N05B, N05C, N06A, N06C , N06D) to pinpoint the exact nature of the differences of psychotropic medication use. Similarly, somatic medication usage was captured by 1) use of somatic medications (yes/no), 2) the total number of different somatic medications, and 3) use of subgroups of somatic medications (yes/no) (specified at the 1st ATC level, e.g., A, B). Medication use was further explored using a hierarchical approach: if significant group differences emerged for subgroups of medication at the 1st level, medication use was 4) further specified at the 2nd ATC level (use yes/no, e.g., A01 to A16), and if

there were significant group differences for the 2nd level use, 5) further specified at the 3rd ATC level (use yes/no, e.g., A02A, A02B). The somatic medications included all medication from all ATC codes, except ADHD and psychotropic medications.

Figure 3.1. *Visual description of the medication outcomes*



Note. Use of psychotropic medication was specified according to the specific subgroups of psychotropic medication (3rd ATC level), and somatic medications were specified into specific subgroups as well (1st ATC level). Significant group differences on these subgroups of somatic medications were further explored at the 2nd ATC level and at the 3rd ATC level if significant group differences emerged at the 2nd ATC level.
ADHD = attention-deficit/hyperactivity disorder, ATC = anatomical therapeutic chemical.

Procedure

Participants were invited directly or through their parents (if no informed consent was available from the participants, but only from their parents) by phone, e-mail, or post. After signing informed consent, assessments took place. Assessments comprised self-reported online questionnaires, other-reported (preferably the significant other) online questionnaires, and two video calls. Pharmacy dispensing records were requested from the pharmacies of participants. The study was approved by the local medical ethics committee of the Amsterdam University Medical Center (AUMC; ABR NL77520.029.21). All data was pseudo anonymized, and participants received 25 euros after completion. See van der Plas, et al. [127] for more details.

Statistical analysis

Attrition analyses were run to test representativeness of the retained sample with pharmacy dispensing records compared to the initial sample at the earliest inclusion (IMAGE, wave I). These analyses used Generalizing Estimating Equation (GEE) with an exchangeable correlation structure to account for familial dependency. Groups were compared on sex, age, estimated total intelligence quotient (TIQ; estimated by the Vocabulary, Similarities, Block Design and Picture Completion subtests of the Wechsler Intelligence Scale for Children [WISC-III] or Wechsler Adult Intelligence Scale [WAIS-III]) [76, 77], average educational level of both parents (or the level of one parent, if only one parent was available; based on the Dutch Verhage scale [80]), and parent-reports of: ADHD symptoms, oppositional defiant disorder symptoms, anxious/shy behavior (using the scales N, A, and D of the Conners' ADHD rating scale long version [78], respectively), and behavioral and emotional difficulties (using the Strengths and Difficulties Questionnaire [79]; not assessed in controls).

Multiple imputation, including parcel summary scores of psychiatric and health measures, was used to impute missing outcome variables with no more than 10% missing data. The percentage of missing data across all psychiatric and health measures varied between 0-7% for the childhood ADHD group, 0-4% for the siblings, and 0-5% for the controls. Pharmacy data were not imputed. Based on the recommendation to impute as many datasets as the percentage of participants with any missing data [71], seven imputed datasets were created. The analyses were rerun seven times using each imputed dataset and subsequently the seven different summary statistics of each analysis were pooled [71].

Medication outcomes were compared across the three groups based on diagnostic status at study entry: 1) childhood ADHD, 2) siblings, and 3) controls. For significant main effects of group, post-hoc analyses were conducted using pairwise group comparisons. To test whether the significant differences in outcomes were driven by potential confounders, sensitivity analyses were run by

repeating all analyses yielding significant pairwise group differences on the medication outcomes. Potential confounders included any demographical characteristic (sex, age, educational level) or psychiatric status (ADHD, MDD, ASPD, anxiety disorder, SUD) that differed between groups.

All analyses used GEE with an exchangeable correlation structure to account for familial dependency in R (v4.3.0) [84]. Outcomes with no variation within any of the three groups were precluded from statistical testing [81]. Effect sizes were quantified by calculating odds ratios (OR) for categorical outcomes and standardized betas for continuous outcome measures. The magnitude of the standardized betas was interpreted as group difference using threshold levels as used to interpret Cohen's *d*, with small for β = 0.20-0.50, moderate for β = 0.50-0.80, and large for $\beta \geq 0.80$) [83].

Results

Attrition analysis

The current study (wave IV) included a total of 335 participants with available pharmacy dispensing records, including 125 participants with childhood ADHD, 109 siblings, and 101 controls. The mean follow-up period from wave I was 17.65 years (*SD* = 0.83). The retained sample did not differ from the initial sample on most of the assessed measures (Table S3.1–Table S3.3). However, retained siblings had higher estimated IQs (Wald χ^2 = 5.18, p = .023) and reported less anxious/shy behavior (Wald χ^2 = 4.22, p = .040) compared to the initial sample of siblings.

Sample characteristics

See Table 3.1 for a description of the characteristics of the three groups. Regarding demographic characteristics at follow-up, the three groups differed on sex (Wald χ^2 = 27.85, p<.001), age (Wald χ^2 = 10.30, p = .006), and educational level (Wald χ^2 = 42.27, p<.001). The childhood ADHD group included more males compared to their siblings (OR = 3.90, 95% CI = 2.28-6.69]) and controls (OR = 2.94, 95% CI = 1.71-5.07]) and had the lowest completed educational level (moderate differences). The siblings were younger compared to the childhood ADHD and control groups (small differences). Given the observed group differences in sex, age, and educational level, sensitivity analyses were run to test whether significant differences in medication outcomes were driven by these demographic factors.

Regarding psychiatric status, the three groups differed on DSM-5 ADHD (Wald χ^2 = 51.73, p <.001) and MDD (Wald χ^2 = 6.67, p=.036). The childhood ADHD group was more likely to have DSM-5 ADHD at follow-up compared to their siblings (OR = 7.82, 95% CI = 3.80-16.12]) and controls (OR = 8.98, 95% CI = 4.08-19.77]), and more likely to have DSM-5 MDD compared to their siblings (OR = 3.37, 95% CI = 1.21-9.39]). No other differences in psychiatric status were observed. Given the

observed group differences in DSM-5 ADHD and MDD, sensitivity analyses were run to test whether significant differences in medication outcomes were driven by these specific psychiatric outcomes.

Medication outcomes

See Table 3.2 for main effects of group on the medication outcomes and results of the subsequent pairwise group comparisons, see Table S3.4 for the effect sizes of the subsequent pairwise group comparisons.

ADHD medication

Regarding ADHD medication, main effects of group were found for the number of participants on ADHD medication and the number of different prescriptions of ADHD medications (ATC code N06B). Pairwise group comparisons showed that the childhood ADHD group more often used ADHD medication (OR = 8.35 [95% CI 2.83-24.63], OR = 5.86 [95% CI 2.36-14.68]) and had more different ADHD medications prescriptions (ATC codes under N06B; moderate differences) compared to controls and siblings, respectively. The siblings and controls did not differ on ADHD medication.

Other psychotropic medication

Regarding other psychotropic medication, main effects of group were found for psychotropic medication use and number of different prescriptions of psychotropic medications. No main effects of group were found at the level of subgroups of psychotropic medication (3rd ATC level, ATC codes N05B, N06A). Pairwise group comparisons showed that the childhood ADHD group more often used psychotropic medication (OR = 3.82 [95% CI 1.24-11.79]) and had more different psychotropic medications prescriptions (small difference) compared to controls. No other pairwise group differences were found.

Somatic medication

Regarding somatic medication, no main effects of group were found for medication use and total number of different prescriptions. At the level of subgroups of somatic medications (1st ATC level) main effects of group were found for neurological medications other than psychotropic medications (ATC code N; "neurological") and musculo-skeletal medications (ATC code M). Explorative analyses at the 2nd and 3rd ATC level were used to further understand the nature of these findings. Main group effects on neurological medications could be traced back to analgesics (ATC code N02) at the 2nd ATC level, whereas the main group effect on musculo-skeletal medications was completely driven by 3rd level non-steroid anti-inflammatory and antirheumatic medications (ATC code M01A; "NSAIDs"). No main group effects were found for other somatic medications at the 1st ATC level (ATC codes A, B, C, D, G, H, J, P, R, S). Pairwise group comparisons

showed that the childhood ADHD group was more often on neurological medications compared to controls (ATC code N, OR = 5.15 [95% CI 1.46-18.18]) and their siblings (OR = 3.25 [95% CI 1.17-9.04]). Again, explorative analyses at the 2nd and 3rd ATC level were used to further understand the nature of these group findings. Group differences could be traced back to the childhood ADHD group being more often on analgesics at the 2nd ATC level (ATC code N02, childhood ADHD vs controls: OR = 4.12 [95% CI 1.15-14.84]; childhood ADHD vs siblings OR = 4.43 [95% CI 1.25-15.72]) and NSAIDs at the 3rd ATC level (ATC code M01A, childhood ADHD vs controls: OR = 6.98 [95% CI 2.02-24.18]; childhood ADHD vs siblings: OR = 3.63 [95% CI 1.43-9.2]).

Sensitivity analyses: medication use controlling for demographic and psychiatric differences

As groups differed significantly in terms of demographic characteristics (sex, age, educational level), these demographic differences were entered as covariates in a sensitivity analysis of the medication outcomes with significant pairwise group differences (see Table 3.2). All significant pairwise group comparisons were replicated with comparable effect sizes, except that the childhood ADHD group no longer differed from controls on analgesics (ATC code N02A, Table S3.5).

As groups also differed significantly in terms of psychiatric status (ADHD, MDD), these psychiatric outcomes were entered as covariates in a sensitivity analysis of the medication outcomes with significant pairwise group differences (see Table 3.2). The childhood ADHD group no longer differed from controls on psychotropic medication use (Table S3.6). Also, the childhood ADHD group was no longer different from both controls and siblings on neurological medications (ATC code N02) and analgesics (ATC code N02A). The significant pairwise group differences in ADHD medication, number of different psychotropic medications, and NSDAIDs were replicated with similar effect sizes.

Table 3.1. *Sample characteristics of adults with childhood ADHD, their siblings, and controls*

	Childhood ADHD (*n* = 125)	Siblings (*n* = 109)	Controls (*n* = 101)	Main group effects	Pairwise group comparisons
Demographics, *M* (*SD*)					
Age in years	28.53 (3.62)	28.07 (3.54)	29.81 (4.56)	Wald χ^2 = 10.30**	A, C > S
Male sex, *n* (%)	85 (68%)	38 (35%)	42 (42%)	Wald χ^2 = 27.85***	A > S, C
Level of highest completed education	5.18 (1.25)	5.96 (0.80)	6.00 (0.80)	Wald χ^2 = 42.27***	C, S > A
Psychiatric status, *n* (%)					
DSM-5 ADHD	57 (46%)	11 (10%)	8 (8%)	Wald χ^2 = 51.73***	A > S, C
DSM-5 MDD	21 (17%)	7 (6%)	9 (9%)	Wald χ^2 = 6.67*	A > S
DSM-5 ASPD	4 (3%)	0 (0%)	1 (1%)	N/A[a]	
DSM-5 any anxiety disorder	14 (11%)	5 (5%)	7 (7%)	Wald χ^2 = 2.32	
DSM-5 any SUD	8 (6%)	9 (8%)	3 (3%)	Wald χ^2 = 1.64	

Note. Non-significant pairwise group comparisons are not reported.
A = childhood ADHD, ADHD = attention-deficit/hyperactivity disorder, ASPD = antisocial personality disorder, C = controls, DSM = diagnostic and statistical manual of mental disorders, MDD = major depressive disorder, S = siblings, SUD = substance use disorder.
[a] Due to no variance in the sibling group, no formal statistical testing was conducted for this outcome represented by N/A in the table.
*p < .05 **p < .01 ***p < .001.

Table 3.2. *Medication use in adults with childhood ADHD, their siblings, and controls*

	ATC code	Childhood ADHD (*n* = 125)	Siblings (*n* = 109)	Controls (*n* = 101)	Main group effects	Pairwise group comparisons
ADHD medication use						
ADHD medication, *n* (%)	All 5th ATC level of N06B	32 (26%)	6 (6%)	4 (4%)	Wald χ^2 = 25.40***	A > S, C
ADHD medication, number of different medications, *M* (*SD*)	All 5th ATC level of N06B	0.26 (0.46)	0.06 (0.23)	0.04 (0.20)	Wald χ^2 = 25.34***	A > S, C
Psychotropic medication use, *n* (%)						
Psychotropic medications	All 3rd ATC level psychotropic medications[a]	17 (14%)	8 (7%)	4 (4%)	Wald χ^2 = 6.35*	A > C
Psychotropic medications, number of different medications, *M* (*SD*)	All 3rd ATC level psychotropic medications[a]	0.20 (0.55)	0.09 (0.37)	0.04 (0.20)	Wald χ^2 = 9.75**	A > C
Antipsychotics	N05A	5 (4%)	1 (1%)	0 (0%)	N/A[b]	
Anxiolytics	N05B	3 (2%)	2 (2%)	1 (1%)	Wald χ^2 = 0.60	
Hypnotics and sedatives	N05C	4 (3%)	4 (4%)	0 (0%)	N/A[b]	
Antidepressants	N06A	11 (9%)	3 (3%)	3 (3%)	Wald χ^2 = 5.19	
Somatic medication use, *n* (%)						
Somatic medications	All 1st ATC level somatic medications[c]	72 (58%)	70 (64%)	55 (54%)	Wald χ^2 = 2.12	
Somatic medications, number of different medications, *M* (*SD*)	All 1st ATC level somatic medications[c]	1.75 (2.32)	1.68 (1.97)	1.48 (2.27)	Wald χ^2 = 0.90	
Alimentary tract and metabolism	A	17 (14%)	16 (15%)	8 (8%)	Wald χ^2 = 2.55	
Blood and blood forming organs	B	1 (1%)	5 (5%)	2 (2%)	Wald χ^2 = 3.09	
Cardiovascular system	C	1 (1%)	4 (4%)	1 (1%)	Wald χ^2 = 2.76	

	ATC code	Childhood ADHD (*n* = 125)	Siblings (*n* = 109)	Controls (*n* = 101)	Main group effects	Pairwise group comparisons
Dermatologicals	D	26 (21%)	21 (19%)	12 (12%)	Wald χ^2 = 3.41	
Genito urinary system and sex hormones	G	21 (17%)	21 (19%)	23 (23%)	Wald χ^2 = 1.25	
Systemic hormonal preparations, excluding sex hormones and insulins	H	2 (2%)	2 (2%)	2 (2%)	Wald χ^2 = 0.05	
Anti-infectives for systemic use	J	17 (14%)	21 (19%)	15 (15%)	Wald χ^2 = 1.57	
Antineoplastic and immunomodulating agents	L	0 (0%)	0 (0%)	1 (1%)	N/A[b]	
Musculo-skeletal system; anti-inflammatory and antirheumatic products; NSAIDs [d]	M; M01; M01A	22 (18%)	6 (6%)	3 (3%)	Wald χ^2 = 14.39**	A > S, C
Neurological, other than psychotropic medications	N	17 (14%)	5 (5%)	3 (3%)	Wald χ^2 = 9.76**	A > S, C
Anesthetics	N01	2 (2%)	2 (2%)	0 (0%)	N/A[b]	
Analgesics	N02	14 (11%)	3 (3%)	3 (3%)	Wald χ^2 = 8.94*	A > S, C
Opioids	N02A	8 (6%)	2 (2%)	2 (2%)	Wald χ^2 = 4.10	
Other analgesics and antipyretics	N02B	3 (2%)	1 (1%)	0 (0%)	N/A[b]	
Antimigraine preparations	N02C	4 (3%)	1 (1%)	1 (1%)	Wald χ^2 = 2.00	
Other nervous system drugs	N07	1 (1%)	0 (0%)	0 (0%)	N/A[b]	
Antiparasitic products, insecticides, and repellents	P	3 (2%)	5 (5%)	8 (8%)	Wald χ^2 = 3.44	
Respiratory system	R	30 (24%)	18 (17%)	20 (20%)	Wald χ^2 = 2.16	
Sensory organs	S	11 (9%)	7 (6%)	9 (9%)	Wald χ^2 = 0.58	
Various	V	0 (0%)	1 (1%)	0 (0%)	N/A[b]	

Note. Non-significant pairwise group comparisons are not reported. Several subgroups of psychotropic medications (N06C, N06D) and somatic medications (M01B, M01C, M02, M03, M04, M05, M09, N03, N04) were not included in the table, as these were not prescribed in

any of the childhood groups.
A = childhood ADHD, ADHD = attention-deficit/hyperactivity disorder, ATC = anatomical therapeutic chemical, C = controls, NSAIDS = non-steroids anti-inflammatory and antirheumatic products, S = siblings.
[a] All subgroups of psychotropic medication (3rd ATC level) include N05A, N05B, N05C, N06A, N06C, N06D (excluding ADHD medication, N06B).
[b] Due to no variance in any group, no formal statistical testing was conducted for this outcome represented by N/A in the table.
[c] All subgroups of somatic medications (1st ATC level) include A, B, C, D, G, H, J, K, L M, N, N, P, R, S, V.
[d] All prescriptions in the musculo-skeletal system (1st ATC level, M) are from the subgroup NSAIDS (3rd ATC level M01A) and therefore shown together.
$^{*}p < .05$ $^{**}p < .01$ $^{***}p < .001$.

Discussion

This 18-year prospective cohort study investigated medication use in adults with childhood ADHD, their siblings and controls without an ADHD diagnosis at study entry and showed childhood ADHD was related to elevated medication use, although this was partly attributable to current psychiatric status. As siblings had similar medication use to controls, we found no evidence of the influence of shared childhood factors on adult medication use. As expected, the childhood ADHD group was 6 to 8 times more likely to be on ADHD medication (26%) and was prescribed more different ADHD medications compared to both their siblings and controls. Also, the childhood ADHD group was 4 times more likely to be on other psychotropic medication and prescribed a larger number of different psychotropic medications compared to controls. Finally, adults with a childhood ADHD diagnosis were 3 to 7 times more likely to be on neurological medications, specifically analgesics and NSAIDs compared to both siblings and controls. No group differences were found for the other subgroups of psychotropic or somatic medication.

In line with our hypotheses, childhood ADHD was related to increased use of specific medications, including ADHD medication use, psychotropic medication use, and neurological medications, specifically analgesics, and NSAID. Our results strengthen previous findings from two Swedish register-based studies [27, 124]. Specifically, the added value of our study is that we specified differences in medication subgroups prescriptions, where medication subgroups were not investigated in the study on medication costs [27]. Also, we investigated medication use in a sample of whom only 26% currently used ADHD medication in contrast to the previous study including only adults using ADHD medication [124].

After controlling for current ADHD and MDD, groups no longer differed on psychotropic medication use, but the childhood ADHD group still had an increased risk for ADHD medication use, NSAIDs use, and more different psychotropic medication prescriptions, suggesting both childhood ADHD and current psychiatric status are associated with elevated adult medication use. Analgesics and NSAIDs are often prescribed for pain and inflammation, which have been associated with both ADHD [128, 129] and MDD [130, 131]. Therefore, the association with the use of these specific medications might be influenced or exacerbated by higher current ADHD and MDD rates in this group. Prevention and interventions strategies should consider co-occurring symptoms such as pain and inflammation, particularly in individuals with childhood ADHD who are at increased risk for MDD.

Importantly, despite elevated medication use in adults with a childhood ADHD diagnosis, our results show that most adults with childhood ADHD do not use any medication. Specifically, the majority (74%) of all adults with childhood ADHD

were not prescribed any ADHD medication. Furthermore, the total number of different psychotropic prescriptions was relatively low in the childhood ADHD group (M = 0.20) compared to the number found in another study (M = 2.22) [27], and a relatively limited number of specific somatic medication subgroups was found to differ. Similarly, a registry study into medication costs found that ADHD persistence but not ADHD remittance was related to more somatic medication costs [27], implying that adults with a current ADHD diagnosis might be more vulnerable and experience more problems associated with somatic medication prescriptions. This is in line with the physical health outcomes of our cohort, where adults with persistent ADHD had worse general health perceptions and sleep quality compared to adults with remitted ADHD [127]. While we found that childhood ADHD was not associated with the use of the majority of somatic medications, ADHD has previously been linked to increased risk for several somatic conditions in a registry study [122]. However, the effects reported in that study might have been overestimated due to inclusion of individuals with the most severe ADHD symptoms, as the ADHD diagnosis was based on health claims and the prevalence of individuals with ADHD was lower than expected (1.79%). Our study suggests that childhood ADHD is only related to medication use for a limited number of somatic health problems.

In contrast to expectation, medication use of the siblings of adults with a childhood diagnosis of ADHD did not differ from controls, implying the shared genetic and childhood environment do not relate to adult medication use, at least as measured in the current study. This could imply that the elevated medication use seen in the adults with childhood ADHD is not due to shared childhood factors but rather to unique factors potentially linked to an ADHD diagnosis in childhood and/or current psychiatric status, i.e., higher current rates of ADHD and MDD. In contrast, siblings were not at an increased risk in terms of current psychiatric status. However, the siblings included in the current follow-up had a higher IQ and less anxiety symptoms compared to the initial sample of siblings at study entry, leaving the possibility that some siblings with elevated medication use might have been lost to follow-up. Nonetheless, children with ADHD seem to have more frequent exposure to healthcare services compared to their siblings and controls [132, 133]. Therefore, individuals with a childhood ADHD diagnosis may potentially be subjected to a surveillance bias, with an increased chance of detection of other conditions accompanied with treatment with medication [134]. The lack of elevated medication use of siblings, despite shared childhood factors, suggests that medication use could be influenced by unique effects of adults with childhood ADHD, potentially including comorbid problems and iatrogenic effects.

Our study has some limitations. Firstly, the current sample size allowed us to detect moderate to large effects. A larger sample would have allowed detection of smaller effects and might have turned the non-significant difference in antidepressant prescriptions (childhood ADHD group = 9% versus other groups =

3%) into a significant finding. Secondly, medication was based on pharmacy dispensing records, which do not inform on actual use or adherence, while this might differ between groups [2, 135]. Therefore, the observed group differences may reflect medication prescriptions instead of medication use. Thirdly, medication use does not include non-prescription medication, such as over-the-counter painkillers or medication abuse. Given the accessibility of over-the-counter painkillers and elevated pain medication prescriptions (analgesics, NSAIDs) and substance abuse for adults with childhood ADHD [16], our effect estimates likely are conservative. Future studies should include self-reported medication use and adherence.

To conclude, our 18-year longitudinal study was among the first to objectively assess medication use using recent pharmacy dispensing records in adults diagnosed with ADHD in childhood, offering insights into the long-term health burden of those with a childhood ADHD diagnosis. Furthermore, our novel design including siblings of adults with childhood ADHD showed that unique factors of adults with childhood ADHD are more important than shared factors for adult medication use. Potential mechanisms of therapeutic interventions on pain and inflammation in adults with childhood ADHD should be investigated to prevent and treat these phenomena [128, 136]. Overall, our findings confirm that adults with a childhood ADHD diagnosis are more likely to experience a long-term health burden.

Table S3.1. *Comparison of successfully retained participants with childhood ADHD to the initially participating sample (wave I)*

Wave I measure, *M* (*SD*)	Retained (*n* = 125)	Initial sample (*n* = 510)	Retained vs initial sample
Age in years	10.79 (2.76)	10.95 (2.80)	Wald χ^2 = 0.23
Male, *n* (%)	81 (75%)	400 (78%)	Wald χ^2 = 0.77
Estimated TIQ	99.67 (12.49)	98.88 (11.99)	Wald χ^2 = 0.27
Parental education level	5.25 (0.73)	5.19 (0.74)	Wald χ^2 = 0.40
ADHD symptoms	77.14 (9.29)	75.29 (9.80)	Wald χ^2 = 3.57
ODD symptoms	65.98 (12.06)	66.09 (12.37)	Wald χ^2 = 0.01
Anxious/shy behavior	56.91 (13.72)	58.01 (13.74)	Wald χ^2 = 0.49
Behavioral and emotional difficulties	18.59 (5.51)	18.92 (6.18)	Wald χ^2 = 0.36

Note. For a description of the measures displayed in the table, see main text.
ADHD = attention-deficit/hyperactivity disorder, ODD = oppositional defiance disorder, TIQ = total intelligence quotient.

Table S3.2. *Comparison of successfully retained siblings to the initially participating sample (wave I)*

Wave I measure, *M* (*SD*)	Retained (*n* = 109)	Initial sample (*n* = 361)	Retained vs initial sample
Age in years	10.85 (3.63)	10.79 (3.63)	Wald χ^2 = 0.04
Male, *n* (%)	36 (37%)	158 (44%)	Wald χ^2 = 1.93
Estimated TIQ	105.35 (10.88)	102.11 (11.28)	Wald χ^2 = 5.18*
Parental education level	5.15 (0.81)	5.15 (0.77)	Wald χ^2 = 0.01
ADHD symptoms	50.59 (9.84)	50.96 (9.82)	Wald χ^2 = 0.04
ODD symptoms	49.34 (9.36)	51.01 (10.19)	Wald χ^2 = 2.28
Anxious/shy behavior	48.60 (7.85)	50.63 (10.32)	Wald χ^2 = 4.22*
Behavioral and emotional difficulties	6.82 (6.00)	7.18 (5.83)	Wald χ^2 = 0.27

Note. For a description of the measures displayed in the table, see main text.
ADHD = attention-deficit/hyperactivity disorder, ODD = oppositional defiance disorder, TIQ = total intelligence quotient.
*p<.05.

Table S3.3. *Comparison of successfully retained controls to the initially participating sample (wave I)*

Wave I measure, *M* (*SD*)	Retained (*n* = 101)	Initial sample (*n* = 281)	Retained vs initial sample
Age in years	11.11 (3.25)	11.17 (3.27)	Wald χ^2=0.00
Male, *n* (%)	32 (39%)	117 (42%)	Wald χ^2=0.17
Estimated TIQ	106.34 (10.52)	106.15 (10.38)	Wald χ^2=0.04
Parental education level	5.38 (0.52)	5.29 (0.58)	Wald χ^2=2.00
ADHD symptoms	46.83 (4.75)	46.59 (4.63)	Wald χ^2=0.28
ODD symptoms	47.26 (6.70)	47.12 (6.66)	Wald χ^2=0.01
Anxious/shy behavior	48.60 (8.36)	48.75 (7.88)	Wald χ^2=0.05
Behavioral and emotional difficulties	N/A	N/A	N/A

Note. For a description of the measures displayed in the table, see main text.
ADHD = attention-deficit/hyperactivity disorder, ODD = oppositional defiance disorder, TIQ = total intelligence quotient.

Table S3.4. *Effect sizes of differences in medication use between adults with childhood ADHD, their siblings, and controls*

	Controls vs childhood ADHD	Siblings vs childhood ADHD	Controls vs siblings
ADHD medication use			
ADHD medication	OR = 8.35***	OR = 5.89***	OR = 1.42
ADHD medication, number of different medications	β = 0.65***	β = 0.61***	β = 0.05
Psychotropic medications use			
Psychotropic medication	OR = 3.82*	OR = 1.99	OR = 0.13
Psychotropic medication, number of different medications	β = 0.38**	β = 0.26	β = 1.92
Somatic medications use			
NSAIDs[a]	OR = 6.98**	OR = 3.63**	OR = 1.92
Neurological, other than psychotropic medications	OR = 5.15*	OR = 3.25*	OR = 1.58
Analgesics	OR = 4.12*	OR = 4.43*	OR = 0.93

Note. ADHD = attention-deficit/hyperactivity disorder, NSAIDs = non-steroids anti-inflammatory and antirheumatic products, OR = odds ratio.
[a] All prescriptions in the musculo-skeletal system (1st ATC level, M) are from the subgroup NSAIDS (3rd ATC level M01A) and therefore shown together.
*p < .05 **p < .01 ***p < .001.

Table S3.5. *Medication use in adults with childhood ADHD, their siblings, and controls, controlling for demographic differences*

	Controls vs childhood ADHD	Siblings vs childhood ADHD	Pairwise group comparisons
ADHD medication use			
ADHD medication	OR = 7.66***	OR = 5.64**	A > S, C
ADHD medication, number of different medications	β = 0.61***	β = 0.58***	A > S, C
Psychotropic medication use			
Psychotropic medication	OR = 3.92*		A > C
Psychotropic medication, number of different medications	β = 0.36**		A > C
Somatic medications use			
NSAIDs[a]	OR = 9.17**	OR = 5.03**	A > S, C
Neurological, other than psychotropic medications	OR = 5.28*	OR = 3.13*	A > S, C
Analgesics	OR = 3.75	OR = 3.87*	A > S

Note. Only medication outcomes with significant pairwise group differences were subjected to sensitivity analysis including demographic differences (sex, age, educational level) that differed between groups as covariates. Non-significant pairwise group comparisons are not reported.
A = childhood ADHD, ADHD = attention-deficit/hyperactivity disorder, C = controls, NSAIDs = non-steroids anti-inflammatory and antirheumatic products, S = siblings.
[a] All prescriptions in the musculo-skeletal system (1st ATC level, M) are from the subgroup NSAIDS (3rd ATC level M01A) and therefore shown together.
*p < .05 **p < .01 ***p < .001.

Table S3.6. *Medication use in adults with childhood ADHD, their siblings, and controls, controlling for psychiatric differences*

	Controls vs childhood ADHD	Siblings vs childhood ADHD	Pairwise group comparisons
ADHD medication use			
ADHD medication	OR = 6.19**	OR = 4.50**	A > S, C
ADHD medication, number of different medications	β = 0.52**	β = 0.48***	A > S, C
Psychotropic medication use			
Psychotropic medication	OR = 3.16		
Psychotropic medication, number of different medications	β = 0.38*		
Somatic medications use			
NSAIDs[a]	OR = 5.83*	OR = 3.03*	A > S, C
Neurological, other than psychotropic medications	OR = 3.17	OR = 2.01	
Analgesics	OR = 2.73	OR = 2.90	

Note. Only medication outcomes with significant pairwise group differences were subjected to sensitivity analysis including psychiatric status (ADHD, MDD) that differed between groups as covariates. Non-significant pairwise group comparisons are not reported.
A = childhood ADHD, ADHD = attention-deficit/hyperactivity disorder, C = controls, NSAIDs = non-steroids anti-inflammatory and antirheumatic products, S = siblings.
[a] All prescriptions in the musculo-skeletal system (1st ATC level, M) are from the subgroup NSAIDS (3rd ATC level M01A) and therefore shown together.
*p < .05 **p < .01 ***p < .001.



CHAPTER 4

Differences between males and females in long-term outcomes of ADHD

van der Plas, N. E., Kaag, A. M., Franke, B., Hartman, C. A., Hoekstra, P. J., Rommelse, N. N. J., Sprooten, E., Oosterlaan, J., Luman, M., & Noordermeer, S. D. S. (2026). Differences between males and females in long-term outcomes of ADHD. *Neurodiversity.*

Abstract

Background. Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder, with increased risk for negative adult long-term outcomes. These outcomes may differ between males and females with ADHD, but whether these differences are more pronounced in ADHD or similar to those in the general population remains unclear.

Method. In an 18-year follow-up of 283 children (M_{age} = 28.48) we assessed if sex moderated 51 long-term outcomes across 7 domains: psychiatric status, behavioral/emotional problems, academic/professional functioning, adaptive functioning, neurocognition, physical health, and healthcare service use in those with ADHD ($n_{females}$ = 50, n_{males} = 104), and without ADHD ($n_{females}$ = 77, n_{males} = 52). Additionally, we aimed to explore the moderating role of gender-expression.

Results. Sex interacted with group for social functioning: males with ADHD were more likely to show lower social functioning compared to females with ADHD and controls. There were no sex differences on the other outcomes. As sex and gender-expression were highly similar (r = .94), specific effects of gender-expression could not be studied.

Conclusions. Generally, sex did not have a more pronounced effect on long-term outcomes of childhood ADHD in individuals with ADHD compared to the general population. Gender-expression could not be studied in our predominantly cisgendered sample.

Key words: ADHD, sex, functioning, long-term, gender

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed behavioral disorders in children, with an estimated global prevalence of 3% to 14% in children and 3% and 7% in adults, depending on the definition used [12, 60]. In childhood, the prevalence rates of ADHD are 3 to 16 times higher in boys compared to girls [5]. This gap attenuates during adulthood to a males to females ratio between 2:1 and 1:1 [6]. This might be due to, for example, a differential developmental trajectory of ADHD in males and females, or sex-related differences in recognition and referral in childhood. These differences can lead to more diagnoses in boys or missed diagnoses in girls [4, 137]. For instance, females do show hyperactive-impulsive symptoms, but with a different, less overt, expression, resulting in under-recognition [10].

The developmental trajectory of ADHD into adulthood is heterogenous, but more than 60% of all children with ADHD still experience some functional impairment in adulthood. Also, these children are at an increased risk for negative long-term outcomes on several domains of functioning in adulthood [3, 127]. Specifically, these adults are at an increased risk to develop psychiatric conditions including major depressive disorder (MDD) and substance use disorder (SUD), as well as behavioral/emotional problems including emotional dysregulation and autistic traits [16, 17]. Further affected domains are academic/professional functioning (e.g., not finishing high school and more likely to receive public assistance), adaptive functioning (e.g., reduced social functioning), neurocognitive functioning (e.g., reduced attentional span and executive functioning), physical health (e.g., increased risk for obesity and somatic conditions), and healthcare service use (e.g., higher healthcare utilization) [4, 16, 18, 23, 24, 27, 122].

Currently, information on possible differences between males and females in long-term outcomes of ADHD is primarily based on studies of adults with ADHD [5, 6, 30, 31]. These studies underscore the importance of considering differences between males and females in long-term outcomes of ADHD. For example, males with ADHD have more difficulties with complex attention and show higher levels of antisocial behaviors compared to females with ADHD, while females with ADHD report more symptoms of mood disorders and higher levels of stress compared to males with ADHD [5, 6, 30, 31]. However, these differences are primarily observed in cross-sectional studies including adults with ADHD. Importantly, those studies do not disentangle whether the observed sex differences are related to childhood or adulthood ADHD. Therefore, they do not inform whether the differences are long-term effects of childhood ADHD or effects of current ADHD, while childhood ADHD may be associated with specific risks.

Some potential sex differences were suggested from prospective cohort studies. Specifically, the long-term outcomes of a female-only cohort differed from the

long-term outcomes from predominantly male samples, including problems with depression, self-harm, sexual behavior, and intimate partner violence [5]. Therefore, although prospective cohort studies are necessary to investigate potential sex differences in long-term outcomes of childhood ADHD, these are sparse leaving this domain understudied.

Although sex-specific developmental patterns are already present in the general population, they may be more pronounced in ADHD. For example, females with ADHD engage in more risky sexual behavior than males with ADHD and females without ADHD, increasing the risk of sexually transmitted infections and unplanned parenthood [10, 32]. Despite a review reporting no impact of adult ADHD on sex differences in psychiatric disorders [138], a later cohort study did find more pronounced sex-specific associations between timing of ADHD diagnosis and negative adolescent outcomes, including psychiatric and educational outcomes [139]. A later diagnosis of ADHD was more strongly associated with depression in females than males. Additionally, a large registry study found that females with ADHD had more psychiatric comorbidities, greater medication use, and more health care utilization than males with ADHD and female controls [140]. However, previous studies have not specifically investigated long-term outcomes of childhood ADHD. Further, it remains unknown if potential sex differences are more pronounced in ADHD compared to the general population for other important domains of functioning, such as adaptive or neurocognitive functioning.

Similarly, it remains underexplored whether potential sex differences in long-term outcomes in individuals with ADHD might (partially) be due to gender-related factors, rather than biological sex-related factors. Gender refers to the socially constructed roles, behaviors, expression and identities that a given society considers appropriate for males and females [29]. While sex- and gender-related factors are often conflated in previous research, both constructs operate through partly different mechanisms. This also means that those different mechanisms have specific effects, and gender-related factors may uniquely influence expression and recognition of ADHD. For example, gender roles, often defined as masculinity and femininity, that are based on social norms (gendered expectations) may shape the perception and presentation of ADHD behaviors. For instance, ADHD symptoms may be underrecognized in girls, despite similar levels of objectively measured ADHD symptoms in boys and girls, suggesting a recognition bias [141]. This bias may not only be caused by biological sex-related factors, but may also be caused by gendered perceptions in which hyperactive behavior is seen as gender normative behavior for males (masculinity) but not females (femininity). Therefore, parents and teachers may interpret hyperactive behavior differently for males and females, with hyperactivity being more overt in boys and thus more readily interpreted as stereotypical ADHD behavior, while the same behavior in girls may be misinterpreted as excitement or emotionality rather

than an indication of ADHD [142]. Additionally, females may more often mask and camouflage their hyperactive behavior as it is not gender normative behavior. These gendered perceptions may lead to underrecognition and underdiagnosis of ADHD in females, which may result in long-term problems due to missing support provided by a timely diagnosis. Furthermore, gender norms (i.e., social gender-related expectations) may shape experiences and risks differently for males and females. For example, females with ADHD may face stronger social stigma than males around behaviors, such as risky sexual behavior [10]. This stigma can cause social and relational problems (e.g., bullying or abuse), which may in turn be associated with a heightened risk for negative long-term outcomes. Thus, some problems linked to ADHD (e.g., risky sexual behavior) may partly reflect effects of restrictive gender biases (i.e., a specific gender is favored in a specific situation) [10]. Notably, ADHD seems to have a higher prevalence in transgender individuals compared to the general population [143], which further emphasizes the relevance of investigating gender on top of sex in ADHD. Importantly, as there currently is a lack of research into what drives differences between males and females, previously described sex differences may (partly) reflect gender-related differences.

Notably, we have used biological sex-based terms (males/females) throughout the manuscript, with biological sex defined as sex-assignment at birth. However, we acknowledge that the observed sex differences cannot be attributed to biology alone and likely emerge from the combined influence of biological and gender-related sociocultural dimensions [30].

Currently, most knowledge on differences between males and females with ADHD comes from studies using cross-sectional designs or from participants with ADHD in adulthood. Therefore, it remains unclear whether there are sex differences in long-term outcomes of adults with a childhood ADHD diagnosis; there are only a few prospective cohort studies available on long-term outcomes of childhood ADHD and those included few females [5]. Consequently, the aim of the current study was to investigate the potential moderating role of sex in the association between ADHD and long-term outcomes, thereby investigating if differences between males and females in long-term outcomes of childhood ADHD are more pronounced in an ADHD group compared to the general population. This was investigated using an 18-year follow-up of a large cohort of individuals diagnosed with ADHD in childhood and a control group without childhood ADHD. A broad range of long-term outcomes was assessed across several domains of functioning: psychiatric status, behavioral/emotional problems, academic/professional functioning, adaptive functioning, neurocognitive functioning, physical health, and healthcare service use. Also, we explored the potential moderating role of gender roles in this association.

Methods

Sample

For the current study, 283 participants were re-assessed from a longitudinal cohort study initiated as part of the Dutch branch of the International Multicenter ADHD Genetics (IMAGE) study [58], of which the current study is an 18-year follow-up (as described in van der Plas, et al. [127]). Initially, children diagnosed with ADHD were recruited via specialized child mental health care centers. Control children were recruited through regular primary schools. After enrollment in the cohort (wave I, 2003-2005), follow-ups took place in 2009-2012 (wave II, NeuroIMAGE) and 2015-2016 (wave III, NeuroIMAGE2) [59]. Inclusion criteria at wave I were: aged 5-19 years, Caucasian descent, IQ ≥70, and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders or known genetic disorders. Both ADHD and control families were recruited. ADHD families had at least one child with ADHD combined type, while control families had at least one child without ADHD and did not have any first-degree family members diagnosed with ADHD. Similar inclusion criteria were used in waves II and III, except that in these waves any ADHD subtype for newly recruited participants with ADHD was allowed. In the current follow-up (wave IV, 2021-2024), all participants who participated in any of the previous waves were invited and reassessed, leading to the data used in the current study. The current study included only childhood ADHD cases from an ADHD family with an ADHD diagnosis at study entry in the ADHD group, and control participants from a control family at study entry in the control group.

Outcomes at follow-up (wave IV)

The assessment targeted the following outcome domains: 1) psychiatric status (DSM-5 diagnoses of ADHD, MDD, anxiety disorders, antisocial personality disorder [ASPD], and SUD); 2) behavioral and emotional problems (ADHD symptoms, externalizing and internalizing problems, autistic traits, mood dysregulation, callous-unemotional traits, rule breaking and aggression, substance use, and gaming), 3) academic and professional functioning (educational achievement, grade retention, and employment), 4) adaptive functioning (perceived stress, risk-taking and risk perception, social functioning, emotional well-being, quality of life, significant life events, and creativity), 5) neurocognitive functioning (estimated total intelligence quotient, memory, cognitive flexibility), 6) physical health (body mass index, physical activity, general health perceptions, physical functioning, pain, energy/vitality, sleep quality, diet), and 7) healthcare service use (visits to healthcare institutions, medication use). All domains were assessed using several measures resulting in a total of 51 outcomes.

Table S2.1 provides a description of the instruments used, selected based on strong psychometric characteristics, and the derived dependent variables. Also, two custom-made questionnaires were used to assess: 1) diet (domain physical health), using a visual analogue scale to assess diet health and adherence to diet advice of the Netherlands Nutrition Centre; and 2) number of visits to healthcare institutions in the last year (domain healthcare service use), using an extensive list of all healthcare institutions, including all medical specialists. Demographic information was assessed through self-report, including 1) age and sex, 2) current living situation, and 3) information on the participant's offspring, if applicable, including number of children, their birth date, sex, and any possible diagnoses. The demographic information was used only to describe the sample. In this study, sex was defined as sex-assignment at birth male, female, or intersex) and will be referred to as sex.

Medication use (domain healthcare service use) of one full year (the most recent full year available) was assessed using pharmacy dispensing records. If the most recent full year overlapped more than a month with the period of the COVID pandemic with healthcare-related restrictions (February 2020 until February 2022), the year before the start of the COVID pandemic was chosen (January 2019 to January 2020) to obtain generalizable information on medication use unobstructed from COVID healthcare restrictions [65-67, 144]. Use of ADHD medication (yes/no) was based on the presence of at least one prescription of amphetamines, methylphenidate, or atomoxetine, using anatomical therapeutic chemical (ATC) codes. General medication use was captured by the total number of different ATC codes prescribed.

Gender

Gender roles (hereafter referred to as gender-expression) were defined by expression of gender roles as measured by the Traditional Masculinity-Femininity (TMF) scale [145]. The TMF assesses how masculine or feminine an individual defines themselves according to social norms for males and females using six self-rated items which load to one factor: a one-dimensional masculinity-femininity construct. Five items are measured on an 8-point-scale, ranging from 0 (very masculine) to 7 (very feminine). The remaining item, "Ideally, I would like to be male or female…", was rated on a two-point scale using the extreme values of the other items (males = 0, females = 7). All responses were summed to obtain a total score (range = 0 – 42), with higher scores reflecting more traditional femininity. The TMF reliably measures masculinity and femininity (α = .94) and correlates moderately with other measures of gender (all r > 0.31) [145]. Internal consistency of the TMF in the current study was excellent (α = .98).

Procedure (wave IV)

Before follow-up assessment took place, all participants signed informed consent. Assessments comprised self-reported online questionnaires, other-reported online questionnaires, and two (secured) video calls, see Table S2.1 for included measures at each assessment part.

The assessments started with the participant's completion of the self-reported online questionnaires. The participants forwarded the link for the other-reported questionnaires to, preferably, their significant other, otherwise their parents or someone else closest to them. Before assessments by video call took place, participants completed online screening questions of the Structured Clinical Interview for DSM-5 Disorders (SCID-5) modules MDD, anxiety disorders, and ASPD [68], as these psychiatric disorders are most prevalent in adults with childhood ADHD [28]. The SCID-5 module SUD was screened using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST-Lite) [69], which provides a reliable indication of problematic substance use. If the screening questions (SCID-5 or ASSIST-Lite) yielded scores indicative of any diagnosis, the corresponding full SCID-5 module (i.e., MDD, anxiety disorder, ASPD, SUD) was assessed via an interview. The diagnostic interview included the SCID-5 ADHD module for all participants. This interview was administered by researchers certified and trained in SCID-5 administration.

During the second video call, assessment of the cognitive tests took place. Trained researchers administered tests according to a standardized protocol and using standardized instructions. Participants were instructed to call from a laptop/computer (or tablet if no laptop/computer was available), with a webcam and proper internet connection, and to be alone in a room without any distractions. Finally, pharmacy dispensing records were requested from the pharmacies of participants who gave permission to do so.

The study procedure was similar for all participants. However, if participants were unwilling to participate in the video calls, they were allowed to only complete the online questionnaires to increase participant retention. The study was approved by the local medical ethics committee of the Amsterdam Universities Medical Centers (ABR NL77520.029.21). All data was pseudoanonymized, and participants received 25 euros after completion.

Statistical analyses

Attrition analyses were run to test representativeness of the retained sample compared to the initial sample at the earliest inclusion (IMAGE, wave I), with separate analyses run for four childhood groups: males with childhood ADHD, females with childhood ADHD, male controls, and female controls. The attrition analyses were run on data collected in wave I, using Generalizing Estimating

Equation (GEE) with an exchangeable correlation structure to account for familial dependency for each of the four groups. Groups were compared on sex, age, estimated total intelligence quotient (TIQ; estimated by the Vocabulary, Similarities, Block Design and Picture Completion subtests of the Wechsler Intelligence Scale for Children [WISC-III] or WAIS-III) [76, 77], average educational level of both parents (or one parent, if only information on one parent was available), parent-reported symptoms of ADHD, oppositional defiant disorder (ODD), anxious/shy behavior (using scale N, A, and D of the Conners' ADHD rating scale long version [78], respectively), and behavioral and emotional difficulties (using the Strengths and Difficulties Questionnaire [79]; not assessed in controls).

Multiple imputation, including parcel summary scores of online questionnaires and video call measures, was used to impute missing outcome variables with maximum 10% missing. Percentage of missing data across all outcomes of the online questionnaires and video calls varied between 0-8%, with 20 participants (7%) not participating in the online video calls. Pharmacy data were not imputed, as 20% was missing, with 21 participants (7%) not providing consent to obtain their pharmacy records, and pharmacies failing to provide the required information of another 36 participants (13%) despite 3 reminders being sent. Based on the recommendation to impute as many datasets as the percentage of participants with any missing data [71], eight imputed datasets were created. In addition to the parcel summary scores, family and sex were included as auxiliary variables to support the imputation models. The analyses were rerun eight times using each imputed dataset and subsequently the summary statistics of each analysis were pooled [71].

GEE, with an exchangeable correlation structure, was used to compare outcomes. Familial dependency was accounted for, as siblings could have been included in the same group. Outcomes with no variation or complete separation (i.e., where the outcome was predicted perfectly) were precluded from statistical testing [81]. Using the pooled effect sizes (across the eight imputed datasets), the main effects were adjusted for multiple testing using false discovery rate correction (FDR), applied within each of the seven outcome domains [82]. As imputed data was used in the analyses, a complete case analysis of the main model (moderation of sex) was provided for comparison.

Effect sizes were quantified by calculating odds ratios (OR) for categorical outcomes, and standardized betas for continuous outcomes. The magnitude of the standardized betas was interpreted using similar threshold levels as used to interpret Cohen's *d* (small = 0.2 to 0.5, moderate = 0.5 to 0.8, large ≥ 0.8) [83]. Only the interaction effects between group and sex are discussed in the results section, since this was the aim of the current study. A univariate GEE to assess main effects of sex on the outcomes was run to test the validity of the sample in terms of commonly reported sex differences and the results of this analysis are reported in

the Supplemental Material (Table S4.1). This univariate GEE included only sex as a main effect in separate models for each of the 51 outcomes. No covariates were included. A detailed description of the differences between adults with childhood ADHD and controls is provided in [127]. All analyses were performed in R (v4.3.0) [84]. Our data contains sensitive information and is available on request and under specific conditions. However, the analysis code is available on the Open Science Framework (OSF) https://doi.org/10.17605/OSF.IO/E24WB.

Moderation of sex

To examine whether differences in outcomes between childhood ADHD and controls were moderated by sex, GEE models were used to test the interaction effects between sex and diagnostic group. Specifically, diagnostic group at baseline (ADHD or control) and sex were included as main effects, in addition to the interaction between group and sex, in separate models for each of the 51 outcomes. Again, no covariates were included. Only FDR-corrected *p*-values are provided. Significant interactions were further investigated by comparing groups using post-hoc estimated marginal means for both analyses based on the imputed data and the complete case analysis.

As inclusion criteria differed between wave I versus wave II and II on ADHD subtype, the models were repeated in a sensitivity analysis including inclusion wave (wave I or wave II and III) as a covariate, to assess if the difference in inclusion criteria influenced findings.

Exploratory models of gender

The GEE models were repeated using gender-expression instead of sex to explore moderating effects of gender roles. Post-hoc estimated marginal means were based on baseline status and gender-expression groups ('feminine' and 'masculine') constructed by median split. Finally, to explore distinct moderating effects of gender-expression over and above the moderating effects of sex, GEE analyses on those outcomes with significant interaction effects from the previous models were performed, including both interactions of sex and gender-expression with diagnostic group.

Results

Attrition analysis

This follow-up successfully included 46% of females (*n* = 50) and 26% of males (*n* = 104) with childhood ADHD, and 47% of female controls (*n* = 77) and 44% of male controls (*n* = 52). None of the participants were intersex. Table S4.2-S4.5 show the initial groups and the retained groups, along with the attrition analyses testing representativeness of the retained sample. None of the retained groups differed

from the initial groups in terms of sex, age, estimated TIQ, parental education level, ADHD symptoms, ODD symptoms, anxious/shy behavior, and behavioral and emotional difficulties.

Moderation of sex

Our sample seemed representative in terms of main effects of sex (Table S4.1), as these are consistent with sex differences typically reported in the general population [146-149]. Specifically, in line with what is shown in the general population, females in our study showed more internalizing problems, stress, and general medication use (β range = 0.32 to 0.59), while males showed more callous-unemotional traits, antisocial behaviors, substance use, gaming addiction symptoms, and risk taking behaviors (β range = -0.27 to -0.57).

Regarding demographics, group interacted with sex on being married (OR = 0.11 [95% CI 0.03-0.46], p_{FDR} = .017). The main effect of sex (OR = 3.77 [95% CI 1.35 - 10.53], p_{FDR} = .027) but not group (OR = 2.94 [95% CI 1.06 - 8.16], p_{FDR} = .134) was significant. Post-hoc analyses revealed that both females without childhood ADHD and males with childhood ADHD were more likely to be married than males without childhood ADHD, while females without childhood ADHD were also more likely to be married than females with childhood ADHD.

We tested whether sex modified outcomes for the childhood ADHD and control group by testing the interaction effects between group and sex on the seven domains of functioning. Table 4.1 provides a description of follow-up measures, distinguishing between group and sex, and a description of the significant moderation. See Table 4.2 for effect sizes of sex, diagnostic group, and the moderation.

For adaptive functioning, group and sex interacted on social functioning (ß = 0.74, p_{FDR} = .034). The main effect of group (ß = -0.72, p_{FDR} <.001) but not sex (ß = -0.37, p_{FDR} = .074) was significant. Post-hoc group comparison showed that males with childhood ADHD had lower social functioning compared to females with childhood ADHD and both males and females without childhood ADHD. The average score for males with childhood ADHD was more than 1 standard deviation below the average of Dutch adults [150], indicating difficulties in this domain. Also, females without childhood ADHD had lower social functioning compared to males without childhood ADHD, but their average scores were still within one standard deviation of the average scores of adults [150], indicating no difficulties.

No significant interaction effects between sex and group were observed in the remaining six domains. The complete case analysis showed that the results remained highly similar, suggesting the results of the moderation of sex and group were not influenced by imputed values (Table S4.6). The proportion of complete

cases differed across outcome measures ($range_{females\ ADHD}$ = 85% to 100%, $range_{female\ controls}$ = 90% to 100%, $range_{males\ ADHD}$ = 84% to 100%, $range_{male\ controls}$ = 83% to 100%).

A sensitivity analysis assessed if the difference in inclusion criteria regarding ADHD subtypes between wave I versus wave II and III influenced the results, and showed results remained the same after controlling for inclusion wave across the seven outcome domains (Table S4.7).

Table 4.1. *Follow-up measures for adults diagnosed with childhood ADHD and controls distinguishing between females and males*

Outcome	ADHD females (*n* = 50)	Control females (*n* = 77)	ADHD males (*n* = 104)	Control males (*n* = 52)	Significant sex*group interactions[a]
Demographics, *n* (%)					
Gender, *M* (*SD*)	34.15 (6.87)	35.97 (4.51)	5.69 (4.88)	7.00 (4.87)	-
Age, years (*SD*)	27.36 (4.55)	28.32 (3.67)	29.40 (3.02)	27.94 (3.33)	-
Family status[b]					
Single	18 (36%)	21 (27%)	33 (32%)	15 (29%)	ns
Cohabitation	19 (38%)	27 (35%)	37 (36%)	22 (42%)	ns
Married	6 (12%)	23 (30%)	24 (23%)	5 (10%)	FC, MA > MC; FC > FA
Children at home[c]	3 (33%)	17 (63%)	10 (50%)	3 (60%)	
Co-parenting[c]	1 (11%)	2 (7%)	0 (0%)	0 (0%)	N/A[d]
Living at home with parents/caregivers	7 (14%)	8 (10%)	10 (10%)	8 (15%)	ns
Children (yes/no)	9 (18%)	27 (35%)	20 (19%)	5 (10%)	ns
Number of children, *M* (*SD*)[c]	1.89 (0.93)	1.67 (0.83)	1.70 (0.86)	1.00 (0)	ns
Children with an ADHD diagnosis[c]	0 (0%)	0 (0%)	3 (15%)	0 (0%)	N/A[d]
Children with any diagnosis other than ADHD[c]	3 (33%)	5 (19%)	5 (25%)	0 (0%)	N/A[d]
Psychiatric status, *n* (%)					
DSM-5 ADHD	24 (48%)	7 (9%)	46 (44%)	4 (8%)	ns
DSM-5 MDD	11 (22%)	8 (10%)	17 (16%)	2 (4%)	ns
DSM-5 any anxiety disorder	7 (14%)	8 (10%)	10 (10%)	1 (2%)	ns
DSM-5 ASPD	0 (0%)	1 (1%)	4 (4%)	0 (0%)	N/A[d]
DSM-5 any SUD	3 (6%)	1 (1%)	8 (8%)	4 (8%)	ns
Behavioral and emotional problems, *M* (*SD*)					
ADHD index, Self-reported (CAARS)	63.82 (9.65)	52.39 (11.18)	58.45 (9.93)	48.46 (9.50)	ns

Outcome	ADHD females (*n* = 50)	Control females (*n* = 77)	ADHD males (*n* = 104)	Control males (*n* = 52)	Significant sex*group interactions[a]
ADHD index, Other-reported (CAARS)	56.75 (12.76)	43.68 (8.88)	51.52 (10.74)	40.40 (7.82)	ns
Externalizing problems (ASEBA-ASR)	14.06 (8.10)	6.80 (6.63)	12.97 (8.48)	6.41 (5.94)	ns
Internalizing problems (ASEBA-ASR)	21.22 (13.93)	13.46 (11.48)	13.49 (11.81)	9.47 (8.07)	ns
Autistic traits (ASBQ)	28.86 (15.04)	12.73 (11.67)	25.19 (14.03)	9.33 (9.82)	ns
Mood dysregulation (ARI)	2.84 (2.61)	1.37 (2.15)	2.07 (2.35)	0.84 (1.23)	ns
Callous-unemotional traits (ICU)	18.86 (6.37)	15.23 (5.58)	20.18 (6.64)	19.42 (6.33)	ns
Rule-breaking behavior (STAB)	1.04 (1.89)	0.52 (1.12)	1.62 (2.71)	1.08 (2.79)	ns
Physical aggression (STAB)	5.96 (4.67)	3.38 (3.54)	7.08 (5.83)	3.62 (3.92)	ns
Social aggression (STAB)	6.24 (4.51)	4.31 (4.51)	7.70 (5.32)	5.25 (4.54)	ns
Tobacco use (ASSIST-Lite)	5.11 (7.26)	2.21 (4.94)	4.28 (7.21)	3.54 (7.03)	ns
Alcohol use (ASSIST-Lite)	4.34 (3.62)	3.45 (2.37)	4.69 (3.63)	4.73 (4.04)	ns
Drug use (ASSIST-Lite)	0.91 (2.23)	1.30 (3.40)	2.65 (6.59)	1.94 (4.13)	ns
Gaming addiction symptoms (GAS)	1.02 (2.25)	0.19 (0.86)	2.15 (3.32)	1.35 (2.76)	ns
Academic and professional functioning					
Education Verhage, *M* (*SD*)	5.24 (1.38)	6.12 (0.79)	5.37 (1.15)	6.06 (0.80)	ns
Repeated grade (primary and secondary education), *n* (%)	22 (44%)	15 (19%)	43 (41%)	22 (42%)	ns
Employed, *n* (%)	45 (90%)	71 (92%)	90 (87%)	48 (92%)	ns
Number of times switched jobs, *M* (*SD*)	2.84 (2.53)	1.83 (2.65)	2.63 (3.59)	2.38 (2.35)	ns
Adaptive functioning, *M* (*SD*)					
Perceived stress (PSS)	15.66 (6.06)	11.10 (5.58)	11.54 (5.31)	8.88 (4.77)	ns
Risk-taking (DOSPERT)	17.05 (4.78)	16.48 (3.83)	19.74 (4.67)	19.05 (3.69)	ns
Risk perception (DOSPERT)	29.73 (7.19)	31.01 (3.18)	29.74 (3.32)	29.13 (3.08)	ns

Outcome	ADHD females (*n* = 50)	Control females (*n* = 77)	ADHD males (*n* = 104)	Control males (*n* = 52)	Significant sex*group interactions[a]
Social functioning (SF36)	66.99 (22.15)	66.58 (21.04)	58.84 (19.97)	74.35 (20.11)	MC > FC > MA; FA > MA
Emotional wellbeing (SF36)	61.79 (18.04)	72.81 (15.65)	69.59 (18.82)	75.56 (13.05)	ns
Quality of life – Outlook	54.93 (21.67)	65.72 (15.57)	63.63 (18.32)	69.57 (15.89)	ns
Quality of life – Relationships	57.30 (23.65)	70.45 (18.12)	67.21 (19.85)	74.62 (14.51)	ns
Significant life events (after age 16) (LTE)	4.83 (2.51)	5.16 (2.38)	4.87 (2.80)	4.27 (2.70)	ns
Creative achievement (CAQ)	4.07 (5.97)	3.71 (6.41)	4.77 (9.03)	7.06 (10.63)	ns
Neurocognitive functioning, *M* (*SD*)					
Estimated TIQ (WAIS)	87.58 (13.14)	95.54 (12.10)	91.10 (13.26)	100.01 (9.56)	ns
Short-term memory – digits (WAIS)	8.70 (2.02)	9.39 (2.03)	8.90 (2.13)	9.94 (1.96)	ns
Short-term memory – words (15WT)	47.57 (9.22)	51.61 (9.27)	46.09 (10.24)	51.41 (8.29)	ns
Long-term memory (15WT)	10.14 (2.45)	11.00 (2.65)	9.48 (3.31)	11.00 (2.14)	ns
Working memory (WAIS)	17.19 (4.16)	20.69 (3.82)	18.36 (3.97)	20.55 (3.96)	ns
Letter fluency score (COWAT)	29.07 (9.02)	37.58 (9.69)	31.76 (10.02)	34.43 (11.43)	ns
Physical health, *M* (*SD*)					
BMI	26.47 (5.24)	24.95 (4.60)	26.16 (4.67)	23.15 (2.07)	ns
MET minutes per week (IPAQ)	4246.65 (4305.95)	3077.73 (3103.73)	4962.56 (4887.94)	4712.29 (3861.91)	ns
General health perceptions (SF36)	63.62 (21.74)	70.81 (17.94)	68.17 (19.43)	75.00 (17.74)	ns
Physical functioning (SF36)	81.49 (14.14)	82.97 (13.60)	85.10 (10.36)	87.79 (4.36)	ns
Pain (SF36)	79.95 (21.92)	87.16 (18.25)	86.48 (19.50)	90.58 (14.69)	ns
Energy/vitality (SF36)	50.85 (18.37)	60.07 (17.66)	61.12 (20.58)	63.65 (15.81)	ns
Role limitations due to physical health (SF36)	100 (0)	100 (0)	100 (0)	100 (0)	N/A[d]

Outcome	ADHD females (*n* = 50)	Control females (*n* = 77)	ADHD males (*n* = 104)	Control males (*n* = 52)	Significant sex*group interactions[a]
Role limitations due to emotional problems (SF36)	100 (0)	100 (0)	100 (0)	100 (0)	N/A[d]
Sleep quality (PSQI)	6.73 (4.43)	4.90 (2.66)	5.09 (3.23)	4.24 (3.09)	ns
Healthy diet	6.38 (1.50)	6.60 (1.44)	6.18 (1.80)	6.96 (1.41)	ns
Diet adherence	5.77 (2.14)	6.73 (1.71)	5.50 (2.22)	6.83 (1.54)	ns
Healthcare service use, *M* (*SD*)					
Number of visits to social welfare and/or occupational health and safety service institutes last year	0.34 (1.03)	0.21 (0.94)	0.17 (0.74)	0.13 (0.56)	ns
Number of visits to mental healthcare institutes last year	8.38 (18.77)	2.23 (4.42)	5.40 (30.21)	0.81 (3.72)	ns
Number of visits to physical healthcare institutes last year	14.17 (19.83)	7.88 (9.05)	10.11 (37.61)	6.90 (18.35)	ns
Current ADHD medication use, *n* (%)	9 (18%)	3 (4%)	23 (22%)	1 (2%)	ns
Current general medication use	3.00 (2.79)	1.71 (1.97)	1.28 (1.65)	0.48 (0.99)	ns

Note. Model 1 included diagnostic group, sex, and the interaction between group and sex (FA = childhood ADHD - females, FC = control - females, MA = childhood ADHD - males, MC = control - males).
ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, CAARS = Conners' adult ADHD rating scales, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, DSM-5 = diagnostic and statistical manual of mental disorders fifth edition, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LTE = long-term difficulties questionnaire, MDD = major depressive disorder, MET = metabolic equivalent, PSS = perceived stress scale, PSQI = Pittsburgh sleep quality index, SF36 = short form health survey, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.

[a] Non-significant interactions based on FDR-corrected *p*-values are represented by 'ns' for non significant.
[b] Participants could select several family status measures, so the numbers could add up to be more than 100%.
[c] Assessed only for participants with a child/children (n = 61).
[d] Due to insufficient variation or complete separation, some analyses were impossible to run and are represented by N/A in model comparison columns.

Table 4.2. *Interaction between sex and group on follow-up outcomes in adults with childhood ADHD and controls*

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Demographics			
Family status			
Single			
Group	1.18 (OR)	[95% CI, 0.54 - 2.58]	.800
Sex	0.96 (OR)	[95% CI, 0.39 - 2.37]	.930
Group*Sex	1.23 (OR)	[95% CI, 0.39 - 3.93]	.723
Cohabitation			
Group	0.73 (OR)	[95% CI, 0.36 - 1.46]	.521
Sex	0.68 (OR)	[95% CI, 0.32 - 1.45]	.494
Group*Sex	1.64 (OR)	[95% CI, 0.57 - 4.70]	.491
Married			
Group	2.94 (OR)	[95% CI, 1.06 - 8.16]	.134
Sex	3.77 (OR)	[95% CI, 1.35 - 10.53]	**.027**
Group*Sex	0.13 (OR)	[95% CI, 0.03 - 0.51]	**.028**
Children at home[a]			
Group	0.86 (OR)	[95% CI, 0.11 - 6.77]	.888
Sex	1.13 (OR)	[95% CI, 0.16 - 8.14]	.930
Group*Sex	0.34 (OR)	[95% CI, 0.02 - 4.80]	.491
Co-parenting[a]	N/A[b]	N/A[b]	N/A[b]
Living at home with parents/caregivers			
Group	0.59 (OR)	[95% CI, 0.23 - 1.55]	.497
Sex	0.62 (OR)	[95% CI, 0.23 - 1.70]	.494
Group*Sex	2.37 (OR)	[95% CI, 0.55 - 10.22]	.429
Children (yes/no)			
Group	2.31 (OR)	[95% CI, 0.83 - 6.41]	.255
Sex	4.91 (OR)	[95% CI, 1.80 - 13.37]	**.007**
Group*Sex	0.19 (OR)	[95% CI, 0.05 - 0.70]	**.044**
Number of children[a]			
Group	0.83	0.23	**.004**
Sex	0.80	0.19	**.001**
Group*Sex	-0.59	0.46	.429
Children with an ADHD diagnosis[a]	N/A[b]	N/A[b]	N/A[b]
Children with any diagnosis other than ADHD[a]	N/A[b]	N/A[b]	N/A[b]
Psychiatric status			
DSM-5 ADHD			
Group	8.75 (OR)	[95% CI, 2.98 - 25.64]	**<.001**
Sex	1.08 (OR)	[95% CI, 0.31 - 3.80]	.902
Group*Sex	1.08 (OR)	[95% CI, 0.24 - 4.87]	.922
DSM-5 MDD			
Group	7.03 (OR)	[95% CI, 1.60 - 30.84]	**.020**
Sex	2.82 (OR)	[95% CI, 0.82 - 9.65]	.172
Group*Sex	0.48 (OR)	[95% CI, 0.10 - 2.36]	.490
DSM-5 any anxiety disorder			
Group	5.35 (OR)	[95% CI, 0.56 - 50.81]	.192
Sex	5.85 (OR)	[95% CI, 0.60 - 57.42]	.172
Group*Sex	0.25 (OR)	[95% CI, 0.02 - 3.13]	.490
DSM-5 ASPD	N/A[b]	N/A[b]	N/A[b]
DSM-5 any SUD			
Group	0.98 (OR)	[95% CI, 0.34 - 2.80]	.965
Sex	0.19 (OR)	[95% CI, 0.04 - 1.01]	.172

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Group*Sex	2.76 (OR)	[95% CI, 0.32 - 23.79]	.490
Behavioral and emotional problems			
ADHD index (CAARS)			
Group	0.86	0.14	**<.001**
Sex	0.32	0.15	.097
Group*Sex	0.12	0.21	.847
ADHD index, Other-reported (CAARS)			
Group	0.90	0.13	**<.001**
Sex	0.25	0.11	.097
Group*Sex	0.22	0.21	.822
Externalizing problems (ASEBA-ASR)			
Group	0.70	0.15	**<.001**
Sex	0.01	0.14	.959
Group*Sex	0.16	0.23	.822
Internalizing problems (ASEBA-ASR)			
Group	0.33	0.14	**.040**
Sex	0.29	0.13	.097
Group*Sex	0.23	0.24	.822
Autistic traits, Other-reported (ASBQ)			
Group	1.01	0.14	**<.001**
Sex	0.18	0.13	.255
Group*Sex	0.10	0.22	.847
Mood dysregulation (ARI)			
Group	0.57	0.13	**<.001**
Sex	0.27	0.13	.100
Group*Sex	0.00	0.24	.987
Callous-unemotional traits (ICU)			
Group	0.12	0.16	.504
Sex	-0.63	0.15	**<.001**
Group*Sex	0.42	0.23	.822
Rule-breaking behavior (STAB)			
Group	0.21	0.21	.453
Sex	-0.24	0.18	.293
Group*Sex	0.02	0.25	.987
Physical aggression (STAB)			
Group	0.69	0.15	**<.001**
Sex	-0.04	0.13	.817
Group*Sex	-0.17	0.21	.822
Social aggression (STAB)			
Group	0.49	0.17	**.008**
Sex	-0.19	0.16	.332
Group*Sex	-0.10	0.23	.847
Tobacco use (ASSIST-Lite)			
Group	0.13	0.18	.504
Sex	-0.17	0.15	.332
Group*Sex	0.32	0.25	.822
Alcohol use (ASSIST-Lite)			
Group	0.03	0.19	.868
Sex	-0.34	0.17	.100
Group*Sex	0.22	0.26	.822
Drug use (ASSIST-Lite)			
Group	0.16	0.18	.481
Sex	-0.13	0.14	.431

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Group*Sex	-0.21	0.21	.822
Gaming addiction symptoms (GAS)			
Group	0.33	0.19	.128
Sex	-0.38	0.15	.071
Group*Sex	-0.04	0.23	.987
Academic and professional functioning			
Education Verhage			
Group	-0.65	0.15	**<.001**
Sex	0.02	0.13	.937
Group*Sex	-0.14	0.23	.654
Repeated grade (primary and secondary education)			
Group	0.97 (OR)	[95% CI, 0.47 - 2.00]	.937
Sex	0.34 (OR)	[95% CI, 0.15 - 0.78]	**.047**
Group*Sex	3.30 (OR)	[95% CI, 1.10 - 9.93]	.135
Employed			
Group	0.51 (OR)	[95% CI, 0.16 - 1.70]	.550
Sex	0.95 (OR)	[95% CI, 0.25 - 3.59]	.937
Group*Sex	1.48 (OR)	[95% CI, 0.27 - 8.16]	.654
Number of times switched jobs			
Group	0.09	0.16	.757
Sex	-0.17	0.15	.531
Group*Sex	0.24	0.22	.578
Adaptive functioning			
Perceived stress (PSS)			
Group	0.47	0.15	**.009**
Sex	0.41	0.15	**.015**
Group*Sex	0.25	0.24	.436
Risk-taking (DOSPERT)			
Group	0.10	0.16	.532
Sex	-0.56	0.15	**.003**
Group*Sex	0.01	0.23	.975
Risk perception (DOSPERT)			
Group	0.12	0.13	.403
Sex	0.45	0.13	**.003**
Group*Sex	-0.41	0.27	.436
Social functioning (SF36)			
Group	-0.72	0.16	**<.001**
Sex	-0.37	0.17	.071
Group*Sex	0.74	0.25	**.029**
Emotional wellbeing (SF36)			
Group	-0.35	0.15	**.045**
Sex	-0.13	0.13	.327
Group*Sex	-0.26	0.23	.436
Quality of life – Outlook			
Group	-0.35	0.16	**.048**
Sex	-0.23	0.15	.168
Group*Sex	-0.08	0.24	.828
Quality of life – Relationships			
Group	-0.36	0.14	**.038**
Sex	-0.17	0.14	.239
Group*Sex	-0.16	0.22	.599
Significant life events (after age 16) (LTE)			

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Group	0.24	0.17	.225
Sex	0.31	0.16	.089
Group*Sex	-0.29	0.24	.436
Creative achievement (CAQ)			
Group	-0.28	0.20	.225
Sex	-0.39	0.19	.071
Group*Sex	0.32	0.24	.436
Neurocognitive functioning			
Estimated TIQ (WAIS)			
Group	-0.64	0.16	**<.001**
Sex	-0.33	0.16	.295
Group*Sex	0.19	0.24	.530
Working memory (WAIS)			
Group	-0.55	0.16	**.001**
Sex	-0.04	0.16	.823
Group*Sex	-0.24	0.23	.530
Short-term memory – digits (WAIS)			
Group	-0.48	0.16	**.004**
Sex	-0.26	0.16	.305
Group*Sex	0.13	0.24	.594
Short-term memory – words (15WT)			
Group	-0.56	0.16	**.001**
Sex	-0.06	0.17	.823
Group*Sex	0.21	0.25	.530
Long-term memory (15WT)			
Group	-0.57	0.16	**.001**
Sex	-0.04	0.16	.823
Group*Sex	0.30	0.23	.530
Letter fluency score (COWAT)			
Group	-0.32	0.19	.089
Sex	0.22	0.18	.467
Group*Sex	-0.40	0.25	.530
Physical health			
BMI			
Group	0.64	0.12	**<.001**
Sex	0.38	0.13	**.013**
Group*Sex	-0.29	0.22	.591
MET minutes per week (IPAQ)			
Group	0.06	0.18	.725
Sex	-0.37	0.16	.074
Group*Sex	0.16	0.25	.704
General health perceptions (SF36)			
Group	-0.34	0.16	.061
Sex	-0.19	0.16	.265
Group*Sex	-0.08	0.25	.763
Physical functioning (SF36)			
Group	-0.23	0.10	**.049**
Sex	-0.41	0.14	**.013**
Group*Sex	0.08	0.24	.763
Pain (SF36)			
Group	-0.21	0.14	.177
Sex	-0.17	0.14	.265

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Group*Sex	-0.17	0.25	.704
Energy/vitality (SF36)			
Group	-0.17	0.15	.278
Sex	-0.18	0.14	.265
Group*Sex	-0.31	0.22	.591
Role limitations due to physical health (SF36)	N/A[b]	N/A[b]	N/A[b]
Role limitations due to emotional problems (SF36)	N/A[b]	N/A[b]	N/A[b]
Sleep quality (PSQI)			
Group	0.26	0.16	.164
Sex	0.21	0.15	.265
Group*Sex	0.25	0.27	.704
Healthy diet			
Group	-0.48	0.16	**.010**
Sex	-0.21	0.16	.265
Group*Sex	0.31	0.23	.591
Diet adherence			
Group	-0.65	0.15	**<.001**
Sex	-0.05	0.15	.744
Group*Sex	0.14	0.24	.704
Healthcare service use			
Number of visits to mental healthcare institutes last year			
Group	0.00	0.13	.998
Sex	0.09	0.16	.695
Group*Sex	0.10	0.25	.873
Number of visits to social welfare and/or occupational health and safety service institutes last year			
Group	0.25	0.15	.203
Sex	0.07	0.03	.089
Group*Sex	0.02	0.21	.935
Number of visits to physical healthcare institutes last year			
Group	0.13	0.17	.559
Sex	0.04	0.10	.695
Group*Sex	0.09	0.20	.873
ADHD medication use			
Group	13.90 (OR)	[95% CI, 2.00 - 96.87]	**.020**
Sex	2.06 (OR)	[95% CI, 0.25 - 17.09]	.695
Group*Sex	0.36 (OR)	[95% CI, 0.04 - 3.64]	.873
General medication use			
Group	0.40	0.12	**.003**
Sex	0.59	0.13	**<.001**
Group*Sex	0.25	0.27	.873

Note. Significant effects are shown in bold. A positive effect size indicates a higher value for females (sex: males = 0, females = 1).

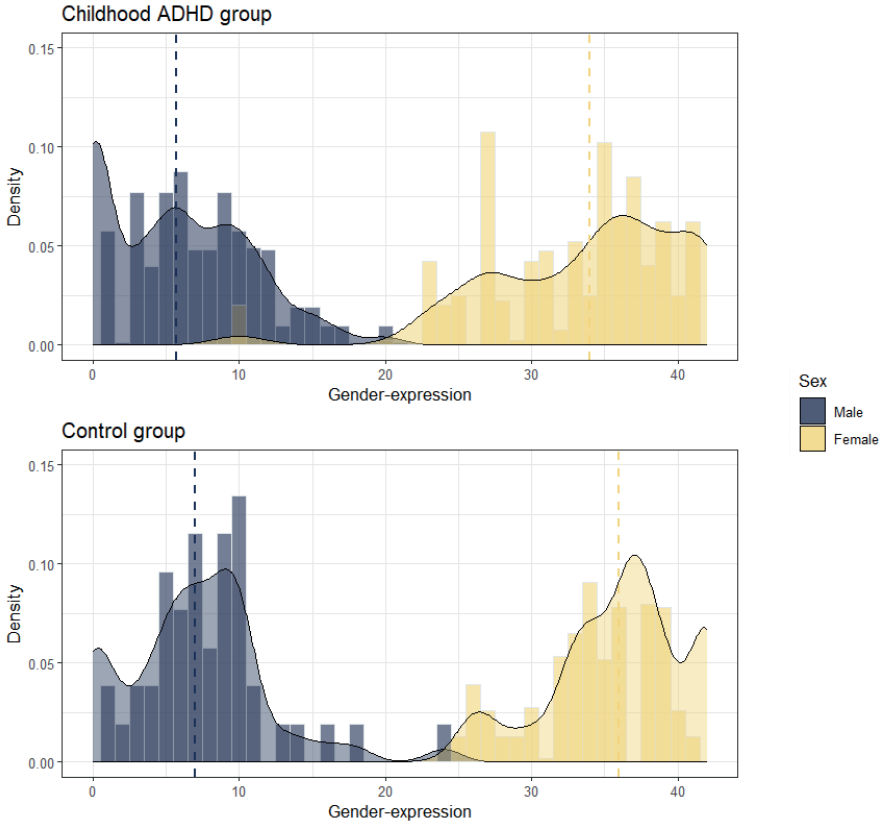
ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self-report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, CAARS = Conners' adult ADHD rating scales, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, DSM-5 = diagnostic and statistical manual of mental disorders fifth edition, GAS = game

addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LTE = long-term difficulties questionnaire, MDD = major depressive disorder, MET = metabolic equivalent, PSS = perceived stress scale, PSQI = Pittsburgh sleep quality index, SF36 = short form health survey, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.
[a] Assessed only for participants with a child/children (n = 61).
[b] Due to insufficient variation or complete separation, analyses were impossible to run and are represented by N/A.

Exploratory models of gender

One sex-assigned woman identified as non-binary, and one sex-assigned man identified as genderfluid/genderqueer. Women rated themselves as having a more traditional feminine gender-expression (M = 35.30, SD = 5.56) and men rated themselves as having a more traditional masculine gender-expression (M = 6.13, SD = 4.90). Despite substantial spread of gender-expression (M = 18.97, SD = 15.31, Figure 4.1), specific effects of gender-expression could not be explored to due the high correlation with sex (r = .94). The relation between sex and gender-expression was similar for both diagnostic groups, with no interaction between sex and group for gender-expression (β = -0.05, p = .573).

Figure 4.1. *Histogram and density plot of gender-expression of males and females for the ADHD and control group*



Note. Dashed lines represent mean gender-expression for males (blue) and females (yellow). A low score on gender-expression represents masculinity, where a high score on gender-expression represents femininity.
ADHD = attention-deficit/hyperactivity disorder.

Discussion

The aim of the current study was to investigate if differences between males and females are more pronounced in long-term outcomes of childhood ADHD compared to the general population. This was investigated by assessing the moderating effects of sex, defined as sex-assignment at birth, in seven domains of long-term outcomes. Moreover, the aim was to explore potential moderating effects of gender, defined as adherence to gender roles in terms of masculine and feminine expression. The observed sex by group interactions were minor, with more pronounced sex differences in long-term outcomes of childhood ADHD only in social functioning, which should be interpreted with some caution given the

power limitations of the current study. Due to high overlap between sex and gender-expression, potential effects of gender could not be explored.

Our findings indicate that the previously identified sex differences between males and females with ADHD are not present when examining the interaction between sex and group in an ADHD and control cohort with multiple outcome domains. The sparse previous studies on sex differences did not investigate sex as a moderator but only as a main effect and suggested that females with ADHD differ from males with ADHD on several outcomes [5, 30, 31, 151]. Importantly, our main effects of sex across the two groups (ADHD and control) are in line with previous findings and are consistent with sex differences typically reported in the general population (Table S2). This includes the findings that females show more internalizing problems and stress compared to males, and males show more callous-unemotional traits, antisocial behaviors, substance use, gaming addiction, and risk-taking behaviors compared to females [146-149]. Therefore, the previously reported sex differences in an ADHD population may merely reflect sex differences already present in the general population, thus differences that are independent of an ADHD diagnosis.

As we were interested in the long-term outcomes of adults with a childhood ADHD diagnosis, our study did not include females with late-onset ADHD who are diagnosed (relatively) late in life (i.e., in adolescence or adulthood). However, the latter group is potentially at highest risk of negative outcomes, such as lower self-esteem, worse mental health, and overall lower wellbeing as compared to males with ADHD and females with early-onset ADHD who were diagnosed in childhood [139, 152]. This heightened risk of negative outcomes for late-diagnosed females might be related to misdiagnosis, inadequate or untimely support, and high levels of masking [5, 153]. This may explain why cross-sectional studies reported sex differences in functioning of adults with ADHD, such as higher levels of stress in females compared to males, that are not observed in our current study. Those samples likely also included late-diagnosed females, while we did not [5, 30, 31, 151]. Similarly, it can explain why our results differ from those of a large registry study which found sex differences, as the mean age of diagnosis in that study was in adulthood [140], in contrast to our sample with ADHD diagnosed in childhood. Importantly, late-onset ADHD might be a different subtype of ADHD with unique risks [154]. Furthermore, a childhood ADHD diagnosis and appropriate interventions may have ameliorated sex differences in the developmental trajectories of ADHD.

In the current study, males with childhood ADHD showed difficulties in social functioning (domain adaptive functioning) compared to males and females without childhood ADHD. In contrast, females with childhood ADHD had comparable social functioning to males and females without childhood ADHD. Likewise, previous studies found that girls with ADHD were more socially

competent compared to boys with ADHD [155, 156]. The current study focused on social functioning defined as impairment in social activities with family, friends, neighbors, or others, due to physical health or emotional problems. No sex differences were reported in studies published before 2011 that used a broader operationalization of social functioning, encompassing relationships, social skills, participation in activities, living situation, and intimate relationships [157]. However, these studies did not investigate a moderation of sex. Nonetheless, this may suggest our observed sex by group differences may be specific to impairment due to physical health and emotional problems, since these are components present in our definition. Overall, our results suggest it may be useful to monitor boys with ADHD on difficulties in social functioning related to physical health or emotional problems for timely intervention but given our power limitation our results need replication.

We could not explore potential effects of gender (masculinity and femininity) over and above studying effects of sex, because it strongly correlated with sex in our study. Possibly, different aspects and operationalizations of gender that overlap less strongly with sex may be more relevant to investigate effects of gender [29]. A suitable approach might be the use of an implicit association task linking concepts to self/others and feminine/masculine, as this task showed the weakest correlation with our measure of gender [145]. Furthermore, studies including samples with more diversity in gender incongruence with sex-assignment at birth might also be better suited to explore the influence of gender in contrast to our cisgendered sample with only two participants with gender incongruence.

Some limitations are important to mention. First, given our large number of outcome domains, our finding of a significant sex by group interaction on social functioning might have been a false positive. However, the chance of a false positive is relatively small given the small number of significant sex by group effects. Replication in other samples is needed to confirm the robustness of our results. Second, our sample size allowed us to detect moderate to large effects (based on a G*Power analysis), suggesting that we were underpowered to detect small effects and thus may have missed potential smaller sex by group interactions. Although we used an FDR-correction within each of the seven domains to control for multiple testing, our findings should therefore be interpreted with caution. Third, in the first wave of this cohort only children with ADHD combined presentation were recruited and in later waves all types of ADHD were allowed, which resulted in some subtype differences between boys and girls. In both boys and girls, the combined presentation was the most prevalent (boys = 93%, girls = 58%). However, the hyperactive presentation was more prevalent in girls compared to boys (boys = 4%, girls = 36%). As sex-effects in long-term outcomes of ADHD may differ for the subtypes of ADHD [10], our results might have been influenced by subtype-effects instead of sex-effects. Nonetheless, findings remained highly similar after controlling for inclusion wave. Inclusion

wave was used as a proxy for presentation given the differential inclusion criteria (combined presentation in wave I versus any presentation in later waves). This suggests that differences in presentations between males and females did not drive the findings regarding the moderation of sex and group. Fourth, attrition rates were high, but selective attrition seemed absent, as the retained groups were similar to the initial cohort in important demographic and behavioral characteristics. This implies that the results are mostly generalizable to the initial cohort. Finally, small potential group differences may have been concealed by our control group, given that 13 control participants (17%) received an ADHD diagnosis at a later timepoint after study entry. However, we specifically aimed to investigate the long-term outcomes of a childhood ADHD diagnosis, where controls received an ADHD diagnosis at a later point in time are part of natural developmental patterns present in the general population [158]. Moreover, a sensitivity analysis excluding the controls with a later ADHD diagnosis could not be reliably conducted due to the limited sample size and therewith statistical power.

Despite the limitations, our cohort was unique in terms of sample composition, follow-up period, and inclusion of a broad range of long-term outcomes of children diagnosed with ADHD. Both males and females were well represented in our cohort, adding to the generalizability of our results for adults with childhood ADHD. The sample appeared to be suitable for detecting interaction effects, as main effects of group and sex followed the expected patterns. See van der Plas, et al. [127] for overall functioning of the childhood ADHD group.

To conclude, we did not find more pronounced sex differences in long-term outcomes of childhood-diagnosed ADHD, except for social functioning, while our main effects of sex showed a consistent pattern of what is typically reported. Therefore, differences between males and females with ADHD seem to show similar patterns as observed in the general population, implying these differences to be independent of an ADHD diagnosis in childhood. One exception should be noted: males with childhood ADHD, but not females, seem to show lower social functioning compared to controls. This is a possible indication that boys with ADHD should be specifically monitored on social functioning to prevent potential difficulties in this domain in adulthood. However, as stated earlier, our findings should be interpreted with caution given the modest sample size relative to the number of outcomes, which increases the chance for false positives. Therefore, replication in larger samples is needed to confirm our results. Finally, gender-expression could not be investigated in the current, predominantly cisgendered sample, suggesting that future studies should use another operationalization of gender.

Table S4.1. *Main effects of sex on follow-up outcomes in adults with childhood ADHD and controls*

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Demographics			
Family status			
Single	1.01 (OR)	[95% CI, 0.58 - 1.75]	.972
Cohabitation	0.92 (OR)	[95% CI, 0.55 - 1.53]	.972
Married	1.27 (OR)	[95% CI, 0.70 - 2.30]	.972
Children at home[a]	1.02 (OR)	[95% CI, 0.35 - 2.99]	.972
Co-parenting[a]	N/A[b]	N/A[b]	N/A[b]
Living at home with parents/caregivers	0.99 (OR)	[95% CI, 0.48 - 2.04]	.972
Children (yes/no)	1.99 (OR)	[95% CI, 1.12 - 3.54]	.133
Number of children[a]	0.21	0.25	.972
Children with an ADHD diagnosis[a]	N/A[b]	N/A[b]	N/A[b]
Children with any diagnosis other than ADHD[a]	N/A[b]	N/A[b]	N/A[b]
Psychiatric status			
DSM-5 ADHD	0.72 (OR)	[95% CI, 0.43 - 1.22]	.299
DSM-5 MDD	1.14 (OR)	[95% CI, 0.55 - 2.37]	.723
DSM-5 any anxiety disorder	1.72 (OR)	[95% CI, 0.73 - 4.04]	.299
DSM-5 ASPD	N/A[b]	N/A[b]	N/A[b]
DSM-5 any SUD	0.32 (OR)	[95% CI, 0.11 - 0.92]	.138
Behavioral and emotional problems			
ADHD index (CAARS)	0.17	0.11	.227
ADHD index, Other-reported (CAARS)	0.12	0.11	.348
Externalizing problems (ASEBA-ASR)	-0.07	0.12	.573
Internalizing problems (ASEBA-ASR)	0.32	0.12	**.026**
Autistic traits, Other-reported (ASBQ)	-0.03	0.12	.833
Mood dysregulation (ARI)	0.13	0.12	.371
Callous-unemotional traits (ICU)	-0.48	0.11	**<.001**
Rule-breaking behavior (STAB)	-0.28	0.12	**.038**
Physical aggression (STAB)	-0.27	0.11	**.038**
Social aggression (STAB)	-0.35	0.12	**.015**
Tobacco use (ASSIST-Lite)	-0.08	0.12	.573
Alcohol use (ASSIST-Lite)	-0.25	0.12	.051
Drug use (ASSIST-Lite)	-0.25	0.11	.051
Gaming addiction symptoms (GAS)	-0.48	0.12	**<.001**
Academic and professional functioning			
Education Verhage	0.12	0.12	.443
Repeated grade (primary and secondary education)	0.59 (OR)	[95% CI, 0.35 - 0.99]	.187
Employed	1.37 (OR)	[95% CI, 0.63 - 2.98]	.443
Number of times switched jobs	-0.09	0.12	.443
Adaptive functioning			
Perceived stress (PSS)	0.41	0.12	**.003**
Risk-taking (DOSPERT)	-0.57	0.11	**<.001**
Risk perception (DOSPERT)	0.26	0.12	.108
Social functioning (SF36)	0.12	0.12	.327
Emotional wellbeing (SF36)	-0.16	0.12	.227
Quality of life – Outlook	-0.18	0.12	.227
Quality of life – Relationships	-0.16	0.11	.227
Significant life events (after age 16) (LTE)	0.13	0.12	.295

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Creative achievement (CAQ)	-0.19	0.11	.227
Neurocognitive functioning			
Estimated TIQ (WAIS)	-0.11	0.12	.550
Working memory (WAIS)	-0.03	0.12	.807
Short-term memory – digits (WAIS)	-0.09	0.12	.550
Short-term memory – words (15WT)	0.17	0.13	.527
Long-term memory (15WT)	0.23	0.12	.383
Letter fluency score (COWAT)	0.13	0.12	.550
Physical health			
BMI	0.12	0.11	.326
MET minutes per week (IPAQ)	-0.32	0.12	**.038**
General health perceptions (SF36)	-0.13	0.12	.326
Physical functioning (SF36)	-0.32	0.12	**.038**
Pain (SF36)	-0.18	0.12	.216
Energy/vitality (SF36)	-0.27	0.11	.063
Role limitations due to physical health (SF36)	N/A[b]	N/A[b]	N/A[b]
Role limitations due to emotional problems (SF36)	N/A[b]	N/A[b]	N/A[b]
Sleep quality (PSQI)	0.23	0.12	.149
Healthy diet	0.04	0.12	.758
Diet adherence	0.18	0.12	.216
Healthcare service use			
Number of visits to mental healthcare institutes last year	0.13	0.12	.510
Number of visits to social welfare and/or occupational health and safety service institutes last year	0.02	0.12	.916
Number of visits to physical healthcare institutes last year	0.04	0.11	.906
ADHD medication use	0.58 (OR)	[95% CI, 0.28 - 1.20]	.356
General medication use	0.59	0.13	**<.001**

Note. Significant effects are shown in bold. A positive effect size indicates a higher value for females (sex: males = 0, females = 1).
ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self-report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, CAARS = Conners' adult ADHD rating scales, CAQ = creative achievement questionnaire, CI = confidence interval, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, DSM-5 = diagnostic and statistical manual of mental disorders fifth edition, FDR = false discovery rate, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LTE = long-term difficulties questionnaire, MDD = major depressive disorder, MET = metabolic equivalent, OR = odds ratio, PSS = perceived stress scale, PSQI = Pittsburgh sleep quality index, SE = standard error, SF36 = short form health survey, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.
[a] Assessed only for participants with a child/children (*n* = 61).
[b] Due to insufficient variation or complete separation, analyses were impossible to run and are represented by N/A.

Table S4.2. *Characteristics at wave I (IMAGE) of females with childhood ADHD successfully retained and initial sample*

M (*SD*)	Retained (*n* = 33)	Initial sample (*n* = 110)	Retained versus initial sample
Age	10.84 (3.18)	10.68 (3.04)	Wald χ^2 = 0.05
Estimated TIQ	98.77 (12.90)	99.81 (11.45)	Wald χ^2 = 0.27
Parental education level[a]	5.21 (0.87)	5.22 (0.70)	Wald χ^2 = 0.03
ADHD symptoms	81.94 (10.24)	79.72 (11.03)	Wald χ^2 = 1.46
ODD symptoms	69.38 (10.33)	66.01 (12.95)	Wald χ^2 = 2.58
Anxious/shy behavior	61.06 (13.60)	59.48 (14.23)	Wald χ^2 = 0.43
Behavioral and emotional difficulties	19.44 (6.51)	17.88 (7.00)	Wald χ^2 = 1.82

Note. Differences in characteristics were tested only for participants included in wave I. As 22 out of 55 females with childhood ADHD entered the cohort at wave II or wave III, the attrition analysis was conducted in a subset excluding these females. No group difference reached statistical significance.
ADHD = attention-deficit/hyperactivity disorder, IMAGE = International Multisite ADHD Genetics, ODD = oppositional defiant disorder, TIQ = total intelligence quotient.
[a] Assessed in wave II as this was not assessed at wave I, assuming these levels did not differ between waves I and II, with successfully followed up *n* = 28; and initial sample at wave II *n* = 82.

Table S4.3. *Characteristics at wave I (IMAGE) of males with childhood ADHD successfully retained and initial sample*

M (*SD*)	Retained (*n* = 100)	Initial sample (*n* = 400)	Retained versus initial sample
Age	11.17 (2.66)	11.03 (2.73)	Wald χ^2 = 0.24
Estimated TIQ	101.39 (12.26)	98.61 (12.15)	Wald χ^2 = 3.61
Parental education level[a]	5.24 (0.80)	5.19 (0.75)	Wald χ^2 = 0.37
ADHD symptoms	75.75 (8.44)	74.09 (9.09)	Wald χ^2 = 2.32
ODD symptoms	64.99 (12.74)	66.12 (12.22)	Wald χ^2 = 0.79
Anxious/shy behavior	55.82 (13.19)	57.61 (13.60)	Wald χ^2 = 1.16
Behavioral and emotional difficulties	18.66 (5.45)	19.20 (5.92)	Wald χ^2 = 1.25

Note. Differences in characteristics were tested only for participants included in wave I. As 4 out of 104 males with childhood ADHD entered the cohort at wave II or wave III, the attrition analysis was conducted in a subset excluding these men. No group difference reached statistical significance.
ADHD = attention-deficit/hyperactivity disorder, IMAGE = International Multisite ADHD Genetics, ODD = oppositional defiant disorder, TIQ = total intelligence quotient.
[a] Assessed in wave II as this was not assessed at wave I, assuming these levels did not differ between waves I and II, with successfully followed up *n* = 96; and initial sample at wave II *n* = 132.

Table S4.4. *Characteristics at Wave I (IMAGE) of female controls successfully retained and initial sample*

M (*SD*)	Retained (*n* = 67)	Initial sample (*n* = 164)	Retained versus initial sample
Age	11.07 (3.25)	11.25 (3.29)	Wald χ^2 = 0.00
Estimated TIQ	107.33 (10.91)	105.93 (10.69)	Wald χ^2 = 0.25
Parental education level[a]	5.35 (0.54)	5.31 (0.61)	Wald χ^2 = 0.11
ADHD symptoms	46.91 (4.41)	46.63 (4.40)	Wald χ^2 = 0.27
ODD symptoms	47.54 (6.43)	48.44 (7.54)	Wald χ^2 = 0.00
Anxious/shy behavior	48.55 (8.87)	48.44 (7.54)	Wald χ^2 = 0.01

Note. Differences in characteristics were tested only for participants included in wave I. As 10 out of 77 control females entered the cohort at wave II or wave III, the attrition analysis was conducted in a subset excluding these females. No group difference reached statistical significance.
ADHD = attention-deficit/hyperactivity disorder, IMAGE = International Multisite ADHD Genetics, ODD = oppositional defiant disorder, TIQ = total intelligence quotient.
[a] Assessed in wave II as this was not assessed at wave I, assuming these levels did not differ between waves I and II, with successfully followed up *n* = 65; and initial sample at wave II *n* = 132.

Table S4.5. *Characteristics at Wave I (IMAGE) of male controls successfully retained and initial sample*

M (*SD*)	Retained (*n* = 39)	Initial sample (*n* = 117)	Retained versus initial sample
Age	11.08 (3.47)	11.05 (3.25)	Wald χ^2 = 0.08
Estimated TIQ	107.98 (9.49)	106.48 (9.95)	Wald χ^2 = 0.62
Parental education level[a]	5.28 (0.55)	5.26 (0.52)	Wald χ^2 = 0.19
ADHD symptoms	46.16 (4.54)	46.54 (4.96)	Wald χ^2 = 0.01
ODD symptoms	46.63 (6.75)	46.77 (7.35)	Wald χ^2 = 0.00
Anxious/shy behavior	48.68 (7.58)	49.20 (8.37)	Wald χ^2 = 0.12

Note. Differences in characteristics were tested only for participants included in wave I. As 13 out of 52 control males entered the cohort at wave II or wave III, the attrition analysis was conducted in a subset excluding these men. No group difference reached statistical significance.
ADHD = attention-deficit/hyperactivity disorder, IMAGE = International Multisite ADHD Genetics, ODD = oppositional defiant disorder, TIQ = total intelligence quotient.
[a] Assessed in wave II as this was not assessed at wave I, assuming these levels did not differ between waves I and II, with successfully followed up *n* = 39; and initial sample at wave II *n* = 93.

Table S4.6. *Interaction between sex and group on follow-up outcomes in adults with childhood ADHD and controls: complete case analysis*

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Demographics			
Family status			
Single			
Group	1.19 (OR)	[95% CI, 0.54 - 2.60]	.781
Sex	0.96 (OR)	[95% CI, 0.39 - 2.36]	.930
Group*Sex	1.22 (OR)	[95% CI, 0.38 - 3.87]	.734
Cohabitation			
Group	0.73 (OR)	[95% CI, 0.36 - 1.46]	.519
Sex	0.68 (OR)	[95% CI, 0.32 - 1.45]	.493
Group*Sex	1.64 (OR)	[95% CI, 0.57 - 4.68]	.500
Married			
Group	2.92 (OR)	[95% CI, 1.06 - 8.06]	.136
Sex	3.77 (OR)	[95% CI, 1.36 - 10.48]	**.025**
Group*Sex	0.13 (OR)	[95% CI, 0.03 - 0.51]	**.027**
Children at home[a]			
Group	0.78 (OR)	[95% CI, 0.10 - 5.89]	.812
Sex	1.13 (OR)	[95% CI, 0.17 - 7.78]	.930
Group*Sex	0.38 (OR)	[95% CI, 0.03 - 5.04]	.541
Co-parenting[a]	N/A[b]	N/A[b]	N/A[b]
Living at home with parents/caregivers			
Group	0.59 (OR)	[95% CI, 0.23 - 1.54]	.490
Sex	0.62 (OR)	[95% CI, 0.23 - 1.70]	.493
Group*Sex	2.38 (OR)	[95% CI, 0.56 - 10.17]	.424
Children (yes/no)			
Group	2.31 (OR)	[95% CI, 0.83 - 6.39]	.252
Sex	4.91 (OR)	[95% CI, 1.81 - 13.31]	**.006**
Group*Sex	0.19 (OR)	[95% CI, 0.05 - 0.69]	**.042**
Number of children[a]			
Group	0.83	0.23	**.002**
Sex	0.80	0.19	**<.001**
Group*Sex	-0.59	0.46	.424
Children with an ADHD diagnosis[a]	N/A[b]	N/A[b]	N/A[b]
Children with any diagnosis other than ADHD[a]	N/A[b]	N/A[b]	N/A[b]
Psychiatric status			
DSM-5 ADHD			
Group	9.08 (OR)	[95% CI, 3.07 - 26.84]	**<.001**
Sex	0.93 (OR)	[95% CI, 0.28 - 3.04]	.900
Group*Sex	1.35 (OR)	[95% CI, 0.33 - 5.47]	.677
DSM-5 MDD			
Group	7.53 (OR)	[95% CI, 1.94 - 29.30]	**.007**
Sex	3.00 (OR)	[95% CI, 0.94 - 9.59]	.127
Group*Sex	0.44 (OR)	[95% CI, 0.09 - 2.10]	.499
DSM-5 any anxiety disorder			
Group	5.35 (OR)	[95% CI, 0.57 - 50.32]	.190
Sex	5.85 (OR)	[95% CI, 0.60 - 56.85]	.171
Group*Sex	0.25 (OR)	[95% CI, 0.02 - 3.10]	.499
DSM-5 ASPD	N/A[b]	N/A[b]	N/A[b]
DSM-5 any SUD			
Group	0.92 (OR)	[95% CI, 0.32 - 2.58]	.867
Sex	0.20 (OR)	[95% CI, 0.04 - 1.05]	.127

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Group*Sex	2.62 (OR)	[95% CI, 0.31 - 21.85]	.499
Behavioral and emotional problems			
ADHD index (CAARS)			
Group	0.86	0.14	**<.001**
Sex	0.32	0.15	.092
Group*Sex	0.12	0.21	.931
ADHD index, Other-reported (CAARS)			
Group	0.93	0.13	**<.001**
Sex	0.25	0.11	.075
Group*Sex	0.16	0.22	.931
Externalizing problems (ASEBA-ASR)			
Group	0.78	0.15	**<.001**
Sex	0.04	0.13	.783
Group*Sex	0.10	0.22	.931
Internalizing problems (ASEBA-ASR)			
Group	0.40	0.14	**.008**
Sex	0.32	0.13	.067
Group*Sex	0.16	0.24	.931
Autistic traits, Other-reported (ASBQ)			
Group	1.05	0.13	**<.001**
Sex	0.20	0.11	.134
Group*Sex	0.02	0.22	.970
Mood dysregulation (ARI)			
Group	0.57	0.13	**<.001**
Sex	0.24	0.13	.134
Group*Sex	0.06	0.24	.970
Callous-unemotional traits (ICU)			
Group	0.12	0.16	.505
Sex	-0.63	0.15	**<.001**
Group*Sex	0.42	0.23	.892
Rule-breaking behavior (STAB)			
Group	0.21	0.21	.452
Sex	-0.24	0.18	.291
Group*Sex	0.02	0.25	.970
Physical aggression (STAB)			
Group	0.69	0.15	**<.001**
Sex	-0.04	0.13	.783
Group*Sex	-0.17	0.21	.931
Social aggression (STAB)			
Group	0.49	0.17	**.007**
Sex	-0.19	0.16	.320
Group*Sex	-0.10	0.23	.931
Tobacco use (ASSIST-Lite)			
Group	0.10	0.19	.640
Sex	-0.20	0.16	.304
Group*Sex	0.31	0.26	.931
Alcohol use (ASSIST-Lite)			
Group	-0.02	0.20	.920
Sex	-0.37	0.18	.092
Group*Sex	0.25	0.26	.931
Drug use (ASSIST-Lite)			
Group	0.15	0.18	.505
Sex	-0.13	0.14	.413

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Group*Sex	-0.23	0.21	.931
Gaming addiction symptoms (GAS)			
Group	0.30	0.20	.187
Sex	-0.43	0.15	**.031**
Group*Sex	0.01	0.23	.970
Academic and professional functioning			
Education Verhage			
Group	-0.65	0.15	**<.001**
Sex	0.02	0.13	.937
Group*Sex	-0.14	0.23	.654
Repeated grade (primary and secondary education)			
Group	0.97 (OR)	[95% CI, 0.47 - 1.99]	.937
Sex	0.34 (OR)	[95% CI, 0.15 - 0.78]	**.045**
Group*Sex	3.30 (OR)	[95% CI, 1.10 - 9.88]	.132
Employed			
Group	0.51 (OR)	[95% CI, 0.16 - 1.69]	.548
Sex	0.95 (OR)	[95% CI, 0.25 - 3.57]	.937
Group*Sex	1.48 (OR)	[95% CI, 0.27 - 8.10]	.654
Number of times switched jobs			
Group	0.09	0.16	.756
Sex	-0.17	0.15	.536
Group*Sex	0.24	0.22	.580
Adaptive functioning			
Perceived stress (PSS)			
Group	0.47	0.15	**.006**
Sex	0.37	0.15	**.039**
Group*Sex	0.30	0.24	.385
Risk-taking (DOSPERT)			
Group	0.10	0.16	.536
Sex	-0.56	0.15	**.002**
Group*Sex	-0.01	0.23	.950
Risk perception (DOSPERT)			
Group	0.17	0.13	.226
Sex	0.47	0.13	**.002**
Group*Sex	-0.45	0.28	.385
Social functioning (SF36)			
Group	-0.73	0.16	**<.001**
Sex	-0.36	0.17	.060
Group*Sex	0.75	0.25	**.022**
Emotional wellbeing (SF36)			
Group	-0.33	0.15	.055
Sex	-0.13	0.13	.336
Group*Sex	-0.26	0.23	.385
Quality of life – Outlook			
Group	-0.34	0.16	.055
Sex	-0.24	0.15	.162
Group*Sex	-0.06	0.24	.912
Quality of life – Relationships			
Group	-0.35	0.14	**.044**
Sex	-0.17	0.14	.241
Group*Sex	-0.15	0.22	.645

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Significant life events (after age 16) (LTE)			
Group	0.24	0.18	.226
Sex	0.30	0.16	.092
Group*Sex	-0.35	0.24	.385
Creative achievement (CAQ)			
Group	-0.28	0.20	.226
Sex	-0.40	0.19	.060
Group*Sex	0.28	0.24	.385
Neurocognitive functioning			
Estimated TIQ (WAIS)			
Group	-0.74	0.15	**<.001**
Sex	-0.40	0.16	.075
Group*Sex	0.19	0.24	.478
Working memory (WAIS)			
Group	-0.57	0.16	**.001**
Sex	-0.04	0.15	.826
Group*Sex	-0.24	0.23	.478
Short-term memory – digits (WAIS)			
Group	-0.50	0.16	**.003**
Sex	-0.29	0.15	.162
Group*Sex	0.16	0.23	.478
Short-term memory – words (15WT)			
Group	-0.56	0.16	**.001**
Sex	-0.04	0.17	.826
Group*Sex	0.19	0.25	.478
Long-term memory (15WT)			
Group	-0.57	0.16	**.001**
Sex	-0.04	0.16	.826
Group*Sex	0.29	0.23	.478
Letter fluency score (COWAT)			
Group	-0.32	0.18	.084
Sex	0.24	0.19	.393
Group*Sex	-0.45	0.24	.355
Physical health			
BMI			
Group	0.64	0.12	**<.001**
Sex	0.38	0.13	**.011**
Group*Sex	-0.29	0.22	.588
MET minutes per week (IPAQ)			
Group	0.07	0.18	.684
Sex	-0.37	0.16	.065
Group*Sex	0.18	0.26	.704
General health perceptions (SF36)			
Group	-0.34	0.16	.059
Sex	-0.21	0.16	.266
Group*Sex	-0.02	0.25	.942
Physical functioning (SF36)			
Group	-0.23	0.10	**.046**
Sex	-0.42	0.14	**.011**
Group*Sex	0.11	0.23	.704
Pain (SF36)			
Group	-0.21	0.14	.185

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Sex	-0.17	0.14	.266
Group*Sex	-0.14	0.24	.704
Energy/vitality (SF36)			
Group	-0.17	0.15	.293
Sex	-0.18	0.14	.266
Group*Sex	-0.30	0.22	.588
Role limitations due to physical health (SF36)	N/A[b]	N/A[b]	N/A[b]
Role limitations due to emotional problems (SF36)	N/A[b]	N/A[b]	N/A[b]
Sleep quality (PSQI)			
Group	0.25	0.17	.185
Sex	0.16	0.16	.339
Group*Sex	0.25	0.27	.704
Healthy diet			
Group	-0.48	0.16	**.009**
Sex	-0.21	0.16	.266
Group*Sex	0.34	0.23	.588
Diet adherence			
Group	-0.65	0.15	**<.001**
Sex	-0.05	0.15	.743
Group*Sex	0.18	0.24	.704
Healthcare service use			
Number of visits to mental healthcare institutes last year			
Group	0.00	0.13	.983
Sex	0.08	0.16	.695
Group*Sex	0.12	0.26	.822
Number of visits to social welfare and/or occupational health and safety service institutes last year			
Group	0.23	0.15	.209
Sex	0.07	0.04	.086
Group*Sex	0.05	0.21	.822
Number of visits to physical healthcare institutes last year			
Group	0.12	0.17	.581
Sex	0.04	0.10	.695
Group*Sex	0.09	0.20	.822
ADHD medication use			
Group	13.90 (OR)	[95% CI, 2.02 - 95.84]	**.019**
Sex	2.06 (OR)	[95% CI, 0.25 - 16.89]	.695
Group*Sex	0.36 (OR)	[95% CI, 0.04 - 3.59]	.822
General medication use			
Group	0.40	0.12	**.003**
Sex	0.59	0.13	**<.001**
Group*Sex	0.25	0.27	.822

Note. Significant effects are shown in bold. A positive effect size indicates a higher value for females (sex: males = 0, females = 1). Non-imputed data was used to perform the complete case analysis. The proportion of complete cases differed across outcome measures (range = 80% to 100%).

ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self-report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, CAARS =

Conners' adult ADHD rating scales, CAQ = creative achievement questionnaire, CI = confidence interval, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, DSM-5 = diagnostic and statistical manual of mental disorders fifth edition, FDR = false discovery rate, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LTE = long-term difficulties questionnaire, MDD = major depressive disorder, MET = metabolic equivalent, OR = odds ratio, PSS = perceived stress scale, PSQI = Pittsburgh sleep quality index, SE = standard error, SF36 = short form health survey, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.
[a] Assessed only for participants with a child/children (n = 61).
[b] Due to insufficient variation or complete separation, analyses were impossible to run and are represented by N/A.

Table S4.7. *Interaction between sex and group on follow-up outcomes in adults with childhood ADHD and controls, controlling for inclusion wave*

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Demographics			
Family status			
Single			
Group	1.36 (OR)	[95% CI, 0.58 - 3.18]	.666
Sex	1.07 (OR)	[95% CI, 0.42 - 2.72]	.892
Group*Sex	0.93 (OR)	[95% CI, 0.26 - 3.31]	.905
Inclusion wave	1.75 (OR)	[95% CI, 0.84 - 3.63]	.155
Cohabitation			
Group	0.58 (OR)	[95% CI, 0.28 - 1.23]	.336
Sex	0.57 (OR)	[95% CI, 0.27 - 1.22]	.260
Group*Sex	2.51 (OR)	[95% CI, 0.83 - 7.57]	.235
Inclusion wave	0.42 (OR)	[95% CI, 0.19 - 0.92]	.054
Married			
Group	2.43 (OR)	[95% CI, 0.87 - 6.81]	.314
Sex	3.45 (OR)	[95% CI, 1.24 - 9.59]	**.042**
Group*Sex	0.19 (OR)	[95% CI, 0.05 - 0.75]	.127
Inclusion wave	0.24 (OR)	[95% CI, 0.07 - 0.83]	.054
Children at home[a]	N/A[b]	N/A[b]	N/A[b]
Co-parenting[a]	N/A[b]	N/A[b]	N/A[b]
Living at home with parents/caregivers			
Group	0.83 (OR)	[95% CI, 0.30 - 2.31]	.774
Sex	0.77 (OR)	[95% CI, 0.28 - 2.14]	.815
Group*Sex	1.21 (OR)	[95% CI, 0.27 - 5.43]	.905
Inclusion wave	3.27 (OR)	[95% CI, 1.40 - 7.60]	**.022**
Children (yes/no)			
Group	1.98 (OR)	[95% CI, 0.71 - 5.56]	.336
Sex	4.56 (OR)	[95% CI, 1.65 - 12.61]	**.012**
Group*Sex	0.25 (OR)	[95% CI, 0.07 - 0.97]	.155
Inclusion wave	0.40 (OR)	[95% CI, 0.14 - 1.15]	.123
Number of children[a]			
Group	0.81	0.25	**.014**
Sex	0.79	0.21	**.003**
Group*Sex	-0.57	0.48	.332
Inclusion wave	-0.08	0.55	.886
Children with an ADHD diagnosis[a]	N/A[b]	N/A[b]	N/A[b]
Children with any diagnosis other than ADHD[a]	N/A[b]	N/A[b]	N/A[b]

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Psychiatric status			
DSM-5 ADHD			
Group	9.89 (OR)	[95% CI, 3.52 - 27.79]	**<.001**
Sex	1.16 (OR)	[95% CI, 0.34 - 3.98]	.919
Group*Sex	0.88 (OR)	[95% CI, 0.20 - 3.89]	.867
Inclusion wave	1.57 (OR)	[95% CI, 0.66 - 3.75]	.480
DSM-5 MDD			
Group	0.40 (OR)	[95% CI, 0.00 - 7558.02]	.723
Sex	0.92 (OR)	[95% CI, 0.10 - 8.45]	.919
Group*Sex	2.10 (OR)	[95% CI, 0.07 - 64.15]	.851
Inclusion wave	0.57 (OR)	[95% CI, 0.10 - 3.16]	.480
DSM-5 any anxiety disorder			
Group	4.64 (OR)	[95% CI, 0.56 - 38.44]	.309
Sex	5.23 (OR)	[95% CI, 0.59 - 46.44]	.275
Group*Sex	0.33 (OR)	[95% CI, 0.03 - 3.27]	.851
Inclusion wave	0.51 (OR)	[95% CI, 0.12 - 2.24]	.480
DSM-5 ASPD	N/A[b]	N/A[b]	N/A[b]
DSM-5 any SUD			
Group	1.26 (OR)	[95% CI, 0.43 - 3.66]	.723
Sex	0.22 (OR)	[95% CI, 0.04 - 1.14]	.275
Group*Sex	1.71 (OR)	[95% CI, 0.18 - 15.94]	.851
Inclusion wave	2.38 (OR)	[95% CI, 0.75 - 7.57]	.480
Behavioral and emotional problems			
ADHD index (CAARS)			
Group	0.89	0.14	**<.001**
Sex	0.33	0.15	.081
Group*Sex	0.07	0.22	.921
Inclusion wave	0.11	0.14	.538
ADHD index, Other-reported (CAARS)			
Group	0.93	0.13	**<.001**
Sex	0.27	0.11	.081
Group*Sex	0.15	0.22	.921
Inclusion wave	0.15	0.15	.455
Externalizing problems (ASEBA-ASR)			
Group	0.77	0.16	**<.001**
Sex	0.05	0.15	.781
Group*Sex	0.03	0.24	.921
Inclusion wave	0.32	0.16	.233
Internalizing problems (ASEBA-ASR)			
Group	0.39	0.15	**.019**
Sex	0.32	0.14	.081
Group*Sex	0.13	0.25	.921
Inclusion wave	0.29	0.15	.233
Autistic traits, Other-reported (ASBQ)			
Group	1.08	0.14	**<.001**
Sex	0.22	0.13	.169
Group*Sex	-0.03	0.24	.921
Inclusion wave	0.29	0.17	.242
Mood dysregulation (ARI)			
Group	0.59	0.13	**<.001**
Sex	0.28	0.13	.081
Group*Sex	-0.02	0.23	.921
Inclusion wave	0.06	0.15	.741

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Callous-unemotional traits (ICU)			
Group	0.18	0.17	.307
Sex	-0.59	0.15	**.002**
Group*Sex	0.31	0.24	.921
Inclusion wave	0.23	0.18	.374
Rule-breaking behavior (STAB)			
Group	0.26	0.23	.307
Sex	-0.21	0.19	.426
Group*Sex	-0.07	0.27	.921
Inclusion wave	0.20	0.17	.394
Physical aggression (STAB)			
Group	0.72	0.16	**<.001**
Sex	-0.02	0.13	.864
Group*Sex	-0.22	0.22	.921
Inclusion wave	0.11	0.15	.538
Social aggression (STAB)			
Group	0.58	0.17	**.002**
Sex	-0.13	0.17	.545
Group*Sex	-0.28	0.23	.921
Inclusion wave	0.39	0.17	.233
Tobacco use (ASSIST-Lite)			
Group	0.20	0.18	.307
Sex	-0.13	0.16	.545
Group*Sex	0.18	0.26	.921
Inclusion wave	0.32	0.18	.233
Alcohol use (ASSIST-Lite)			
Group	0.11	0.18	.520
Sex	-0.29	0.16	.136
Group*Sex	0.06	0.25	.921
Inclusion wave	0.36	0.20	.233
Drug use (ASSIST-Lite)			
Group	0.19	0.18	.307
Sex	-0.10	0.14	.545
Group*Sex	-0.28	0.20	.921
Inclusion wave	0.16	0.14	.394
Gaming addiction symptoms (GAS)			
Group	0.33	0.19	.135
Sex	-0.38	0.15	.081
Group*Sex	-0.04	0.23	.921
Inclusion wave	0.00	0.16	.965
Academic and professional functioning			
Education Verhage			
Group	-0.67	0.15	**<.001**
Sex	0.01	0.13	.940
Group*Sex	-0.10	0.25	.682
Inclusion wave	-0.08	0.14	.745
Repeated grade (primary and secondary education)			
Group	0.92 (OR)	[95% CI, 0.43 - 1.94]	.824
Sex	0.32 (OR)	[95% CI, 0.14 - 0.77]	**.045**
Group*Sex	3.69 (OR)	[95% CI, 1.13 - 12.06]	.122
Inclusion wave	0.78 (OR)	[95% CI, 0.35 - 1.71]	.745
Employed			

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Group	0.51 (OR)	[95% CI, 0.15 - 1.74]	.555
Sex	0.95 (OR)	[95% CI, 0.25 - 3.65]	.940
Group*Sex	1.48 (OR)	[95% CI, 0.25 - 8.75]	.682
Inclusion wave	0.99 (OR)	[95% CI, 0.31 - 3.15]	.985
Number of times switched jobs			
Group	0.14	0.17	.555
Sex	-0.14	0.16	.759
Group*Sex	0.15	0.26	.682
Inclusion wave	0.19	0.23	.745
Adaptive functioning			
Perceived stress (PSS)			
Group	0.48	0.15	**.009**
Sex	0.42	0.15	**.014**
Group*Sex	0.23	0.25	.689
Inclusion wave	0.05	0.15	.834
Risk-taking (DOSPERT)			
Group	0.15	0.16	.419
Sex	-0.53	0.15	**.005**
Group*Sex	-0.08	0.25	.840
Inclusion wave	0.22	0.17	.584
Risk perception (DOSPERT)			
Group	0.08	0.14	.584
Sex	0.42	0.13	**.007**
Group*Sex	-0.32	0.27	.689
Inclusion wave	-0.20	0.19	.584
Social functioning (SF36)			
Group	-0.74	0.16	**<.001**
Sex	-0.38	0.17	.060
Group*Sex	0.77	0.25	**.021**
Inclusion wave	-0.07	0.19	.834
Emotional wellbeing (SF36)			
Group	-0.38	0.15	**.029**
Sex	-0.14	0.13	.281
Group*Sex	-0.22	0.24	.689
Inclusion wave	-0.12	0.15	.647
Quality of life – Outlook			
Group	-0.39	0.16	**.029**
Sex	-0.26	0.16	.132
Group*Sex	-0.01	0.26	.974
Inclusion wave	-0.18	0.18	.584
Quality of life – Relationships			
Group	-0.36	0.15	**.029**
Sex	-0.18	0.14	.238
Group*Sex	-0.16	0.24	.689
Inclusion wave	-0.01	0.15	.927
Significant life events (after age 16) (LTE)			
Group	0.16	0.17	.419
Sex	0.26	0.16	.132
Group*Sex	-0.14	0.23	.689
Inclusion wave	-0.34	0.17	.390
Creative achievement (CAQ)			
Group	-0.20	0.21	.419
Sex	-0.33	0.19	.132

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Group*Sex	0.17	0.25	.689
Inclusion wave	0.34	0.20	.390
Neurocognitive functioning			
Estimated TIQ (WAIS)			
Group	-0.60	0.16	**.001**
Sex	-0.30	0.16	.242
Group*Sex	0.11	0.23	.646
Inclusion wave	0.21	0.16	.594
Working memory (WAIS)			
Group	-0.62	0.16	**.001**
Sex	-0.08	0.16	.725
Group*Sex	-0.11	0.24	.646
Inclusion wave	-0.32	0.18	.515
Short-term memory – digits (WAIS)			
Group	-0.51	0.17	**.003**
Sex	-0.27	0.16	.242
Group*Sex	0.18	0.23	.646
Inclusion wave	-0.13	0.20	.626
Short-term memory – words (15WT)			
Group	-0.59	0.16	**.001**
Sex	-0.07	0.17	.725
Group*Sex	0.27	0.25	.562
Inclusion wave	-0.12	0.19	.626
Long-term memory (15WT)			
Group	-0.61	0.17	**.001**
Sex	-0.06	0.16	.725
Group*Sex	0.37	0.24	.533
Inclusion wave	-0.15	0.17	.626
Letter fluency score (COWAT)			
Group	-0.34	0.19	.081
Sex	0.20	0.19	.553
Group*Sex	-0.35	0.26	.533
Inclusion wave	-0.09	0.20	.666
Physical health			
BMI			
Group	0.59	0.12	**<.001**
Sex	0.35	0.12	**.022**
Group*Sex	-0.20	0.23	.789
Inclusion wave	-0.22	0.15	.816
MET minutes per week (IPAQ)			
Group	0.06	0.18	.743
Sex	-0.37	0.17	.088
Group*Sex	0.16	0.26	.789
Inclusion wave	-0.01	0.16	.995
General health perceptions (SF36)			
Group	-0.36	0.16	.062
Sex	-0.20	0.16	.260
Group*Sex	-0.04	0.27	.879
Inclusion wave	-0.08	0.17	.816
Physical functioning (SF36)			
Group	-0.22	0.11	.076
Sex	-0.40	0.14	**.022**

Outcome	ß or OR	*SE* or 95% CI	p_{FDR}
Group*Sex	0.05	0.25	.879
Inclusion wave	0.07	0.14	.816
Pain (SF36)			
Group	-0.27	0.15	.090
Sex	-0.21	0.13	.260
Group*Sex	-0.06	0.24	.879
Inclusion wave	-0.26	0.20	.816
Energy/vitality (SF36)			
Group	-0.20	0.15	.219
Sex	-0.19	0.14	.260
Group*Sex	-0.27	0.24	.789
Inclusion wave	-0.12	0.16	.816
Role limitations due to physical health (SF36)	N/A[b]	N/A[b]	N/A[b]
Role limitations due to emotional problems (SF36)	N/A[b]	N/A[b]	N/A[b]
Sleep quality (PSQI)			
Group	0.23	0.17	.208
Sex	0.19	0.16	.260
Group*Sex	0.30	0.28	.789
Inclusion wave	-0.11	0.17	.816
Healthy diet			
Group	-0.48	0.16	**.010**
Sex	-0.21	0.16	.260
Group*Sex	0.31	0.24	.789
Inclusion wave	0.00	0.17	.995
Diet adherence			
Group	-0.67	0.16	**<.001**
Sex	-0.06	0.15	.676
Group*Sex	0.19	0.25	.789
Inclusion wave	-0.10	0.17	.816
Healthcare service use			
Number of visits to mental healthcare institutes last year			
Group	-0.03	0.13	.836
Sex	0.07	0.15	.697
Group*Sex	0.15	0.26	.686
Inclusion wave	-0.12	0.14	.649
Number of visits to social welfare and/or occupational health and safety service institutes last year			
Group	0.21	0.15	.304
Sex	0.05	0.04	.495
Group*Sex	0.09	0.22	.686
Inclusion wave	-0.17	0.09	.257
Number of visits to physical healthcare institutes last year			
Group	0.13	0.17	.552
Sex	0.04	0.10	.697
Group*Sex	0.09	0.20	.686
Inclusion wave	-0.01	0.10	.986
ADHD medication use			
Group	12.56 (OR)	[95% CI, 1.75 - 90.24]	**.030**
Sex	1.94 (OR)	[95% CI, 0.22 - 17.43]	.697
Group*Sex	0.46 (OR)	[95% CI, 0.04 - 5.80]	.686

Outcome	*ß* or OR	*SE* or 95% CI	p_{FDR}
Inclusion wave	0.50 (OR)	[95% CI, 0.12 - 2.17]	.649
General medication use			
Group	0.40	0.13	**.009**
Sex	0.59	0.14	**<.001**
Group*Sex	0.26	0.28	.686
Inclusion wave	0.00	0.18	.986

Note. Significant effects are shown in bold. A positive effect size indicates a higher value for females (sex: males = 0, females = 1).
ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self-report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, CAARS = Conners' adult ADHD rating scales, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, DSM-5 = diagnostic and statistical manual of mental disorders fifth edition, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LTE = long-term difficulties questionnaire, MDD = major depressive disorder, MET = metabolic equivalent, PSS = perceived stress scale, PSQI = Pittsburgh sleep quality index, SF36 = short form health survey, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.
[a] Assessed only for participants with a child/children (*n* = 61).
[b] Due to insufficient variation or complete separation, analyses were impossible to run and are represented by N/A.

PART 2

Predictors of long-term outcomes of childhood ADHD



CHAPTER 5

Systematic review and meta-analysis: predictors of adult psychiatric outcomes of childhood ADHD

van der Plas, N. E., Noordermeer, S. D. S., Oosterlaan, J., & Luman, M. (2026). Systematic Review and Meta-Analysis: Predictors of Adult Psychiatric Outcomes of Childhood Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 65(2), 231-249.

Abstract

Objective. Psychiatric disorders are highly prevalent in adults with childhood-onset attention-deficit/hyperactivity disorder (ADHD). Currently, little is known about childhood predictors for these outcomes.

Method. PubMed, PsychInfo, WoS, and EMBASE were searched until June 2024. Eligible studies investigated childhood predictors of persistent ADHD, substance use disorders (SUD), conduct disorder, antisocial personality disorder, major depressive disorder (MDD), and/or anxiety disorders in adults diagnosed with childhood ADHD (PROSPERO #CRD42022320887). Meta-analytic models were tested when $N \geq 3$ for a predictor with similar effect measures, otherwise predictors were discussed narratively when $N \geq 2$. Newcastle-Ottawa scale was used to assess study quality.

Results. The selected 36 studies included 119 predictors, with 10 predictors eligible for meta-analyses. History of stimulant treatment (OR = 1.88, 95% CI 1.28-2.75, p = .001) was associated with increased, and higher childhood IQ with decreased (OR = 0.99, 95% CI 0.98-1.00, p =.039), risk of ADHD persistence in adulthood. ADHD persistence was associated with increased risk of SUDs (OR = 2.12, 95% CI 1.53-3.17, p =.004) and MDD (OR = 3.19, 95% CI 1.71-5.95, p <.001). Narratively reviewed predictors of fair/good quality studies showed potential predictors for ADHD persistence (i.e., ADHD combined type, hyperactive/impulsive symptoms, anxiety disorders, externalizing problems, social dysfunctioning, and socioeconomic status).

Conclusion. We confirmed earlier reported childhood predictors (i.e., stimulant treatment history, ADHD persistence) and identified potential new predictors (i.e., childhood anxiety disorders, social problems, socioeconomic status) for psychiatric outcomes of ADHD. However, the available literature is hampered by methodological shortcomings. Future studies should focus on studying combined effects of potential predictors.

Key words: ADHD, mental disorders, comorbidity, risk factors, cohort studies

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a predominantly childhood-onset neurodevelopmental disorder characterized by a persistent pattern of hyperactive-impulsive and/or inattentive behaviors [3]. The developmental trajectory of ADHD is highly variable, ranging from full remittance to full persistence. Approximately 75% of individuals with ADHD experience remittance of their ADHD diagnosis at a certain point, but impairing symptoms of ADHD persist in the majority of the cases [11, 13]. Meta-analyzed point estimations of ADHD persistence rates range between 3.3% and 25.7%, depending on the type of sample (clinical versus population-based), diagnostic classification system and diagnostic tools used, sex distribution of the sample, and geographic region [2, 12]. However, in cohort studies with clinical samples, the ADHD persistence rates reported are often higher, up to 77% [13]. Although the long-term outcome of childhood ADHD is heterogeneous, many individuals show impairments due to their ADHD symptoms and the development of comorbid problems [159].

Childhood ADHD is an early warning sign for later psychopathology, both for adults with persistent ADHD, and for those with remitted childhood ADHD [160, 161]. Childhood ADHD increases the risk for developing psychiatric outcomes by 2.5 times [16]. Besides ADHD persistence, the most common psychiatric adult outcomes of childhood ADHD include substance use disorders (SUDs; estimated prevalence 21%-36%), mood disorders (e.g., major depressive disorder [MDD]; estimated prevalence 21-22%), anxiety disorders (e.g., generalized anxiety disorder [GAD]; estimated prevalences 23%-25%), and disorders involving antisocial behavior (e.g., conduct disorder [CD] and antisocial personality disorder [ASPD], estimated prevalences 27%-34%) [3, 28]. These outcomes negatively impact global and daily functioning, including an increased risk for long-term work disability, delinquency, negative life events, suicidality and premature death [16, 162-167]. Identifying predictors of prevalent psychiatric outcomes in adults with childhood ADHD is important, as this may open-up possibilities for early intervention, enhance outcomes and reduce healthcare costs [162, 168].

A substantial number of studies have addressed predictors for adult psychiatric outcomes of childhood ADHD. The only available review aggregated 16 studies on predictors for ADHD (symptom) persistence and reported higher ADHD severity, receiving pharmacological treatment for ADHD, comorbid CD, and comorbid MDD to be predictive of ADHD persistence into adulthood [33]. There is currently no review or meta-analysis on predictors, other than ADHD (symptom persistence) of adult psychiatric outcomes of childhood ADHD [3, 33].

The current systematic review and meta-analysis aimed to aggregate existing longitudinal studies focusing on childhood predictors for the development of the most common psychiatric outcomes in adults diagnosed with childhood ADHD,

including ADHD persistence, SUDs, CD, ASPD, MDD, and anxiety disorders. We critically appraised the current state of evidence, and formulated recommendations for future research.

Method

Design

The systematic review and meta-analysis was conducted in agreement with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (PRISMA checklists are outlined in Table S5.1 and Table S5.2, available online) [169]. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; #CRD42022320887).

Study selection

Studies were selected if they (1) contained a sample of adults with a childhood ADHD diagnosis (according to DSM-III, ICD-9, or later versions criteria), where childhood ADHD should have been diagnosed before the age of 18, or retrospectively by reliable clinical interviews; (2) investigated childhood (mean age < 18) predictors of most prevalent (estimated prevalence ≥ 20%) adult (mean age ≥ 18) DSM or ICD based psychiatric outcomes (i.e., persistent ADHD, SUDs, CD, ASPD, MDD, and/or anxiety disorders [GAD, agoraphobia, social phobia, panic disorder, and specific phobia]); (3) employed a retrospective or longitudinal design, where the sample was measured at least at two time points, of which at least one measurement took place at a mean age of <18 years and at least one measurement at a mean age of ≥ 18 years; and (4) was published in a peer-reviewed journal (last search May 2024).

PubMed, PsychInfo, Web of Science, and EMBASE (including MEDLINE) were searched for relevant studies, combining search terms of ADHD, predictors, and adult psychiatric outcomes (full search strategy in Supplemental Methods 5.1, available online). Reference lists were searched for additional studies. The web app Rayyan was used to detect duplicates [170]. Two raters NP and either DJ, ML, SN or JO, independently judged articles for eligibility based on titles and abstracts. Thereafter, full-text articles were checked by two raters for eligibility. If studies reported on overlapping samples, we used a hierarchical selection process to select one study. Preferably, we selected the study that reported on the largest number of predictors. If multiple studies had the same number of predictors, we selected the study with the longest follow-up interval (i.e., the oldest age at assessment).

Data extraction

The first 60% of the data extraction was done in duplicate (NP and DJ), and the remainder was done by one of the authors (NP). Extracted data included total

sample size, sex distribution, age at last follow-up, ADHD sub-groups and accompanying group size, attrition rates, statistical approach, reported effect sizes of the statistical model, risk factors studied, statistical controls, and psychiatric outcomes. Findings of studies that investigated predictors that assessed highly similar constructs were merged: findings were pooled for presence/absence of (1) oppositional defiance disorder (ODD) and CD, (2) parental psychiatric problems, (3) maternal psychiatric problems, (4) paternal psychiatric problems, (5) educational difficulties, and (6) family stress factors, see Table S5.3 (available online). Table S5.3, also includes all operationalizations of predictors found in at least two studies. Likewise, several outcome measures were merged, including outcomes of (1) SUDs, (2) anxiety disorders (i.e., panic disorder, social anxiety disorder, separation anxiety disorder, specific phobia, selective mutism, GAD, and agoraphobia).

Study quality

Two raters independently assessed study quality using the Newcastle-Ottawa quality assessment scale (NOS) for cohort studies (Supplemental Methods 5.2, available online) [171]. Inconsistencies in ratings were solved by consensus, and, if needed, by discussion with a third rater. Studies were classified as poor, fair or good quality corresponding to the Agency for Health Research and Quality standard [172].

Statistical analyses

Multivariate meta-analysis was used to account for studies that included several effect sizes of the same predictor of the studied psychiatric outcomes. This analysis used three levels, including 1) primary study summary statistics (i.e., all relevant effect sizes provided by one study), 2) nested within study (i.e., one effect size per study), and 3) nested within one effect size (i.e., meta-analysis of one effect size across all studies) to control for several effect sizes within one study. Robust variance estimation was used to provide valid standard errors of the point estimates and valid significance tests [173]. All multivariate meta-analyses used a random effects model to calculate aggregated point estimates using R [174]. Where possible, effect sizes were selected which adjusted for the largest number of possible confounding variables of a study, irrespective of the type of confounder (e.g., age, sex, ADHD severity) to better approximate the true effect of the specific predictor. Higgin's I^2 index was measured and Cochran's Q test was conducted to indicate heterogeneity among studies. Only cases of potential high heterogeneity were reported in the text.

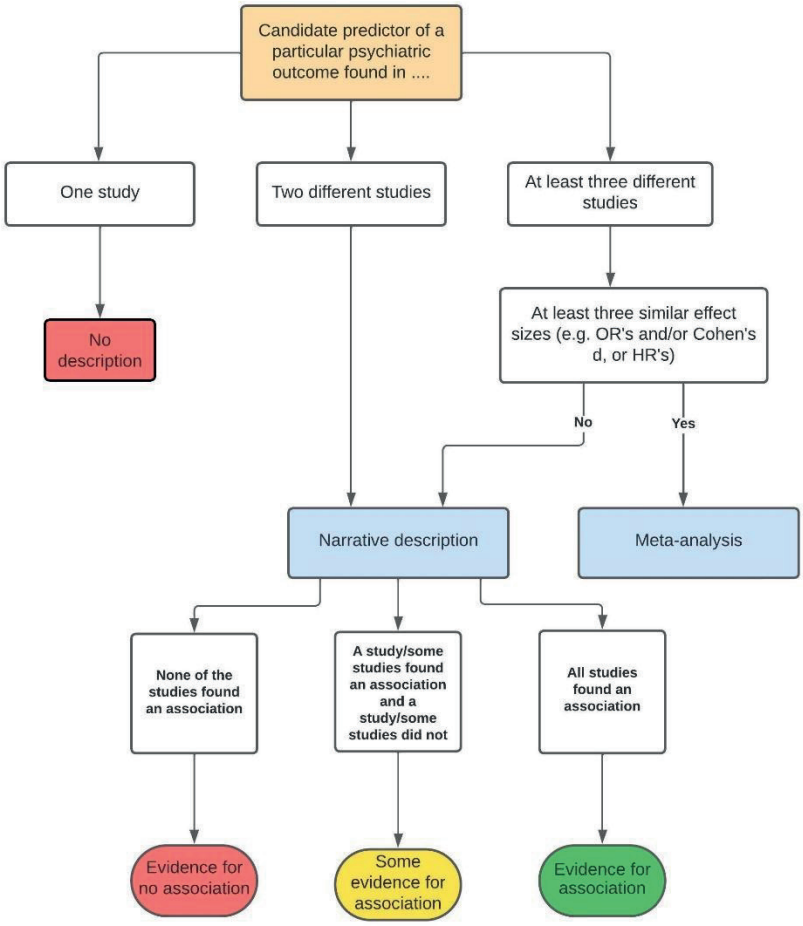
If a meta-analysis was unfeasible (i.e., when there were fewer than three studies looking at a specific predictor or when effect sizes were not comparable), a narrative review was provided for those predictors of a particular psychiatric outcome included in at least two studies. The narrative systematic review reported

terms of evidence as: (1) evidence for an association, if all studies found an association; (2) some evidence for an association, if a study/some studies found an association and a study/some studies did not; (3) evidence for no association, if all studies found no association. See Figure 5.1 for a flowchart of decisions made for our analyses

For the narrative review, multiple effect sizes of the same predictor of the psychiatric outcomes studied were first averaged within studies to have each study contributing a single effect size per predictor to the narrative review, where possible using ORs or HRs. When merging was not possible, e.g., for studies which did not report effect sizes, we assumed: evidence for no association, if all effect sizes or the majority of the effect sizes were non-significant; evidence for an association, if all effect sizes or the majority of the effect sizes were significant; some evidence for an association, if the effect sizes were equally divided between significant and non-significant significant.

Sensitivity analyses for the multivariate meta-analyses and narrative review were performed excluding poor quality studies.

Figure 5.1. *Flowchart of decisions made for narrative description and meta-analysis*



Note. First, meta-analytic and narrative review was described including all studies (poor/fair/good study quality). Consecutively, findings of only fair and good quality studies were discussed.
OR's = odds ratios, HR's = hazard ratios.

Results

The systematic search revealed a total of 2,729 unique studies (Figure S5.1, available online). Of these, 2,558 were excluded at title/abstract level, and 133 after full-text assessment (Supplemental Methods 5.3, available online). In total, 34 prospective and two retrospective longitudinal studies in adults with childhood ADHD were included, with 17 studies looking into ADHD persistence, 19 studies into SUDs, 4 studies into CD, 5 studies into ASPD, 8 studies into MDD, and 4 studies into anxiety disorders (Table 5.1, and Table S5.4-S5.9 available online). Studies reported on several predictors for each outcome (Table S5.10-S5.11, available online). The available data allowed multivariate meta-analyses of in total 10 predictors of ADHD persistence, SUDs, MDD, and anxiety disorders (Table 5.2). A narrative review was provided for a subsequent 31 predictors that were studied at least twice. Sixteen out of 36 studies were of fair or good study quality (Table S5.12, available online). Notably, 53% of studies did not control for any confounding variables.

Table 5.1. *Overview of all included studies (N = 36 studies)*

Study	N childhood ADHD (% male)	Ethnicity/race in %	Age at last follow-up (groups specified) (*M*, *SD*, range)	Criteria used to diagnose ADHD in childhood	Follow-up rate in %	Mean age of study sample at baseline wave and follow-up assessments	Psychiatric disorders assessed at outcome	At which assessments were psychiatric disorders measured	Method of assessment psychiatric outcomes
Agnew-Blais et al., 2016	247 (42)	*Unk.*., representative of all socioeconomic conditions of the UK[f]	18, 0, 0	DSM-IV diagnosis based on PR and TR	93	5, 7, 10, 12, 18	ADHD, any SUD, CD, any anxiety disorder, MDD	ADHD measured at all assessments; Others at T4	DIS
Biederman et al., 2008a[a]	112 (100)	White	No stimulant treatment: 23, 4, *Unk.*. Stimulant treatment: 21, 3, *Unk.*.	Clinical diagnosis, ADHD screening questionnaire and K-SADS-E	80	No stimulant history: 12, *Unk.*., 23 Stimulant group: 10, *Unk.*., 21	Any SUD	All	K-SADS-E
Biederman et al., 2008b[a]	112 (100)	White	21, *Unk.*.	Clinical diagnosis, ADHD screening questionnaire and K-SADS-E	80	11, 12, 15, 21	any SUD, CD, ASPD, MDD	All	K-SADS-E
Biederman et al., 2009a[a]	217 (100)	White	No stimulant treatment: 23, 3.7, 15-30 Stimulant treatment: 21, 3, 15-30	Clinical diagnosis, ADHD screening questionnaire and K-SADS-E	80	11, 12, 15, 21	CD, MDD	All	K-SADS-E
Biederman et al., 2009b[a]	563 (59)	White	20, 14, *Unk.*.	Clinical diagnosis, ADHD screening	*Unk.*.	Boys study: 11, 15, 21	ADHD	All	K-SADS-E/SCID

Study	N childhood ADHD (% male)	Ethnicity/race in %	Age at last follow-up (groups specified) (*M*, *SD*, range)	Criteria used to diagnose ADHD in childhood	Follow-up rate in %	Mean age of study sample at baseline wave and follow-up assessments	Psychiatric disorders assessed at outcome	At which assessments were psychiatric disorders measured	Method of assessment psychiatric outcomes
				questionnaire and K-SADS-E		Girls study: 11, 16 Genetic study: retrospective			
Biederman et al., 2011[a]	217 (100)	White	22, 4, 15-31	Clinical diagnosis, ADHD screening questionnaire and K-SADS-E	80	11, 12, 15, 22	ADHD	All	K-SADS-E, SCID
Biederman et al., 2012a[a]	96 (0)	Predominantly White[f]	22, 3, 15-30	Clinical diagnosis, ADHD screening questionnaire and K-SADS-E	69	11, 16, 22	ADHD, any SUD, MDD	All	K-SADS-E
Biederman et al., 2012b[a]	213 (55)	Predominantly White[f]	Non-smoking 22, 3, *Unk.*. Smoking 23, 3, *Unk.*.	Clinical diagnosis, ADHD screening questionnaire and K-SADS-E	*Unk.*.	Males: 11, 12, 15, 21 Females: 11, 16, 22	Any SUD	All	K-SADS-E, SCID
Breyer et al., 2014[c]	150 (81)	Predominantly White[f]	Remitted ADHD 22, 1, *Unk.*. Persistent ADHD 22, 1, *Unk.*.	PR DICA	89	9, 11, 13, 18, 20, 22	ADHD, any SUD	All	ADI
Cheung et al., 2015	110 (86)	White	18, 3, 11-26	PACS	63	12, 18	ADHD	All	DIVA
Clarke et al., 2011	38 (100)	Australian[f]	22, *Unk.*.	Clinical diagnosis (DSM-IV)	95	10, 22	ADHD	All	CAARS

Study	N childhood ADHD (% male)	Ethnicity/race in %	Age at last follow-up (groups specified) (*M*, *SD*, range)	Criteria used to diagnose ADHD in childhood	Follow-up rate in %	Mean age of study sample at baseline wave and follow-up assessments	Psychiatric disorders assessed at outcome	At which assessments were psychiatric disorders measured	Method of assessment psychiatric outcomes
Dalsgaard et al., 2014	208 (88)	Danish[f]	31, 7, *Unk.*.	Reassessment of ADHD registry records according to DSM-IV/ICD-10 ADHD criteria	100	8, 31	Any SUD	All	DPCR data (ICD codes)
Elkins et al., 2020	807 (45)	Predominantly White[f]	24, 1, *Unk.*.	Primary caregiver and child reports on the DICA-R, modified for DSM-IV	81	11, 14, 17, 24	ADHD	Persistence based on symptoms age 17 and/or 24. Any SUD at age 24 (any period between 18-24 y)	DICA-R, CIDI
Gao et al., 2015[e]	399 (82)	Han Chinese	19, 1, 18-24	Chinese translation of CDIS	72	12, 18	ADHD	All	CAADI
Halperin et al., 2011[b]	90 (87)	*Unk.*., childhood sample: African-American 41, Hispanic 26, Mixed or other Ethnicity 11, White 22	18, 2, 16–26	PR CBCL and DISC, TR IOWA Conners	59	9, 18	ADHD, any SUD	ADHD: both, any SUD at follow-up	K-SADS-PL
Harty et al., 2013[b]	97 (*Unk.*., childhood	*Unk.*., childhood sample:	18, 2	PR CBCL and DISC, TR IOWA Conners	57	9, 18	Any SUD	Any SUD at follow-up	K-SADS-PL

Study	N childhood ADHD (% male)	Ethnicity/race in %	Age at last follow-up (groups specified) (*M*, *SD*, range)	Criteria used to diagnose ADHD in childhood	Follow-up rate in %	Mean age of study sample at baseline wave and follow-up assessments	Psychiatric disorders assessed at outcome	At which assessments were psychiatric disorders measured	Method of assessment psychiatric outcomes
	sample: 89)	African-American 28, Hispanic 31, Mixed or other Ethnicity10, White 25							
Hechtman et al., 2016[d]	476 (*Unk.*.)	*Unk.*., childhood sample: African-American 20, Hispanic 8, White 61	25, *Unk.*., 19-28	DISC	82	8, 9, 10, 10, 11, 14, 16, 18, 20, 22, 25	Any SUD	At 20, 22, and/or 25 years	DISC
Huss et al., 2008	215 (91)	*Unk.*.	22, 5, 15-*Unk.*.	Clinical diagnosis (ICD-9/DSM-III-R or ICD-10/DSM-IV)	N/A	N/A (retrospective)	Any SUD	Present	CIDI
Ilbegi et al., 2018	189 (57)	White	21, *Unk.*.	CPRS-R:L, CTRS-R:L	*Unk.*.	11, *Unk.*., 21	Any SUD	All	DAST-20; FTND; SMAST SUD diagnosis according to the DSM-IV criteria
Ivanov et al., 2018[b]	40 (93)	African-American 23, Hispanic 43, Mixed or other	25, 2, *Unk.*.	PR CBCL and DISC, TR IOWA Conners	36	9, 18, 24	ASPD	All	SCID-II

Study	N childhood ADHD (% male)	Ethnicity/race in %	Age at last follow-up (groups specified) (*M*, *SD*, range)	Criteria used to diagnose ADHD in childhood	Follow-up rate in %	Mean age of study sample at baseline wave and follow-up assessments	Psychiatric disorders assessed at outcome	At which assessments were psychiatric disorders measured	Method of assessment psychiatric outcomes
Kessler et al., 2005	3,197 (59)	Ethnicity 8, White 28 Black 10, Hispanic 11, Mixed or other Ethnicity 4, White 75	*Unk.*., 18-44	NCR-S assessment based on DIS for DSM-IV	N/A	N/A (retrospective)	ADHD	Retrospectively and present	Clinician-assessed
Lambert et al., 1998	214 (85)	*Unk.*., childhood sample: representative of the East Bay Region of the San Francisco Metropolitan Area, with members of minority ethnic groups 23[f]	*Unk.*.	CAAS	81	Evaluated prospectively from kindergarten-fifth grade to the end of high school, and as young adults	Any SUD	Adult follow-up	QDIS-III-R, CSBS
Lecendreux et al., 2019	492 (50)	Representative of the French population[f]	18, *Unk.*.	K-SADS-E updated for DSM-5 diagnosis	49	9, 13, 18	ADHD	All	K-SADS-E
Li et al., 2013[e]	193 (82)	Han Chinese	19, 1, *Unk.*.	CDIS	75	12, 19	ADHD	All	CAADI
Miller et al., 2008[b]	96 (87)	African-American 23,	18, 2, *Unk.*.	PR CBCL and DISC, TR IOWA Conners	*Unk.*.	9, 18	ASPD	CD, OD at baseline,	SCID-II

Study	N childhood ADHD (% male)	Ethnicity/race in %	Age at last follow-up (groups specified) (*M*, *SD*, range)	Criteria used to diagnose ADHD in childhood	Follow-up rate in %	Mean age of study sample at baseline wave and follow-up assessments	Psychiatric disorders assessed at outcome	At which assessments were psychiatric disorders measured	Method of assessment psychiatric outcomes
		Hispanic 33, Mixed or other Ethnicity 20 White 24						ASPD at follow-up	
Molina et al., 2023[d]	579 (80)	*Unk.*., childhood sample: African-American 20, Hispanic 8, White 61	25, 1, *Unk.*.	DISC	81	11, 12, 15, 17, 19, 21, 23, 25	Any SUD	*Unk.*.	DISC
Øie et al., 2023	19 (100)	White	37, 2, *Unk.*.	Semi-structured clinical interviews and standardized rating scale with mental health professionals (DSM-III-R)	95	14, 27, 37	ADHD	All	MINI
Qian et al., 2016[e]	68 (82)	Han Chinese	*Unk.*., 18-24	DSM-IV criteria based on semi-structured parent and child interviews	76	13, *Unk.*.	ADHD	All	CAADI
Rasmussen et al., 2000	50 (76)	Swedish [f]	22, 0, *Unk.*.	ADHD DSM-IV checklist (parent interview)	89	6, 22	ASPD, MDD	All	Child and adolescent psychiatrists according to

Study	N childhood ADHD (% male)	Ethnicity/race in %	Age at last follow-up (groups specified) (*M*, *SD*, range)	Criteria used to diagnose ADHD in childhood	Follow-up rate in %	Mean age of study sample at baseline wave and follow-up assessments	Psychiatric disorders assessed at outcome	At which assessments were psychiatric disorders measured	Method of assessment psychiatric outcomes
									operationalized criteria
Roy et al., 2016 [d]	453 (78)	African-American 19, Asian 1, Black Hispanic 1, Mixed or other Ethnicity 8, non-Black Hispanic 7 White 63	25, *Unk.*.	DISC	78	8, 21, 23, 25	ADHD	All	CAARS (DSM-5 symptoms)
Shaw et al., 2013	92 (58)	*Unk.*.	24, 4, *Unk.*.	DICA	55	11, 24	ADHD, any anxiety disorder, MDD	All	CAARS, SCID
Steinhausen et al., 2014	2,0742 (75)	Danish[f]	*M* age at time of first diagnosis SUD 25	DPCR ICD codes	N/A	*M* age at ADHD diagnosis 15, *M* age at time of first diagnosis SUD 25	Any SUD	All	DPCR data (ICD codes)
Tsai et al., 2019	214 (66)	Taiwanese	25, 5, 18-36	K-SADS-E	*Unk.*.	12, 24	CD, MDD, any SUD, any anxiety disorder	Both or retrospectively	K-SADS-E
Wilens et al., 2011[a]	257 (52)	White	20, 4, *Unk.*.	Clinical diagnosis, ADHD screening	Female	Males: 11, 12, 15, 21	Any SUD	All	K-SADS-E

Study	N childhood ADHD (% male)	Ethnicity/race in %	Age at last follow-up (groups specified) (*M*, *SD*, range)	Criteria used to diagnose ADHD in childhood	Follow-up rate in %	Mean age of study sample at baseline wave and follow-up assessments	Psychiatric disorders assessed at outcome	At which assessments were psychiatric disorders measured	Method of assessment psychiatric outcomes
				questionnaire and K-SADS-E	participants: 69 Male participants: 80	Females: 11, 16, 22			
Winters et al., 2011[c]	149 (81)	Predominantly White[f]	22, 1, 22-24	DICA-R, modified to DSM-III-R	73	7-9, 11-15, 12-16, 18, 20, 22	Any SUD	Any SUD T4-T6	Updated ADI
Yoshimasu et al., 2018	232 (72)	White	30, *Unk.*.	School/medical records included DSM-IV ADHD criteria, ADHD questionnaire, and/or clinical ADHD diagnosis	66	Birth cohort, 30	Any SUD, ASPD, MDD, any anxiety disorder	All	MINI

Note. ADHD = attention-deficit/hyperactive disorder, ADI = adolescent diagnostic interview, ASPD = antisocial personality disorder, BASC = behavior assessment system for children, BRIEF = behavior rating inventory of executive function, CAADI = Chinese version of the conner's adult ADHD diagnostic interview, CAADID = conners adult ADHD diagnostic interview for DSM-IV, CAARS = Conners' adult ADHD rating scales, CAAS = children's attention and adjustment survey, CBCL = child behavior checklist, CD = conduct disorder, CDIS = clinical diagnostic interview scale, CPRS = Conners' parent rating scale, CSBS = California smoking baseline survey, CTRS = conners teacher rating scale, DAST = drug abuse screening test, DCD = developmental coordination disorder, DICA = diagnostic interview for children and adolescents, DIS = diagnostic interview schedule, DISC = diagnostic interview schedule for children, DIVA = diagnostic interview for ADHD in adults, DPCR = Danish psychiatric central register, DSM = diagnostic and statistical manual of mental disorders, FTND = Fagerström test for nicotine dependence, GAF = global assessment of functioning, ICD = international classification of diseases and related health problems, IMAGE = international multicenter ADHD genetic, K-SADS = kiddie schedule for affective disorders and schizophrenia, *M* = mean, MDD = major depressive disorder, MINI = mini-international neuropsychiatric interview, MNCEP =

Minnesota competence enhancement program, MTA = multimodal treatment study of ADHD, NCS-R = national comorbidity survey - replication, ODD = oppositional defiant disorder, PACS = parental account of childhood symptoms, PR = parent-rated, QDIS = quick diagnostic interview schedule, SCID = structured clinical interview for DSM-IV axis i disorders, *SD* = standard deviation, SES = socioeconomic status, SNAP = Swanson, Nolan, and Pelham rating scale, SMAST = short Michigan alcohol screening test, SUD = substance use disorder, TR = teacher-rated, Unk. = unknown, WAIS = Wechsler adult intelligence scale, WISC = Wechsler intelligence scale for children, WRAT = wide range achievement test.

[a,b,c,d] Studies are part of the same cohort.

[e] Studies possibly have overlapping cohorts.

[f] Exact ethnic/race composition was not reported in the original study and, therefore, data on the ethnic/race composition was not available.

Predictors of ADHD persistence

Five predictors of ADHD persistence were included in the meta-analyses (see Table 5.2). A childhood history of stimulant treatment (OR = 1.88, 95% CI 1.28-2.75, p = .001) was associated with an increased risk for a persistent course of ADHD [178-181], and a higher childhood full-scale IQ (OR = 0.99, 95% CI 0.98-1.00, p = .039) was associated with a decreased risk [160, 181-183]. Severity of childhood ADHD-related impairment was not associated with adulthood ADHD persistence (OR = 2.12, 95% CI 0.99-4.54, p = .054) [178, 181, 184], and findings showed potentially high heterogeneity among studies (Q (2) = 10.44, p = .005, I^2 = 76.9%). Furthermore, childhood ODD/CD (OR = 1.03, 95% CI 0.87-1.24, p = .564) [160, 179, 181, 184, 185], and male sex (OR = 0.93, 95% CI 0.71-1.23 p = .621) [160, 179-182] were not associated with ADHD persistence. Sensitivity analyses excluding poor quality studies for predictors of adulthood ADHD persistence did not change the results for: ADHD-related impairment [178, 181, 184], stimulant treatment history [178, 180, 181], and male sex [180-182], with the single exception that the association for childhood full-scale IQ became non-significant (Table 5.4) [181-183].

An additional 25 predictors for ADHD persistence were included in the narrative review (Table 5.3). There was some evidence for the following predictors being associated with an increased risk of ADHD persistence: ADHD combined type (compared to ADHD inattentive type) [181, 184], total ADHD symptoms [160, 178, 185-189], hyperactive/impulsive symptoms [160, 178-181, 183, 186], inattention symptoms [160, 178-181, 183, 186], anxiety disorders [178, 184, 185], externalizing problems [160, 178-181, 183, 185, 186, 188, 189], social dysfunctioning [178, 183, 185], thought problems [178, 185], unspecified ADHD treatment [184, 186], parental psychopathology [160, 182], maternal psychopathology [160, 178, 184], and low socioeconomic status [160, 178-180, 182, 183, 189]. Some evidence for an association with a protective effect was found for performance IQ [160, 183]. Evidence for no association was found for ADHD hyperactive-impulsive type [181, 184], mood disorders [178, 184, 185], internalizing problems [160, 178, 183, 185], childhood traumatic life events [160, 184], verbal IQ [160, 183], executive functioning [160, 188], genetic biomarkers [187, 190], birth weight [160, 180], paternal psychopathology [178, 184], educational difficulties [178, 185, 186], family stress factors [178, 179, 182, 184, 185], and age [179, 187, 189].

Sensitivity analyses excluding poor quality studies (10 out of 17 studies), showed some evidence for the following predictors being associated with an increased risk of ADHD persistence (Table 5.5): ADHD combined type [181, 184], hyperactive/impulsive symptoms [178, 180, 181, 183], anxiety disorders [178, 185], externalizing problems [178, 180, 181, 183, 188], social dysfunctioning [178, 183], and low socioeconomic status [178, 180, 182, 183]. There was evidence for no association for: ADHD hyperactive-impulsive type [181, 184], inattention

symptoms [178, 180, 181, 183], mood disorders [178, 184], internalizing problems [178, 183], paternal psychopathology [178, 184], maternal psychopathology [178, 184], and family stress factors [178, 182, 184]. Too few studies with fair/good quality were left for a narrative review of the remaining predictors.

Predictors of SUDs

Three predictors were included in the meta-analysis for SUDs in adulthood (see Table 5.2). ADHD persistence was associated with an increased risk of SUDs in adulthood (OR = 2.20, 95% CI 1.26-3.85, p = .018) [160, 177, 179, 185, 191], while stimulant treatment (OR = 1.41, 95% CI 0.72-2.75, p = .142) [177, 192, 193] and ODD/CD (HR = 2.09, 95% CI 0.60-7.30, p = .104) [177, 194, 195] in childhood were not. Findings for ADHD persistence showed moderate-to-high heterogeneity (Q (2) = 25.84, p = .004, I^2 = 59.7%). After exclusion of poor quality studies, too few effect sizes were available for a meta-analysis.

Additionally, three childhood predictors were included in the narrative review (Table 5.3). There was some evidence for later age at initiation of stimulant treatment being associated with an increased risk of SUDs in adulthood [175, 194]. For ADHD combined type [177, 192], and stimulant treatment duration [175, 194, 196] there was evidence for no association.

Sensitivity analyses excluding poor quality studies showed that there was evidence for no association for stimulant treatment duration [175, 196]. Too few studies were left for a narrative review of the remaining predictors.

Predictors of CD

No predictors of CD were eligible for meta-analysis. Narratively, there was some evidence that childhood stimulant treatment history was associated with an increased risk of adult CD (Table 5.3) [192, 197]. Too few studies were left for narrative review after exclusion of the poor quality studies.

Predictors of ASPD

No predictors of ASPD were eligible for meta-analysis. One predictor was included in the narrative review, showing persistent ADHD was associated with an increased risk of adult ASPD (Table 5.3) [191, 198]. However, this result was based on two poor quality studies.

Predictors of MDD

One predictor of MDD was included in the meta-analysis (Table 5.2), showing ADHD persistence to be associated with an increased risk of MDD in adulthood (OR = 3.19, 95% CI 1.71-5.95, p < .001) [160, 185, 189, 191]. After exclusion of poor quality studies, too few effect sizes were available for a meta-analysis.

One additional predictor was included in the narrative review and showed some evidence for childhood stimulant treatment history being associated with an decreased risk of adult MDD (Table 5.3) [192, 197]. Excluding poor quality studies, too few studies were left for narrative review.

Predictors of Anxiety Disorders

One candidate predictor of anxiety disorders was included in the meta-analysis and showed ADHD persistence was not associated with an increased risk of anxiety disorders in adulthood (OR = 3.88, 95% CI 0.24-62.42, p = .165) [160, 189, 191]. No meta-analysis was possible on the studies that remained after exclusion of poor quality studies. There were too few studies to perform a narrative review.

Table 5.2. *Meta-analytic results of childhood predictors of ADHD persistence, SUDs, MDD, and anxiety disorders*

Predictor (OR)	*k*	*n*	OR	95% CI	*p* value	I^2	Q (df), *p* value
Outcome ADHD persistence							
ADHD-related impairment	3	3	2.12	0.99-4.54	.054	76.9%	10.44(2), *p* = .005
ODD/CD classification	5	9	1.03	0.87-1.24	.564	0%	5.53(2), *p* = .700
Stimulant treatment history	4	4	1.88	1.28-2.75	.001	30.4%	4.89 (2), *p* = .180
Full-scale IQ	4	4	0.99	0.98-1.00	.039	7.5%	7.14(2), *p* = .068
Male sex	5	5	0.93	0.71-1.23	.621	16.1%	6.35 (2), *p* = .174
Outcome SUDs							
ADHD persistence	6	11	2.21	1.53-3.17	.004	59.7%	25.84(2), *p* = .004
Stimulant treatment history	4	19	1.22	0.70-2.12	.322	18.5%	8.40(2), *p* = .972
ODD/CD classification (HR)	3	5	2.09	0.60-7.30	.104	80.7%	7.07(2), *p* = .132
Outcome MDD							
ADHD persistence	4	4	3.19	1.71-5.95	<.001	33.9%	3.79(2), *p* = .285
Outcome Anxiety Disorders							
ADHD persistence	3	4	3.88	0.24-62.42	.165	73.1%	6.43(2), *p* = .092

Note. ADHD = attention-deficit/hyperactive disorder, CD = conduct disorder, CI = confidence interval, HR = hazard ratio, I^2 = heterogeneity index, IQ = intelligence quotient, *K* = number of studies, MDD = major depressive disorder, *n* = number of effect sizes, ODD = oppositional defiant disorder, OR = odds ratio.

Table 5.3. *Predictors of adult psychiatric outcomes of childhood ADHD studied in longitudinal research for which a narrative review was possible (N > 1)*

Predictors	Outcomes (number of significant findings for a predictor / number of times predictor studied)					
	ADHD persistence	SUDs	CD	ASPD	MDD	Anxiety disorders
ADHD						
Persistent childhood ADHD		**4/7**[a,e]		**2/2**	**2/4**[a]	1/3[a]
ADHD combined type	**1/2**	0/2				
ADHD hyperactive/impulsive type	0/2					
(Number of) inattention symptoms	**1/7**[c]					
(Number of) hyperactive/impulsive symptoms	**2.5/7**[e]					
Total number of ADHD symptoms	**3.5/7**[e]					
Severity of ADHD-related impairment	2.5/4[a,e]					
Psychopathology (classifications)						
Mood disorders	0/3[c]					
Anxiety disorders	**1/3**					
ODD/CD	1.5/8[a,d]	1/4[a]				
Behavior and emotional problems						
Internalizing problems score	0/4[c]					
Externalizing problems score	**2/10**[c,d]					
Social dysfunctioning score	**1/3**					
Thought problems score	**1/2**					
Childhood traumatic life events (yes/no)	0/2					
Treatment history						
Stimulant treatment history (yes/no)	**3/6**[a]	0/8[a]	**1/2**		**1/2** [b]	
Age at initiation of stimulant treatment		**1/2**				
Stimulant treatment duration (years)		0/3				
Unspecified treatment	½					
Cognitive measures						

Predictors	Outcomes (number of significant findings for a predictor / number of times predictor studied)					
	ADHD persistence	SUDs	CD	ASPD	MDD	Anxiety disorders
Full-scale IQ score	**2/9**[a]					
Performance IQ score	**1/2**[b]					
Verbal IQ score	0/2					
Executive functioning score	0/2					
Biomarkers						
Genetic biomarker	0/2					
Perinatal factors						
Birth weight	0/2					
Parental factors						
Parental psychopathology (yes/no)	**1/2**					
Paternal psychopathology (yes/no)	0/2					
Maternal psychopathology (yes/no)	**1/3**					
Educational factors						
Educational difficulties (yes/no)	0/3[c]					
Family factors						
Family stress factors	0/5[c]					
Demographics						
Sex	2/7[a]					
Age	0/3					
SES	**3/7**					

Note. The table does not show single predictors investigated by only one study (see Table S5.10, available online). ADHD = attention-deficit/hyperactive disorder, ASPD = antisocial personality disorder, CD = conduct disorder, IQ = intelligence quotient, MDD = major depressive disorder, ODD = oppositional defiant disorder, SES = socioeconomic status, SUD = substance use disorder.
[a] Included in our meta-analysis. Bold font indicates (some evidence for) a possible positive association was found,
[b] except for two predictors for which a (possible) negative association was found.

[c] Study was treated as reporting no association, as both/all measures of the same predictor were non-significant, and averaging of effect sizes was not possible.
[d] Study was treated as reporting an association, as both/all measures of the same predictor were significant, and averaging of effect sizes was not possible.
[e] Study included two measures of the same predictor, of which one was significant, and the other was not, and averaging of effect sizes was not possible.

Table 5.4. Meta-analyses of predictors of ADHD persistence using only studies with sufficient study quality

Outcome	Predictor	*k*	*n*	OR	95% CI	*p*-value	I^2 in %	Q(df), *p*- value
ADHD persistence	ADHD-related impairment	3	3	2.12	0.99-4.54	.054	76.9	10.44(2), *p* = .005
ADHD persistence	Stimulant treatment history	4	4	2.30	1.45-3.65	<.001	41.4	5.85(2), *p* = .119
ADHD persistence	IQ	3	3	0.99	0.98-1.01	.291	30.4	6.67(2), *p* = .036
ADHD persistence	Male sex	3	3	1.08	0.82-1.44	.998	0	0.92(2), *p* = .632

Note. ADHD = attention-deficit/hyperactive disorder, CI = confidence interval, I^2 = heterogeneity index, *K* = number of studies, *n* = number of effect sizes, OR = odds ratio, Q = Cochrane's Q.

Table 5.5. Effects of candidate predictors of adult psychiatric outcomes of childhood ADHD studied in longitudinal research after removing studies with insufficient study quality (difference in findings as compared to full sample indicated in bold, and analysis no longer possible indicated in italics)

Predictors	Outcomes (number of significant findings for a predictor / number of times predictor studied in good/sufficient quality studies)					
	ADHD persistence	SUDs	CD	ASPD	MDD	Anxiety disorders
ADHD						
Persistent ADHD		*N/A*		*N/A*	*N/A*	*N/A*
ADHD combined type	1/2	*N/A*				
ADHD predominantly hyperactive/impulsive type	0/2					
(Number of) inattention symptoms	**0/4**[e]					
(Number of) hyperactive/impulsive symptoms	1/4					
Total number ADHD symptoms	1.5/2[d]					

Predictors	Outcomes (number of significant findings for a predictor / number of times predictor studied in good/sufficient quality studies)					
	ADHD persistence	SUDs	CD	ASPD	MDD	Anxiety disorders
Severity of ADHD-related impairment	2.5/4[a,d]					
Psychopathology (classifications)						
Mood disorders	0/2[b]					
Anxiety disorders	1/2					
ODD/CD	*N/A*	*N/A*				
Behavior and emotion						
Internalizing problems score	**0/2**[b]					
Externalizing problems score	2/5[b,c]					
Social functioning	1/2[b]					
Thought problems score	*N/A*					
Traumatic life events (yes/no)	*N/A*					
Treatment						
Stimulant treatment history (yes/no)	3/4[a]	*N/A*	*N/A*		*N/A*	
Age at initiation of stimulant treatment		*N/A*				
Stimulant treatment duration (years)		0/2				
Cognitive measures						
Full scale IQ score	**1/5**[a]					
Performance IQ score	*N/A*					
Verbal IQ score	*N/A*					
Executive functioning score	*N/A*					
Biomarkers						
Genetic biomarker	*N/A*					
Perinatal factors						
Birth weight	*N/A*					
Parental factors						

Predictors	Outcomes (number of significant findings for a predictor / number of times predictor studied in good/sufficient quality studies)					
	ADHD persistence	SUDs	CD	ASPD	MDD	Anxiety disorders
Parental psychopathology (yes/no)	*N/A*					
Paternal psychopathology (yes/no)	0/2					
Maternal psychopathology (yes/no)	**0/2**					
Education						
Educational difficulties (yes/no)	*N/A*					
Family factors						
Family stress factors	0/3					
Demographics						
Sex	0/3[a]					
Age	*N/A*					
SES	2/4					

Note. The table shows only number of fair/good quality studies. Bold font indicates predictors which conclusions changed after exclusion of all studies with poor study quality (i.e., some evidence for an association changing to no evidence for an association). Italics N/A indicates predictors where too few studies were left for a meta-analysis or less than two fair/good quality studies were left for narrative review.
ADHD = attention-deficit/hyperactive disorder, ASPD = antisocial personality disorder, CBCL = child behavior checklist, CD = conduct disorder, IQ = intelligence quotient, MDD = major depressive disorder, N/A = not applicable, ODD = oppositional defiant disorder, SES = socioeconomic status, SUD = substance use disorder.
[a] Included in our meta-analyses.
[b] Study was treated as reporting no association, as both/all measures of the same predictor were non-significant, and averaging of effect sizes was not possible.
[c] Study was treated as reporting association, as both/all measures of the same predictor were significant, and averaging of effect sizes was not possible.
[d] Study included two measures of the same predictor, of which one was significant and the other was not, and averaging of effect sizes was not possible.

Discussion

This meta-analysis and systematic review is the first to aggregate results on a large variety of childhood assessed predictors of adult psychiatric outcomes of childhood ADHD, including ADHD persistence, SUDs, CD, ASPD, MDD, and anxiety disorders. We identified 36 studies including 119 unique predictors. Most outcomes were considered in few studies, and 66% of all predictors were studied only once. The available data allowed meta-analyses of 10 predictors and 31 predictors were narratively reviewed. Only 44% of all included studies were of fair/good study quality. Our meta-analytic results demonstrated that a history of childhood stimulant treatment was associated with an increased risk of ADHD persistence into adulthood, whereas higher IQ was associated with a decreased risk. ADHD persistence was not associated with childhood assessed ADHD-related impairment, ODD/CD, or sex. Although ADHD persistence was associated with an increased risk of SUDs and MDD in adulthood, ADHD persistence was not associated with an increased risk for adulthood anxiety disorders. Adulthood SUDs were not predicted by childhood ODD/CD or stimulant treatment. Sensitivity analysis excluding poor quality studies replicated most meta-analytic findings for ADHD persistence as outcome, showing an association with stimulant treatment history, and no association with ADHD-related impairment and sex, with the single exception that childhood IQ no longer was associated with an increased risk for ADHD persistence.

Limiting the narrative review to fair/good quality studies, our narrative results revealed seven additional potential childhood predictors (showing some evidence) of ADHD persistence, including ADHD combined type, hyperactive/impulsive symptoms, anxiety disorders, externalizing problems, social dysfunctioning, and socioeconomic status. Further, fair/good studies showed no evidence that adult ADHD persistence was predicted by childhood ADHD hyperactive-impulsive type, inattention symptoms, mood disorders, internalizing problems, paternal psychopathology, maternal psychopathology, and family stress factors; and no evidence that SUDs in adulthood were predicted by childhood stimulant treatment duration. However, there was large heterogeneity in our findings across studies. Also, some studies provided several effect sizes per potential predictor, which we dealt with by averaging effect sizes to obtain a single conclusion. However, this approach was limited by the assumption of equal weight of each effect size. Therefore, it is important to interpret the narrative results with caution.

ADHD persistence into adulthood

The meta-analytic results for adult ADHD persistence in relation to childhood stimulant treatment history and sex confirm the findings of an earlier meta-analysis by Caye et al. [33], except that we found an association for childhood IQ and no association for childhood ODD/CD and severity of ADHD-related

impairment. A possible explanation for the discrepancy in the findings on ODD/CD is that our systematic review included only clinical samples with an ADHD diagnosis and looked at a persistent diagnosis of ADHD, while the meta-analysis of Caye et al. [33] also included (subclinical) samples of hyperactive children and included persistent ADHD symptoms as outcome. Possibly, ODD/CD is predictive of ADHD symptom persistence, but not of a diagnosis of ADHD in clinical samples. Further, the results regarding impairment were not significant despite all individual studies reporting significant odds ratios. Substantial heterogeneity between effect sizes likely contributed to our finding, possibly due to different operationalizations of impairment between studies and differences between studies in the adjustment for possible confounding variables. More specifically, one study adjusted for age and residence [181], where the other two studies did not provide adjusted effect sizes [178, 181], which might introduce additional heterogeneity. With regard to our surprising finding on childhood IQ, which reached significance in predicting adult persistent ADHD, the effect was very small with the confidence interval including a rounded 1. Moreover, IQ was no longer significant after removing one poor quality study, indicating this finding may not have been very robust and warrant further investigation [33]. Further, our meta-analysis showed that a childhood history of stimulant treatment was associated with a doubled risk for a persistent course of ADHD in adulthood. Although stimulant treatment has often been reported as a protective factor for a range of ADHD-related outcomes, it is also related to higher symptom severity and level of impairment during time of prescription, suggesting that the most affected children may receive stimulant treatment, which potentially increases the relationship between childhood stimulant treatment and adulthood ADHD persistence [199, 200]. Importantly, studies included in our meta-analyses on stimulant treatment did not control for severity of impairment, stressing the need to look at combined effects of predictors in future studies.

The narrative results of fair/good quality studies hint towards the relevance of childhood symptom severity (symptoms of ADHD, anxiety and externalizing problems) in predicting ADHD persistence in adulthood, corresponding to results from a previous narrative review [201]. In addition, (low) childhood SES might be a relevant factor. In an earlier meta-analysis SES was not associated with an increased risk for ADHD persistence [33], however, in that study they disregarded study quality and included one poor quality study without an effect (out of three studies). Furthermore, participants with lower SES might be more often lost to follow-up, and as low SES increases risk for receiving an ADHD diagnosis in childhood, SES should be further studied as a potential predictor [202, 203].

Our narrative review of fair/good quality studies showed no specific evidence of childhood maternal or paternal psychopathology as predictive factor, but one good quality study did hint towards the predictive value of parental psychopathology as a risk factor for ADHD persistence. Additionally, we found a predictive effect of

maternal psychopathology driven by a poor quality study, also hinting towards potential relevance of parental psychopathology. Similarly, the earlier meta-analysis remained inconclusive on the role of parental psychopathology for ADHD persistence [33]. Parental psychopathology is an umbrella term for several psychiatric problems and thought to act as a risk factor for an ADHD diagnosis in childhood [204]. Our results suggest that although it may influence ADHD in childhood, it may not be associated with ADHD persistence into adulthood. Potentially, only specific aspects of parental psychopathology may impact persistence [204]. In contrast to our findings, Caye et al. [33] identified childhood comorbid MDD as a predictor for adult ADHD persistence. However, the single study with an effect was excluded in our systematic review, as the sample overlapped with another, more recent, included study (without an effect) [184, 205].

To summarize, childhood stimulant treatment history was associated with an increased risk of adult ADHD persistence, while sex was not. The inconsistent findings of childhood ADHD-related impairment, ODD/CD, and IQ warrant further investigation. Additionally, potential childhood predictors of adult ADHD persistence that should be further investigated, preferably by meta-analyses, include ADHD combined type, hyperactive/impulsive symptoms, anxiety disorders, externalizing problems, social dysfunctioning, thought problems, parental psychopathology, and socioeconomic status.

Psychiatric outcomes other than ADHD persistence in adulthood

Our meta-analytic results showed that a persistent course of childhood ADHD was associated with an increased risk of SUDs and MDD in adulthood by more than two and three times, respectively, corroborating previous findings [3]. A persistent course of childhood ADHD was defined by a diagnosis of ADHD in childhood that was subsequently confirmed in adulthood, reflecting not only childhood ADHD, but also adult ADHD. Therefore, alternatively, SUDs and MDD may also be the result of the presence of adult ADHD. However, the underlying mechanism linking ADHD and SUDs/MDD is likely due to a shared neurobiological and familial/genetic underpinnings of the disorders, suggesting that a persistent course of childhood ADHD may indeed be related to an enhanced risk of SUDs and MDD in adulthood [206, 207]. Further, in agreement with a recent review, SUDs were not associated with a childhood history of stimulant treatment [208]. Finally, our results indicate that childhood ODD/CD was not associated with SUDs in adulthood. Despite the ongoing debate (see for example Groenman et al. [209]) our finding suggests that ODD/CD is not driving the risk for SUDs in those with ADHD. Narratively, too few fair/good qualities studies were left to identify potential predictors of SUDs, CD, ASPD, and MDD.

For adult anxiety disorder, we found no evidence that ADHD persistence acts as a risk factor. Our findings build upon suggestions based on the results of another review on the relationship between ADHD and anxiety disorders suggesting that future studies should include other predictors (such as internalizing problems, trauma, childhood aggression or difficulties making friends) when studying the development of anxiety disorders in those with ADHD [210, 211].

Limitations and avenues for future research

Clearly, the current meta-analyses were limited by the number of available studies and type of predictors and outcomes studied. We suggest future studies into the psychiatric long-term outcomes of childhood ADHD to take the following recommendations into account. First, studies should include a wide range of potential predictors, including genetic, prenatal, perinatal, neuroimaging, neurocognitive, environmental, psychological, and social factors in order to get a better understanding of the mechanisms that play a role in the development of adult psychiatric outcomes [3, 212-215]. Second, existing studies rely on linear statistical models including single predictors that do not capture the complex (non-linear) relations between predictors and adult psychiatric outcomes of ADHD. Machine learning might offer promising possibilities as becomes evident in the wider medical field [47, 216]. Third, studies should investigate other highly impairing, although less prevalent, outcomes, to capture all of ADHD's psychiatric outcomes, including eating disorders or obsessive-compulsive disorder [217, 218]. Forth, studies should improve on the adjustment for confounders as this was the primary reason for qualifying almost half of the studies as studies of poor quality. No studies controlled for CD, MDD, or anxiety disorders in childhood while they did study adult presence of these disorders, therewith complicating identification of causal effects. Also, hardly any studies controlled for ADHD severity in childhood. Ideally, future studies should adjust for a standardized set of covariates, such as sex, age, and severity of ADHD-related impairment in childhood, and childhood presence of the psychiatric outcome at hand to be better able to approximate the true effect. Finally, the current meta-analysis was susceptible to ecological fallacy due to the availability of summary data, instead of individual participant data. Therefore, we call for studies to share individual participant data to facilitate individual patient data meta analysis (IPDMA). Ideally, an IPDMA would generate larger sample sizes, increasing the power to detect predictors for psychiatric outcomes of ADHD with lower prevalences (e.g., bipolar disorder, obsessive-compulsive disorder, schizophrenia), which were not included in the current study.

Conclusions

The current meta-analysis and narrative review studied predictors of adult psychiatric outcomes of childhood ADHD, including ADHD persistence, SUDs, CD,

ASPD, MDD, and anxiety disorders. Our meta-analysis added to the existing evidence of some earlier reported predictors (i.e., history of stimulant treatment as predictors for ADHD persistence), and was the first to meta-analytically identify additional predictors (i.e., ADHD persistence as predictor for adult SUD and MDD). Narratively (including only fair/good quality studies), we identified potential new predictors including thought and social problems, anxiety disorders and SES for ADHD persistence. No other predictors of adult psychiatric outcomes were identified, possibly due to limitations in available literature (e.g., clinical and methodological heterogeneity, poor study quality) and the employed statistical approaches. We highlighted avenues for future research to deepen our understanding of childhood predictors of adult ADHD psychiatric outcomes.

For supplemental material (online only), see the pdf of this thesis or go to https://www.jaacap.org/article/S0890-8567(25)00215-1/fulltext

CHAPTER 6

Long-term outcomes of childhood ADHD stimulant use trajectories

Under review as:
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Abstract

Background. Stimulant medication is the first-line pharmacological treatment option for children with attention-deficit/hyperactivity disorder (ADHD). However, long-term effects remain unclear. Therefore, we explored long-term (> 12 years) outcomes of childhood stimulant medication use, using data from the NeuroIMAGE cohort.

Method. Childhood (up to M_{age} = 16.14, SD_{age} = 3.48) stimulant treatment trajectories were detected using K-means clustering based on age at initiation, stop age, total and maximum daily dose, and duration and variability of stimulant use in 324 children. The trajectories were compared across seven domains of adult outcomes (controlling for multiple testing) including psychiatric status, behavioral and emotional functioning, academic and professional functioning, adaptive functioning, neurocognitive functioning, physical health, and healthcare service use.

Results. At follow-up, 143 adults with childhood ADHD (M_{age} = 28.34, SD_{age} = 3.74, 65% males) were part of three stimulant treatment trajectory groups: early-and-intense (n = 46), late-and-moderate (n = 63), and stimulant-naïve (n = 34). The three groups did not differ on most adult outcomes, but group differences were observed for the adaptive, neurocognitive and physical functioning domains on the measures risk perception, cognitive flexibility, and sleep quality. The early-and-intense group had the most favorable mean scores (trend effects) compared to the other groups. Findings did not change after controlling for age and sex.

Discussion. Stimulant medication use in childhood did not predict long-term outcomes in those with childhood ADHD in our sample, with a few exceptions, including some positive outcomes related to risk perception, cognitive flexibility, and sleep quality in those with longer and higher dosages. Our findings suggest that there may be no lasting effects of stimulants on many long-term functional outcomes.

Key words: childhood ADHD, follow-up, outcome, medication use, methylphenidate, central nervous system stimulants

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a prevalent mental health condition [2]. In ADHD, stimulant treatment is the first-line pharmacological treatment option due to its positive short-term effects on reducing ADHD symptoms (i.e., inattention, hyperactivity, impulsivity) [37]. Worldwide, between 0.76 to 3.13% of all children use stimulant medication, with a sustained annual increase in stimulant use observed among both children and adults [34-36], warranting thorough investigation of short- and long-term effects. Besides stimulant treatment being efficacious for reducing ADHD symptoms, other positive short-term effects include improving behavioral symptoms and functioning in daily life [37]. For example, stimulant treatment is associated with reductions in oppositional behavior, conduct problems, and aggression (medium to large effects), anxiety (relative risk = 0.86), and suicide risk (hazard ratio = 0.28 to 0.41), in youth with ADHD [38-40]. However, despite the positive short-term effects of stimulant medication, (very) long-term effects (> 10 years) remain ambiguous, partly because these can only be explored via placebo-controlled discontinuation studies [219], or using naturalistic follow-up studies [41] such as in this current study.

Studies into potential long-term beneficial or detrimental outcomes of childhood stimulant treatment have been limited, with outcomes focused mainly on psychiatric, neurological, health and crime outcomes, but current studies have suggested some evidence for long-term effects [42]. Results from one narrative review paper, including 64 studies with a mean follow-up period of 2.6 years mostly in children and adolescents, suggested that childhood stimulant treatment mitigates the risk for mood problems or depression, anxiety, suicidal behavior, and substance use disorder (SUD) [42]. Another narrative review included 51 studies with a mean follow-up period of 3 years for childhood outcomes and 11 years for adulthood outcomes [220]. Although studies with adult outcomes were underrepresented in this review, results showed beneficial outcomes, especially in childhood and less so in adulthood. Importantly, a referral bias might exist, where children with more severe ADHD symptoms and comorbid problems, are more likely to receive (earlier and longer) treatment, driving differences in outcomes [221]. Also, a review of pharmacoepidemiology studies using health records or registry data suggested some long-term protective effects on injury risk, motor vehicle accidents, SUD, and MDD [41]. In contrast, there is also evidence of potential negative long-term effects of childhood stimulant treatment, such as an increased risk for psychosis and tics [41, 42].

However, the previous findings have been hampered by relatively weak and heterogeneous study designs, as well as questionable definitions of 'long-term' outcomes in terms of follow-up interval. It remains unclear whether the reported effects are actual long-term outcomes, as most studies used a follow-up period of

one to three years and there are only few studies with a follow-up interval beyond three years [41, 42, 222]. Potentially, stimulant treatment might have no lasting effects in adulthood [223]. Additionally, heterogeneity in findings of the long-term outcomes of stimulant treatment is partly due to the variety in variables related to medication use, such as age at initiation, duration, dose, and frequency. For example, children with ADHD using a high dose of stimulant treatment at a young age were at a lower risk of developing SUDs in adolescence, where children initiating stimulant treatment at a later age with a lower dose were not [44], suggesting multiple aspects of stimulant treatment should be considered. A design including subgroups based on several aspects of stimulant treatment can investigate their joint effects on long-term outcomes in adulthood, which has not been done so far in previous studies [42].

Beyond methodological issues, several other concerns limit the generalizability and interpretability of the existing findings. Most of the studies focused on children or adolescents and males, further limiting knowledge on effects in adults and generalizability to females [42]. Also, most studies were limited to the study of a specific set of outcomes and did not provide a complete picture of the effects of stimulants on the main domains of functioning. Furthermore, although several large registry studies have investigated long-term outcomes of stimulant treatment, in these studies identification of participants with ADHD was often based on insurance claims without a standardized diagnostic assessment to confirm the diagnosis of ADHD and comorbid conditions, and it often remains unclear whether observed effects reflect long-term outcomes or effects of current medication use [41, 42].

To effectively inform treatment plans and monitor long-term risks and beneficial effects, more prospective studies are needed into childhood ADHD stimulant use on adult outcomes with a long follow-up period (e.g., > 10 years) that study different characteristics of stimulant use capturing main domains of functioning [224]. Therefore, the current prospective 18-year follow-up study explored the very long-term outcomes of childhood stimulant treatment in a mixed-sex cohort of children with ADHD. Participants were clustered in stimulant treatment trajectory groups based on stimulant treatment characteristics in childhood/adolescence (i.e., age at initiation, stop age, total dose, duration of dose, maximum daily dose, and variability of stimulant use). Observed stimulant treatment trajectory groups were compared on a broad range of very long-term outcomes of ADHD, including psychiatric status, behavioral and emotional problems, academic and professional functioning, adaptive functioning, neurocognitive functioning, physical health, and healthcare service use, as assessed in the adult follow-up (12 years later).

Method

Sample

In total, 143 participants were followed-up from a longitudinal cohort study initiated as part of the Dutch branch of the International Multicenter ADHD Genetics (IMAGE) study [58], of which the current study is an 18-year follow-up (as described in van der Plas et al. [127]). Both ADHD and control families were recruited in IMAGE. After enrollment in the cohort (wave I, 2003-2005), follow-ups took place in 2009-2012 (wave II, NeuroIMAGE) and 2015-2016 (wave III, NeuroIMAGE2). Inclusion criteria at wave I were: aged 5-19 years, Caucasian descent, IQ ≥ 70, and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, or known genetic disorders [58]. ADHD families had at least one child with ADHD combined type, while control families had at least one child without ADHD and did not have any first-degree family members diagnosed with ADHD. In contrast to the inclusion criteria of wave I, the follow-up waves allowed any ADHD subtype for newly recruited participants with ADHD [59]. In the current follow-up (wave IV, 2021-2024), all participants who participated in any of the previous waves were invited. For the current study, only participants for which an ADHD diagnosis was confirmed at either wave I or wave II with available stimulant treatment medication data at wave II were included.

Wave II characteristics

Demographics included for the current study were age at follow-up, sex, and educational level. Educational level was defined as the highest completed educational level based on the Dutch Verhage scale of both parents (or one parent, if only information on one parent was available) [80]. Furthermore, the Conners' rating scale was used for parent-reported symptoms of ADHD, oppositional defiant disorder (ODD), and anxious/shy behavior (using scale N, A, and D, respectively) [78].

The wave II diagnostic interview was a semi-structured clinical interview, the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) [225]. An ADHD diagnosis was based on the K-SADS and Conners' rating scale (teacher-rated and/or self-rated) [78]. More information on wave II (NeuroIMAGE) can be found elsewhere [59].

Stimulant treatment (wave II)

In wave II, pharmacy records and self-reports of medication use were collected to assess the lifetime history of stimulant treatment (immediate- and extended-release methylphenidate or dexamphetamine). For a full description of this procedure, see Schweren et al. [226]. Information on stimulant treatment encompassed the period from birth to age at wave II (M_{age} = 16.14, SD_{age} = 3.48), and

included age at initiation, stop age, total dose, duration of dose, maximum daily dose, and variability of stimulant use.

Outcomes at Follow-Up (wave IV)

The assessments targeted the following outcome domains: 1) psychiatric status, 2) behavioral and emotional problems, 3) academic and professional functioning, 4) adaptive functioning, 5) neurocognitive functioning, 6) physical health, and 7) healthcare service use. All domains were assessed using several measures, see van der Plas et al. [127]. Table S2.1 provides a description of all instruments used, selected based on strong psychometric characteristics, and the derived dependent variables. Also, two custom-made questionnaires were used to assess: 1) diet (domain physical health), using a visual analogue scale to assess diet health and adherence to diet advice of the Netherlands Nutrition Centre; and 2) number of visits to healthcare institutions in the last year (domain healthcare service use), using an extensive list of all healthcare institutions, including all medical specialists.

Demographic information was assessed through self-report, including 1) current living situation and 2) information on the participant's offspring, if applicable including number of children, their birth date, sex-assignment at birth, and any possible diagnoses. Medication use (domain healthcare service use) of one full year (the most recent full year available) was assessed using pharmacy dispensing records. If the most recent full year overlapped more than a month with the period of the COVID pandemic with health-care related restrictions (February 2020 until February 2022), the year before the start of the COVID pandemic was chosen (January 2019 to January 2020) to obtain generalizable information on medication use unobstructed from COVID health-care restrictions [65-67, 144]. Use of ADHD medication (yes/no) was based on the presence of at least one dispensing of amphetamines, methylphenidate, or atomoxetine, using anatomical therapeutic chemical (ATC) codes. General medication use was captured by the total number of different ATC codes dispensed [124].

Procedure of the current follow-up (wave IV)

Participants were invited directly or via their parents (if no informed consent was available from the participants, but only from their parents) by phone, e-mail, or post. Detailed description of the procedure of the wave IV follow-up can be found in van der Plas et al [127]. Briefly, for all participants wave IV assessments comprised self-reported online questionnaires, other-reported online questionnaires, and two video calls including a diagnostic interview and cognitive testing, and a request for their pharmacy records (see Table S2.1). The first video call included the Structured Clinical Interview for DSM-5 Disorders (SCID-5), administered by certified researchers with at least a master's degree in psychology or related discipline. During the second video call, assessment of cognitive

functioning took place. Trained researchers administered tests according to a standardized protocol. If participants were unwilling to participate in the video calls, they were allowed to only complete the online questionnaires to increase participant retention. Pharmacy records were collected for participants who gave specific consent for this collection and were registered in compliant pharmacies. Before assessment took place, all participants signed informed consent. All data was pseudo anonymized, and participants received 25 euros after completion of the questionnaires or the questionnaires and video calls. See the study's registration on the Open Science Framework (OSF) for further details https://doi.org/10.17605/OSF.IO/5Y29Q. The study was approved by the local medical ethics committee of the Amsterdam Medical Center (AUMC; ABR NL77520.029.21).

Statistical analysis

To obtain the stimulant treatment trajectory groups we categorized based on wave II age at initiation, stop age, total dose, duration of use, maximum daily dose, and variability of stimulant use, using K-means clustering. Clustering was done on available wave II medication data from all participants with an ADHD diagnosis at wave I or II ($n_{\text{wave II}}$ = 324, additionally including participants not followed-up at Wave IV) to increase cluster robustness. K-means was used due to its simplicity and intuitive interpretation of clusters [227]. Number of clusters was based on the elbow and silhouette method. Participants with an ADHD diagnosis who had never used stimulants as a child (up until wave II) were categorized as stimulant-naïve ($n_{\text{wave II}}$ = 112 participants). Medication data after wave II was not available. Interpretation of the characteristics of the stimulant treatment trajectory groups was based on z-scores.

As only participants with available wave II stimulant treatment data were included, wave II measures were not imputed. Only the outcome variables with maximum 10% missing based on the entire wave IV followed-up sample ($n_{\text{wave Iv}}$ = 421) were imputed with multiple imputation [228]. All online questionnaires and video call measures were imputed, as these measures had a maximum of 10% missing, and the parcel summary scores of online questionnaires and video call measures were used to impute missing data. Pharmacy data (wave IV) were not imputed as the percentage of missing data was 16%. Based on the recommendation to impute as many datasets as the percentage of participants with any missing data, 10 imputed datasets were created [71]. The analyses were rerun 10 times using each imputed dataset and subsequently the summary statistics of each analysis were pooled.

Attrition analyses were run to test the representativeness of the retained childhood ADHD group compared to the initial childhood ADHD group at the earliest inclusion (IMAGE, wave I). Also, the stimulant treatment trajectory groups were compared on wave II characteristics to check for group differences and identify

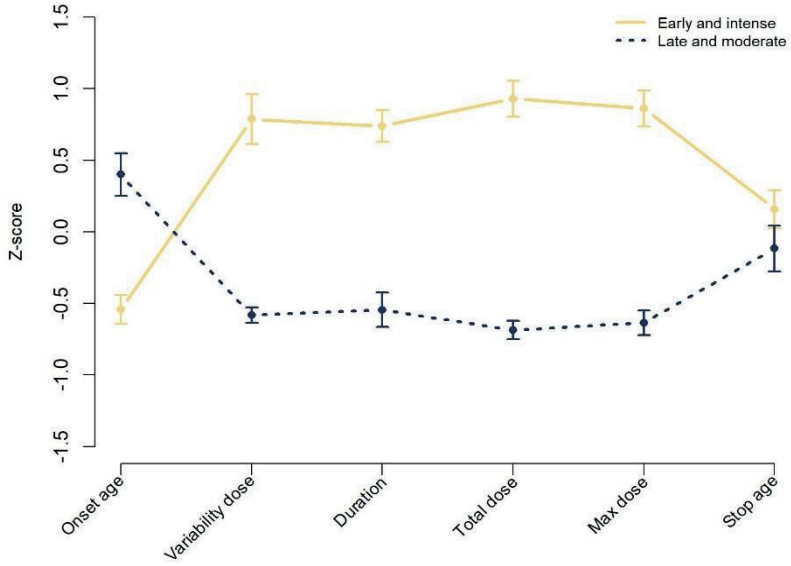
potential confounding variables. Both analyses were done using Generalizing Estimating Equation (GEE) with an exchangeable correlation structure to account for familial dependency, as groups could include sibling pairs. Groups were compared on either wave I or wave II sex, age, average educational level, and parent-reported symptoms of ADHD, ODD, and anxious/shy behavior.

Outcomes were compared across the revealed stimulant treatment trajectory groups. GEE was used with an exchangeable correlation structure to account for familial dependency. Outcomes with no variation were precluded from statistical testing [81]. Using the pooled effect sizes (across 10 imputed datasets, see above), the main effects of childhood medication group were adjusted for multiple testing using false discovery rate correction (FDR) [82], applied within the seven outcome domains. Only the FDR-corrected p-values are provided for the main effects of group. For significant main group differences of childhood medication group, post-hoc analyses were conducted using pair-wise group comparisons to identify the nature of the differences between the stimulant medication trajectory groups. Post-hoc pairwise group comparisons were investigated by varying the reference group to estimate all contrast coefficients from the GEE models, using $\alpha = .05$ to determine significant differences. Finally, to test the influence of potential demographic confounders on the association between stimulant treatment and the outcomes, sensitivity analysis were conducted repeating all analyses including demographic characteristics with significant differences across groups as covariates. All effect sizes were quantified by calculating odds ratios (OR) for categorical outcomes, and standardized betas for continuous outcomes. The magnitude of the standardized beta's was interpreted as group difference using similar threshold levels as used to interpret Cohen's *d* (small = 0.20 to 0.50, moderate = 0.50 to 0.80, large ≥ 0.80) [83]. All analyses were performed in R (v4.3.0) [84].

Results

Both the elbow and silhouette method (see Figure S6.1 and S6.2) suggested two childhood ADHD stimulant treatment trajectories: early-and-intense (n = 46, M_{age} (wave IV) = 27.76, SD_{age} (wave IV) = 2.76, 85% males) and late-and-moderate (n = 63, M_{age} (wave IV) = 27.56, SD_{age} (wave IV) = 3.79, 56% males). Cluster quality was moderate (silhouette score = 0.33, Davies-Bouldin Index = 1.33), with moderately distinct and internally coherent clusters. Based on z-scores, the early-and-intense group was characterized by younger age at treatment onset, variable trajectory of medication dose, longer duration of treatment, and a higher maximum and total dose compared to the late-and-moderate group (see Figure 6.1). Additionally, a third group included 34 followed-up participants who were stimulant-naïve at wave II (M_{age} (wave IV) = 30.59, SD_{age} (wave IV) = 4.01, 56% males).

Figure 6.1. *Characteristics of childhood stimulant treatment trajectory groups at neuroimage wave II using k-means clustering*



Note. The figure describes the childhood stimulant treatment trajectory groups, early-and-intense (solid yellow; $n_{wave\ II}$ = 138) and late-and-moderate (dotted blue; $n_{wave\ II}$ = 187), in terms of age at stimulant initiation, variability of dose (SD), duration of use, total dose, maximum dose, and stop age. The error bars reflect the 95% confidence interval. A third group (not visualized here; $n_{wave\ II}$ = 122) consisted of participants that were stimulant-naïve in childhood.

The mean follow-up duration from wave II to the current follow-up was 11.88 years (*SD* = 0.87) with 28% of the participants being successfully retained. An attrition analysis showed no differences between the initial (wave I) childhood ADHD sample and the current retained childhood ADHD sample, except for ADHD symptoms, where the retained childhood ADHD group showed more ADHD symptoms at wave I than the initial childhood ADHD group (Wald χ^2 = 5.34, p = .021, Table S6.1).

At wave II, the stimulant-naïve group was older than both the early-and-intense (β = 0.65, moderate group difference) and late-and-moderate group (β = 0.73, moderate group difference). Also, the early-and-intense group included more males compared to the late-and-moderate group (OR = 4.49 [95% CI 1.75-11.52]) and the stimulant-naïve group (OR = 4.37 [95% CI 1.53-12.50]). Groups did not differ on any other of the wave II behavioral characteristics (see Table S6.2). Therefore, age and sex were added as covariates in a sensitivity analysis.

Table 6.1 provides a description of wave IV follow-up measures for participants across the stimulant treatment trajectory groups, the main group differences of stimulant treatment trajectory and pair-wise group comparison results. At follow-

up, main stimulant treatment group differences were found on risk perception (Wald χ^2 = 37.41, p_{FDR} <.001, domain adaptive functioning), letter fluency (Wald χ^2 = 15.46, p_{FDR} <.001, domain neurocognitive functioning), and sleep quality (Wald χ^2 = 23.08, p_{FDR} <.001, domain physical health). No group difference was present on any of the other variables across the seven domains and groups did not differ on any of the demographic and/or family status variables, except for age and sex at follow-up (where the stimulant-naïve group was older than both the early-and-intense and late-and-moderate group and the early-and-intense group had more males compared to the late-and-moderate group and the stimulant-naïve group).

Post-hoc pairwise group comparisons showed trend significant group differences. Inspection of the means of risk perception showed that the early-and-intense group reported the highest risk perception (indicating higher susceptibility to perceive a situation as risky), followed by the stimulant-naïve (early-and-intense vs stimulant-naïve: β = 0.32, small group difference), and then the late-and-moderate groups (early-and-intense vs late-and-moderate: β = -0.72, moderate group difference; stimulant-naïve vs late-and-moderate: β = 1.03; large group difference). For letter fluency, the early-and-intense scored the highest (indicating better cognitive flexibility), followed by the late-and-moderate group (early-and-intense vs late-and-moderate: β = 0.56, moderate group difference), and then the stimulant-naïve group (early-and-intense vs stimulant-naïve: β = 0.25; late-and-moderate vs stimulant-naïve: β = -0.31; small group differences). For sleep quality, the stimulant-naïve group reported the worst sleep quality, followed by the late-and-moderate (stimulant-naïve vs late-and-moderate: β = 0.47, small group difference), and then the early-and-intense groups (early-and-intense vs stimulant-naïve: β = -0.03, small group difference; early-and-intense vs late-and-moderate: β = -0.50, moderate group difference;). As the groups differed on age and sex, analyses were repeated with age and sex included as covariates in a sensitivity analysis (Table S6.3), which did not change the results.

Table 6.1. *Follow-up neuroimage wave IV measures for stimulant treatment trajectories: early-and-intense, late-and-moderate, and stimulant-naïve*

	Early-and-intense (n = 46)	Late-and-moderate (n = 63)	Stimulant-naïve (n = 34)	Wald χ^2 of group effect	Significant group differences
Demographics, *n* (%)					
Age, years	27.76 (2.76)	27.56 (3.79)	30.59 (4.01)	Wald χ^2 = 15.71**	SN > EI, LM
Male, *n* (%)	39 (85%)	35 (56%)	19 (56%)	Wald χ^2 = 10.88*	EI > LM, SN
Family status					
Single	17 (37%)	18 (29%)	10 (29%)	Wald χ^2 = 0.86	
Cohabitation	21 (46%)	23 (37%)	11 (32%)	Wald χ^2 = 1.49	
Married	9 (20%)	10 (16%)	6 (18%)	Wald χ^2 = 0.30	
Children at home[a]	3 (7%)	4 (6%)	5 (15%)	N/A[a]	
Co-parenting[a]	0 (0%)	1 (2%)	0 (0%)	N/A[a,c]	
Living at home with parents/caregivers	5 (11%)	9 (14%)	4 (12%)	Wald χ^2 = 0.31	
Children (yes/no)	8 (17%)	11 (17%)	9 (26%)	Wald χ^2 = 1.34	
Number of children, *M* (*SD*)[a]	1.75 (0.71)	1.27 (0.47)	2.22 (0.97)	N/A[a]	
Children with an ADHD diagnosis[a]	1 (2%)	0 (0%)	2 (6%)	N/A[a,c]	
Children with any diagnosis other than ADHD[a]	0 (0%)	3 (5%)	5 (15%)	N/A[a,c]	
Psychiatric status, *n* (%)					
DSM-5 ADHD	20 (43%)	27 (43%)	13 (38%)	Wald χ^2 = 0.65	
DSM-5 MDD	5 (11%)	11 (17%)	6 (18%)	Wald χ^2 = 1.26	
DSM-5 any anxiety disorder	3 (7%)	5 (8%)	4 (12%)	Wald χ^2 = 1.02	
DSM-5 ASPD	0 (0%)	3 (5%)	1 (3%)	Wald χ^2 = 0.55	
DSM-5 any SUD	2 (4%)	8 (13%)	3 (9%)	Wald χ^2 = 1.04	
Behavioral and emotional problems, *M* (*SD*)					

	Early-and-intense (*n* = 46)	Late-and-moderate (*n* = 63)	Stimulant-naïve (*n* = 34)	Wald χ^2 of group effect	Significant group differences
ADHD index, Self-reported (CAARS)	57.07 (10.05)	61.37 (10.47)	61.00 (10.04)	Wald χ^2 = 5.92	
ADHD index, Other-reported (CAARS)	50.61 (9.46)	54.48 (12.47)	50.93 (12.11)	Wald χ^2 = 4.10	
Externalizing problems (ASEBA-ASR)	12.91 (9.09)	11.73 (7.27)	14.32 (8.27)	Wald χ^2 = 2.47	
Internalizing problems (ASEBA-ASR)	13.50 (10.54)	14.97 (12.47)	18.00 (12.72)	Wald χ^2 = 3.20	
Autistic traits (ASBQ)	22.76 (11.13)	27.09 (14.48)	24.84 (15.55)	Wald χ^2 = 3.29	
Mood dysregulation (ARI)	1.42 (1.33)	2.07 (2.51)	2.76 (2.75)	Wald χ^2 = 9.66	
Callous-unemotional traits (ICU)	17.59 (5.88)	19.02 (6.58)	21.09 (6.67)	Wald χ^2 = 6.94	
Rule-breaking behavior (STAB)	1.80 (2.74)	1.17 (2.19)	1.67 (3.05)	Wald χ^2 = 2.14	
Physical aggression (STAB)	6.70 (5.44)	6.32 (5.32)	6.48 (5.26)	Wald χ^2 = 0.39	
Social aggression (STAB)	7.93 (5.19)	6.98 (5.19)	5.82 (3.67)	Wald χ^2 = 3.73	
Tobacco use (ASSIST-Lite)	5.00 (7.22)	3.40 (6.13)	6.09 (7.69)	Wald χ^2 = 2.56	
Alcohol use (ASSIST-Lite)	4.93 (3.73)	4.54 (3.80)	4.38 (3.30)	Wald χ^2 = 0.85	
Drug use (ASSIST-Lite)	3.33 (9.12)	2.42 (5.99)	2.38 (4.61)	Wald χ^2 = 0.43	
Gaming addiction symptoms (GAS)	2.07 (3.31)	1.47 (3.19)	1.97 (3.03)	Wald χ^2 = 0.98	
Academic and professional functioning					
Education Verhage, *M* (*SD*)	5.20 (1.19)	5.52 (0.95)	5.21 (1.27)	Wald χ^2 = 4.60	
Repeated grade (primary and secondary education), *n* (%)	27 (59%)	36 (57%)	18 (53%)	Wald χ^2 = 0.32	
Employed, *n* (%)	42 (91%)	54 (86%)	30 (88%)	Wald χ^2 = 0.79	
Number of times switched jobs, *M* (*SD*)	2.46 (2.85)	2.27 (2.29)	3.41 (3.52)	Wald χ^2 = 2.84	
Adaptive functioning, *M* (*SD*)					
Perceived stress (PSS)	11.81 (5.20)	13.18 (5.93)	13.50 (6.85)	Wald χ^2 = 3.17	
Risk-taking (DOSPERT)	19.01 (4.54)	19.05 (5.23)	19.13 (4.81)	Wald χ^2 = 0.10	

	Early-and-intense (n = 46)	Late-and-moderate (n = 63)	Stimulant-naïve (n = 34)	Wald χ^2 of group effect	Significant group differences
Risk perception (DOSPERT)	30.45 (3.21)	29.16 (5.47)	29.73 (5.06)	Wald χ^2 = 37.41***	Trend effect: EI > SN > LM
Social functioning (SF36)	62.23 (21.82)	62.92 (20.29)	55.98 (19.54)	Wald χ^2 = 3.75	
Emotional wellbeing (SF36)	68.61 (16.39)	67.53 (18.84)	68.97 (19.98)	Wald χ^2 = 0.20	
Quality of life – Outlook	63.82 (17.60)	60.83 (21.81)	57.14 (22.14)	Wald χ^2 = 1.93	
Quality of life – Relationships	68.59 (19.65)	64.29 (24.28)	64.56 (21.44)	Wald χ^2 = 0.47	
Significant life events (after age 16) (LTE)	2.87 (2.69)	2.77 (2.85)	2.42 (2.28)	Wald χ^2 = 2.07	
Creativity (CAQ)	5.80 (10.84)	4.46 (7.76)	2.16 (3.45)	Wald χ^2 = 6.73	
Neurocognitive functioning, *M* (*SD*)					
Estimated TIQ (WAIS)	90.75 (13.97)	89.51 (12.14)	90.06 (14.29)	Wald χ^2 = 0.60	
Short-term memory – digits (WAIS)	8.95 (1.88)	8.57 (2.00)	9.03 (2.07)	Wald χ^2 = 0.41	
Short-term memory – words (15WT)	45.93 (9.77)	46.62 (9.46)	47.15 (12.32)	Wald χ^2 = 1.63	
Long-term memory (15WT)	9.58 (3.23)	9.87 (3.11)	10.00 (3.38)	Wald χ^2 = 0.94	
Working memory (WAIS)	18.19 (3.35)	18.11 (3.95)	18.18 (4.73)	Wald χ^2 = 7.45	
Letter fluency score (COWAT)	33.19 (10.98)	30.47 (7.93)	29.32 (8.10)	Wald χ^2 = 15.46**	Trend effect: EI > LM > SN
Physical health, *M* (*SD*)					
BMI	26.43 (3.77)	26.05 (4.71)	25.26 (5.40)	Wald χ^2 = 1.36	EI > LM
MET minutes per week (IPAQ)	5098.90 (4812.65)	5064.02 (5784.99)	4082.60 (4253.35)	Wald χ^2 = 0.81	
General health perceptions (SF36)	64.24 (17.73)	70.25 (20.96)	62.88 (19.16)	Wald χ^2 = 3.59	
Physical functioning (SF36)	83.59 (12.50)	85.85 (7.61)	84.39 (10.29)	Wald χ^2 = 0.94	
Pain (SF36)	84.08 (20.46)	86.99 (19.33)	88.64 (13.99)	Wald χ^2 = 1.19	
Energy/vitality (SF36)	61.41 (18.85)	58.64 (21.31)	55.45 (20.86)	Wald χ^2 = 2.26	
Role limitations due to physical health (SF36)	100 (0)	100 (0)	100 (0)	N/A[d]	

	Early-and-intense (n = 46)	Late-and-moderate (n = 63)	Stimulant-naïve (n = 34)	Wald χ^2 of group effect	Significant group differences
Role limitations due to emotional problems (SF36)	100 (0)	100 (0)	100 (0)	N/A[d]	
Sleep quality (PSQI)	5.26 (3.71)	5.71 (3.67)	5.94 (3.75)	Wald χ^2 = 23.08***	Trend effect: SN > LM > EI
Healthy diet	6.07 (1.68)	6.33 (1.65)	6.03 (1.70)	Wald χ^2 = 0.81	
Diet adherence	5.80 (2.07)	5.82 (2.24)	5.55 (2.32)	Wald χ^2 = 0.38	
Healthcare service use, *M* (*SD*)					
Number of visits to social welfare and/or occupational health and safety service institutes last year	0.15 (0.67)	0.20 (0.90)	0.44 (1.08)	Wald χ^2 = 1.68	
Number of visits to mental healthcare institutes last year	7.00 (44.19)	3.70 (7.98)	6.76 (15.11)	Wald χ^2 = 2.04	
Number of visits to physical healthcare institutes last year	6.17 (9.08)	15.75 (49.10)	6.03 (5.95)	Wald χ^2 = 2.19	
ADHD medication use[b], *n* (%)	13 (28%)	12 (19%)	3 (9%)	Wald χ^2 = 3.51	
General medication use[b]	1.85 (2.54)	1.83 (2.16)	1.33 (1.82)	Wald χ^2 = 1.76	

Note. Non-significant group comparisons are not reported.
ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self-report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, CAARS = Conners' adult ADHD rating scales, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, DSM-5 = diagnostic and statistical manual of mental disorders fifth edition, EI = early-and-intense, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LM = late-and-moderate, LTE = long-term difficulties questionnaire, MDD = major depressive disorder, MET = metabolic equivalent, PSS = perceived stress scale, PSQI = Pittsburgh sleep quality index, SF36 = short form health survey, SN = stimulant-naïve, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.

[a] Assessed only for participants with a child/children (n = 28), and due to insufficient group size these analyses were not run.
[b] Assessed only for participants with available pharmacy data at wave IV (n = 120).
[c] Due to insufficient variation, some analyses were impossible to run and are represented by N/A in model comparison columns.
FDR-corrected significance per domain, $^{*}p < .05$ $^{**}p < .01$ $^{***}p < .001$.

Discussion

This study aimed to explore the very long-term (> 10 years) outcomes of childhood stimulant treatment trajectories in adults with a childhood ADHD diagnosis, using a prospective follow-up cohort. Three different stimulant treatment trajectory groups were identified: early-and-intense, late-and-moderate, and stimulant-naïve. Our results showed that the three stimulant treatment trajectory groups did not differ on most of the outcomes measured 12 years later in the domains of psychiatric status, behavioral and emotional problems, academic and professional functioning, adaptive functioning, neurocognitive functioning, physical health, and healthcare service use. However, the stimulant treatment trajectory groups differed on three measures in the adaptive, neurocognitive, and physical domains. Specifically, early-and-intense stimulant medication use was found to be related to the most favorable mean scores (trend effects) on risk perception, cognitive flexibility, and sleep quality, as compared to the stimulant naïve and late-and-moderate group with small-to-moderate differences. Both groups who used stimulant medication in childhood (i.e., early-and-intense and late-and-moderate) had more favorable mean scores on cognitive flexibility and sleep quality compared to the group who did not use stimulant medication in childhood (trend effects) with small-to-large differences. Results did not change after controlling for age and sex.

The finding that stimulant use in childhood, assessed by the stimulant treatment trajectories, was not associated with most very long-term (> 10 years) outcomes, is in agreement with the results of a review study showing no beneficial effects of childhood stimulant use on adult outcomes [220] and with the large Multimodal Treatment Study of ADHD (MTA) showing no lasting long-term effects of medication use on ADHD symptoms [229]. However, we did not replicate the previously reported positive outcomes of childhood stimulant use on mood, depression, anxiety, and SUD [41, 42]. Although some studies suggest stimulant treatment might decrease the risk of adult SUD, the majority of these studies had a follow-up period of ≤3 years, whereas our study had a follow-up period of 12 years. Also, our finding is in agreement with a meta-analysis including 4 longitudinal studies on childhood predictors on adult ADHD functioning where childhood stimulant treatment did not predict adult SUD [63]. Furthermore, the majority of the studies showing beneficial effects on low mood or depression and anxiety had a relatively short follow-up period [42]. The single study with a longer follow-up period (> 10 years) only compared outcomes of methylphenidate (stimulant use) with atomoxetine (non-stimulant use), thereby addressing a different pharmacological comparison than that of three stimulant treatment trajectories in the current study [230]. Notably, other potential long-term outcomes of childhood medication use that were reported in large registry studies such as a lower risk of crime, self-harm, unintentional injury, traffic crashes, and all-cause mortality

were not included in the current study [231, 232]. Still, in registry studies, ADHD diagnoses were based on insurance claims, in contrast to a standardized diagnostic assessment in our study to confirm the diagnosis of ADHD and comorbid conditions, and it remains unclear if the identified association actually is a long-term outcome, as the mean follow-up period from medication use to outcome is not reported.

However, main group differences were found for risk perception, cognitive flexibility, and sleep quality, with trend effects suggesting early and intense stimulant medication use having the most favorable outcomes. These findings contrast with previous studies, with shorter follow-up periods, that found no positive lasting effects of stimulant treatment on cognition [223, 233], and ambiguous effects on sleep [42]. A potential explanation may be that stimulant treatment could potentially have lasting effects on the brain, that might translate into beneficial effects on cognitive outcomes [234-236]. However, this explanation is not confirmed by the lack of group differences in other cognitive, adaptive, or health-related outcomes, and therefore might be due to specific brain changes associated with specific outcomes. Similarly, stimulant treatment is suggested to have lasting effects on the dopamine system, which might have a positive effect on sleep [237], but again this is not confirmed by our findings in other domains. The findings on risk perception, cognitive flexibility, and sleep quality should be further investigated, and group differences should be tested in larger studies. Overall, results so far suggest that stimulant treatment might have short-term benefits, possibly only found with continued use, with these effects declining over time and with discontinuation of treatment. Importantly, while stimulant medication does not seem to have lasting effects, positive short-term effects are evident [37].

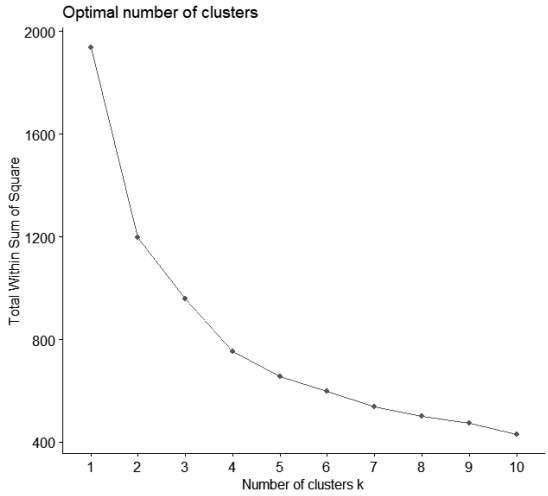
This is the first longitudinal study investigating the joint effects of several characteristics of childhood stimulant use in both males and females across a broad range of very long-term (> 10 years) outcomes. Our stimulant medication groups did not differ on any behavioral problems in adolescence, suggesting that our outcomes were not influenced by preexisting behavioral differences. There were more males in the early-and-intense stimulant group compared to the other two groups. This is unsurprising, as boys with ADHD are more likely to receive stimulant treatment compared to girls with ADHD [238], and girls discontinue their stimulant treatment earlier than boys [239]. Nonetheless, our results did not change after adjusting the analysis for sex (and age). Also, our naturalistic design is a suitable approach for observing potential long-term outcomes of stimulant treatment use, but to study causal long-term effects of stimulant medication use randomized control trials are needed.

Despite the strengths, the current study had some limitations. First, the analysis was potentially underpowered to detect small and moderate group differences due

to the group size of the stimulant-naïve group, which may have resulted in nonsignificant post-hoc pairwise group comparisons [240]. As the stimulant-naïve group is an important comparison group for outcomes of stimulant treatment in ADHD, future studies should aim to include more stimulant-naïve participants, potentially through retrospective cohort studies. Second, group differences might have been confounded by medication use after wave II, with outcomes being confounded by later medication use or reflecting current use instead of long-term outcomes. However, groups did not differ on number of participants on ADHD medication at follow-up (Table 6.1), reducing the likelihood of a confounding effect. Third, the stimulant treatment trajectory group detection with K-means clustering was not externally validated, potentially limiting generalizability. Also, cluster quality was modest with a small distance between clusters, suggesting that some participants in the two clusters might have been close in stimulant medication use, thereby obscuring differences between the groups. In earlier studies on the NeuroIMAGE cohort [44, 226, 241], with a slightly different subsample of children with ADHD, community detection, rather than K-means clustering, was used to construct groups. However, both methods are suitable for group detection, and the K-means clusters showed moderately distinct and internally coherent clusters, with good cluster interpretability. Finally, stimulant treatment data was derived from pharmacy records, which did not inform on medication adherence. Likely, adherence was high, as earlier research in the cohort showed that pharmacy records were congruent with self-reported stimulant use [226].

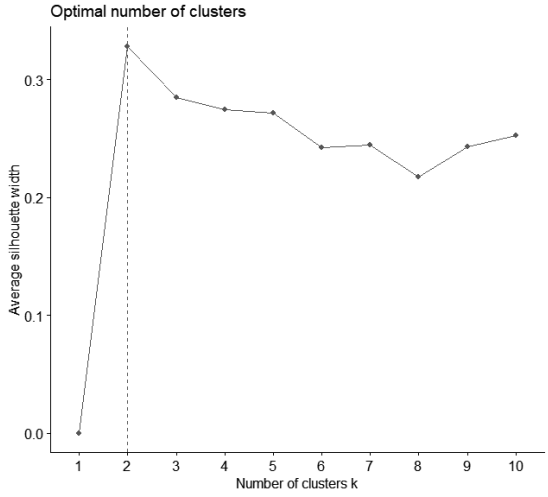
To conclude, the current study adds to earlier findings regarding the possible lack of risk and questionable long-term benefits of stimulant medication use in childhood when studying a cohort of adults diagnosed with ADHD in childhood. We did not see any group differences on most of our domains of adult outcomes, with a few exceptions as early-and-intense stimulant medication group seemed to be associated with some favorable long-term outcomes, including a better risk perception, cognitive flexibility, and sleep quality. Taken together, despite previously identified potential positive short-term effects, there may be no lasting effects of stimulants on many long-term functional outcomes.

Figure S6.1. *Elbow plot for identification of number of stimulant treatment clusters using K-means clustering*



Note. The elbow plot identified k = 2 as optimal number of stimulant treatment clusters using variables age at initiation, stop age, total dose, duration of use, maximum daily dose, and variability of stimulant use.

Figure S6.2. *Plot of the silhouette score for identification of number of stimulant treatment clusters using K-means*



Note. The silhouette score identified k = 2 as optimal number of clusters using variables age at initiation, stop age, total dose, duration of use, maximum daily dose, and variability of stimulant use.

Table S6.1. *Baseline (wave I) characteristics of retained childhood ADHD group compared to the initial childhood ADHD sample*

M (*SD*)	Retained childhood ADHD group (*n* = 123)	Initial childhood ADHD group (*n* = 510)	Wald χ^2 of group effect
Age, years (*SD*)	10.87 (2.77)	10.95 (2.80)	Wald χ^2 = 0.08
Male, *n* (%)	80 (78%)	400 (78%)	Wald χ^2 = 0.06
Parental education level	5.26 (0.71)	5.19 (0.74)	Wald χ^2 = 0.61
ADHD symptoms	77.45 (8.49)	75.29 (9.80)	Wald χ^2 = 5.34*
ODD symptoms	65.98 (11.86)	66.09 (12.37)	Wald χ^2 = 0.02
Anxious/shy behavior	56.38 (13.14)	58.01 (13.74)	Wald χ^2 = 1.27

Note. The retained childhood ADHD group includes participants for which an ADHD diagnosis was confirmed at wave I, with available stimulant treatment medication data at wave II, and who were successfully followed up at wave IV. Despite significant group differences in ADHD symptoms between the initial and retained ADHD sample, ADHD symptoms were not controlled for in a sensitivity analysis as ADHD symptoms did not differ between the three stimulant treatment trajectories (see Table S6.2).
ADHD = attention-deficit/hyperactivity disorder, ODD = oppositional defiant disorder.
*p<.05.

Table S6.2. *NeuroIMAGE wave II measures for stimulant treatment trajectories: early-and-intense, late-and-moderate, and stimulant-naïve*

	Early-and-intense (n = 46)	Late-and-moderate (n = 63)	Stimulant-naïve (n = 34)	Wald χ^2 of group effect	Significant group differences
Age, years (*SD*)	15.78 (2.71)	15.81 (3.45)	18.32 (3.94)	Wald χ^2 = 11.46**	SN > EI, LM
Male, *n* (%)	39 (85%)	35 (56%)	19 (56%)	Wald χ^2 = 10.46**	EI > LM, SN
Parental education level, *M* (*SD*)	5.34 (0.51)	5.11 (0.92)	5.15 (0.81)	Wald χ^2 = 2.30	
ADHD symptoms, *M* (*SD*)	55.21 (14.12)	52.44 (13.57)	54.79 (16.48)	Wald χ^2 = 1.06	
ODD symptoms, *M* (*SD*)	51.36 (10.30)	49.16 (11.77)	53.39 (14.93)	Wald χ^2 = 2.34	
Anxious/shy behavior, *M* (*SD*)	53.36 (11.25)	49.77 (9.47)	49.88 (11.46)	Wald χ^2 = 2.87	

Note. Non-significant group comparisons are not reported. Due to significant group differences, age and sex were added as covariates in a sensitivity analysis.
ADHD = attention-deficit/hyperactivity disorder, EI = early-and-intense, ODD = oppositional defiant disorder, LM = late-and-moderate, SN = stimulant-naïve.
*$p < .05$ **$p < .01$.

Table S6.3. *Results from the sensitivity analysis comparing stimulant treatment trajectories: early-and-intense, late-and-moderate, and stimulant-naïve, controlling for age and sex*

	Wald χ^2 of group effect	Significant group differences
Demographics		
Family status		
Single	Wald χ^2 = 0.86	
Cohabitation	Wald χ^2 = 1.49	
Married	Wald χ^2 = 0.30	
Children at home[a]	N/A[a,c]	
Co-parenting[a]	N/A[a,c]	
Living at home with parents/caregivers	Wald χ^2 = 0.31	
Children (yes/no)	Wald χ^2 = 1.34	
Number of children[a]	N/A[b]	
Children with an ADHD diagnosis[a]	N/A[b]	
Children with any diagnosis other than ADHD[a]	N/A[b]	
Psychiatric status		
DSM-5 ADHD	Wald χ^2 = 0.65	
DSM-5 MDD	Wald χ^2 = 1.26	
DSM-5 any anxiety disorder	Wald χ^2 = 1.02	
DSM-5 ASPD	Wald χ^2 = 0.55	
DSM-5 any SUD	Wald χ^2 = 1.04	
Behavioral and emotional problems		
ADHD index, Self-reported (CAARS)	Wald χ^2 = 5.92	
ADHD index, Other-reported (CAARS)	Wald χ^2 = 4.10	
Externalizing problems (ASEBA-ASR)	Wald χ^2 = 2.47	
Internalizing problems (ASEBA-ASR)	Wald χ^2 = 3.20	
Autistic traits (ASBQ)	Wald χ^2 = 3.29	
Mood dysregulation (ARI)	Wald χ^2 = 9.66	
Callous-unemotional traits (ICU)	Wald χ^2 = 6.94	
Rule-breaking behavior (STAB)	Wald χ^2 = 2.14	
Physical aggression (STAB)	Wald χ^2 = 0.39	
Social aggression (STAB)	Wald χ^2 = 3.73	
Tobacco use (ASSIST-Lite)	Wald χ^2 = 2.56	
Alcohol use (ASSIST-Lite)	Wald χ^2 = 0.85	
Drug use (ASSIST-Lite)	Wald χ^2 = 0.43	
Gaming addiction symptoms (GAS)	Wald χ^2 = 0.98	
Academic and professional functioning		
Education Verhage	Wald χ^2 = 4.60	
Repeated grade (primary and secondary education)	Wald χ^2 = 0.32	
Employed	Wald χ^2 = 0.79	
Number of times switched jobs	Wald χ^2 = 2.84	
Adaptive functioning		
Perceived stress (PSS)	Wald χ^2 = 3.17	

	Wald χ^2 of group effect	Significant group differences
Risk-taking (DOSPERT)	Wald χ^2 = 0.10	
Risk perception (DOSPERT)	Wald χ^2 = 37.41***	Trend: EI > SN > LM
Social functioning (SF36)	Wald χ^2 = 3.75	
Emotional wellbeing (SF36)	Wald χ^2 = 0.20	
Quality of life – Outlook	Wald χ^2 = 1.93	
Quality of life – Relationships	Wald χ^2 = 0.47	
Significant life events (after age 16) (LTE)	Wald χ^2 = 2.07	
Creativity (CAQ)	Wald χ^2 = 6.73	
Neurocognitive functioning		
Estimated TIQ (WAIS)	Wald χ^2 = 0.60	
Short-term memory – digits (WAIS)	Wald χ^2 = 0.41	
Short-term memory – words (15WT)	Wald χ^2 = 1.63	
Long-term memory (15WT)	Wald χ^2 = 0.94	
Working memory (WAIS)	Wald χ^2 = 7.45	
Letter fluency score (COWAT)	Wald χ^2 = 15.46**	Trend: EI > LM > SN
Physical health		
BMI	Wald χ^2 = 1.36	
MET minutes per week (IPAQ)	Wald χ^2 = 0.81	
General health perceptions (SF36)	Wald χ^2 = 3.59	
Physical functioning (SF36)	Wald χ^2 = 0.94	
Pain (SF36)	Wald χ^2 = 1.19	
Energy/vitality (SF36)	Wald χ^2 = 2.26	
Role limitations due to physical health (SF36)	N/A[d]	
Role limitations due to emotional problems (SF36)	N/A[d]	
Sleep quality (PSQI)	Wald χ^2 = 23.08***	Trend: SN > LM > EI
Healthy diet	Wald χ^2 = 0.81	
Diet adherence	Wald χ^2 = 0.38	
Healthcare service use		
Number of visits to social welfare and/or occupational health and safety service institutes last year	Wald χ^2 = 1.68	
Number of visits to mental healthcare institutes last year	Wald χ^2 = 2.04	
Number of visits to physical healthcare institutes last year	Wald χ^2 = 2.19	
ADHD medication use[b]	Wald χ^2 = 3.51	
General medication use[b]	Wald χ^2 = 1.76	

Note. Non-significant group comparisons are not reported.
ADHD = attention-deficit/hyperactivity disorder, ARI = affective reactivity index, ASBQ = adult social behavior questionnaire, ASEBA-ASR = Achenbach system of empirically based assessment adult self-report, ASPD = antisocial personality disorder, ASSIST-Lite = alcohol smoking and substance involvement screening test – lite, BMI = body mass index, CAARS = Conners' adult ADHD rating scales, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, DOSPERT = domain specific risk-taking questionnaire, DSM-5 = diagnostic and statistical manual of mental disorders fifth edition, EI = early-and-

intense, GAS = game addiction scale, ICU = inventory of callous and unemotional traits, IPAQ = international physical activity questionnaire, LM = late-and-moderate, LTE = long-term difficulties questionnaire, MDD = major depressive disorder, MET = metabolic equivalent, PSS = perceived stress scale, PSQI = Pittsburgh sleep quality index, SF36 = short form health survey, SN = stimulant-naïve, STAB = subtypes of antisocial behavior questionnaire, SUD = substance use disorder, TIQ = total intelligence quotient, WAIS-IV = Wechsler adult intelligence scale, 15WT = Dutch verbal learning test.
[a] Assessed only for participants with a child/children (n = 28), and due to insufficient group size these analyses were not run.
[b] Assessed only for participants with available pharmacy data at wave IV (n = 120).
[c] Due to insufficient variation, some analyses were impossible to run and are represented by N/A in model comparison columns.
FDR-corrected significance per domain, $^{**}p < .01$, $^{***}p < .001$.

6

CHAPTER 7

From childhood to adulthood: an attempt to model longterm outcomes of ADHD using machine learning.

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Abstract

Background. Childhood-onset attention-deficit/hyperactivity disorder (ADHD) persists in 28% to 58% of individuals, and is associated with adverse long-term outcomes, like additional psychiatric diagnoses and lower educational attainment. Knowing early life predictors for adverse long-term outcomes might help develop preventive measures, but too few have been identified using conventional statistical models. The current study investigated the potential of machine learning in identifying predictors for ADHD persistence and long-term functioning of adults with childhood-onset ADHD.

Method. A total of 133 adults (M_{age} = 29.53, SD_{age} = 2.83, 75% males) from an 18-year prospective cohort study were assessed on ADHD persistence and long-term functioning. Machine learning models were developed using cross-validation, with and without additional synthetic data, and compared to a conventional logistic regression model. With SHapley Additive exPlanations (SHAP) we explored predictor importance. Childhood predictors encompassed ADHD symptoms and treatment, other psychopathology, cognition, somatic characteristics, ADHD polygenic risk score, and parental demographics and psychopathology.

Results. Accuracy of all models for ADHD persistence and functioning was low. SHAP suggested childhood anxiety symptoms as the most influential predictor for both outcomes. No machine learning model outperformed logistic regression for ADHD persistence (AUC's$_{\text{machine learning}}$ = .50–.56; AUC$_{\text{logistic regression}}$ = .56) or long-term functioning (AUC's$_{\text{machine learning}}$ = .47–.59; AUC$_{\text{logistic regression}}$ = .59). Adding synthetic data did not improve the models.

Conclusions. Findings highlight the complexity of predicting long-term outcomes of ADHD. While conventional models have performed best so far, model improvement is crucial before models can inform clinical practice, e.g., by increasing sample size and investigating additional predictors.

Key words: ADHD, machine learning, predicting, long-term outcomes

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is often diagnosed in childhood and persists in 28% to 58% of all cases into adulthood [3, 28]. Children with ADHD are not only at increased risk of persistent ADHD but are also prone to impaired functioning across several domains in adulthood [3]. For example, adverse long-term outcomes in adulthood include the development of other psychiatric disorders, such as substance use disorder (SUD), major depressive disorder (MDD), and anxiety disorders, with associated healthcare costs [3, 242]. Additionally, childhood ADHD is related to impaired academic and professional functioning, social functioning, physical health problems, and lower quality of life in adulthood [4, 16-18, 24, 243]. However, the developmental trajectory of ADHD from childhood into adulthood is highly heterogenous, with more than 60% experiencing negative outcomes, whereas others do not [3, 4]. Importantly, some adults diagnosed with ADHD as a child experience recovery from ADHD [11]. To investigate potential causes of outcome heterogeneity and work towards prevention of unfavorable outcomes of ADHD, early identification of predictors for unfavorable outcomes is desirable [213].

So far, few robust predictors of long-term outcomes of ADHD have been identified, specifically for ADHD persistence, SUD, and MDD [63]. Narrative reviews have suggested some predictors of ADHD persistence, including ADHD combined type, hyperactive/impulsive symptoms, comorbid problems (e.g., anxiety disorders), and familial characteristics (e.g., lower socioeconomic status) [21, 63]. Even fewer predictors have been identified through meta-analysis. Two meta-analyses showed that ADHD persistence was predicted by a history of stimulant treatment, comorbid conduct disorder (CD), comorbid MDD, and a lower total intelligence quotient (TIQ), though the latter only shown by low quality studies [33, 63]. In turn, ADHD- persistence predicted SUD and MDD in adults with ADHD diagnosed in childhood [63]. Additional predictors have incidentally been suggested for other long-term outcomes of ADHD. For example, most important predictors for a comorbid SUD diagnosis were an adolescent SUD diagnosis, and violent and non-violent crime convictions [54]. Adolescent antisocial behaviors were related to poor educational goals, whereas higher educational goals, as well as good occupational and social functioning in adolescence, predicted more favorable adult functional outcomes [244]. Robust predictors for other long-term outcomes of ADHD, such as functional impairments, remain unknown.

Some predictors have likely remained undetected thus far, as current prediction models of long-term outcomes of ADHD almost exclusively relied on conventional statistical models and often studied predictors in isolation. These models do not consider non-linear relationships and complex interactions that may likely exist between predictors and outcomes. An example of such a complex relationship is the interaction between specific genes and environmental factors on the risk of

comorbid disruptive disorders in ADHD [45]. Machine learning models are promising approaches to predict long-term outcomes of ADHD, because they are suitable for modelling the expected complex interplay between predictors and may therefore more accurately predict outcomes [46].

Machine learning models successfully predicted outcomes in several healthcare fields, including psychiatry, although they have not yet been implemented in clinical practice [47-49]. For example, machine learning approaches predicted suicide behaviors more accurately than conventional statistical models with a predictive accuracy of 80% or higher, although not externally validated [47]. In ADHD research, promising prediction models have been developed for diagnosing ADHD [51], decreasing time needed for screening [52], and for predicting methylphenidate treatment response [53]. Most prediction models in ADHD to date have not included genetic predictors next to clinical or neuroimaging predictors [51], despite their potential predictive value [245]. For ADHD, only few prognostic risk estimation models, and even fewer models investigating early life predictors of adult outcomes, are available. All of the few available models had insufficient model performance (low to moderate accuracy). These prognostic risk models have attempted to predict outcomes, including an adulthood SUD at age 18 or 19 years using predictors available at age 17 [54], adulthood methylphenidate related psychiatric symptoms using childhood and adolescent predictors [55], stability of a childhood ADHD diagnosis 2 years later [246], and adolescent symptom change 4 years later [247]. As model performance and scope remain insufficient, more studies investigating early life predictors of adult outcomes of ADHD are necessary, ideally including both clinical and genetic predictors. Furthermore, given the availability of many different machine learning approaches, it is not immediately clear which model is most suitable for a specific research question, and comparison of several established algorithms is desirable.

The current study explored the added value of using advanced machine learning techniques compared to conventional logistic regression models in predicting adult outcomes of children with ADHD, including ADHD persistence and long-term functioning. Children with ADHD were followed up for 18 years in a prospective Dutch cohort of ADHD families. A range of predictors was assessed in childhood, including ADHD symptoms and treatment, other psychopathology, somatic characteristics, cognition, ADHD polygenic risk score (PRS), and parental demographics and psychopathology. Long-term outcomes were assessed in adulthood, including measures in the domains of psychiatric status, behavioral and emotional functioning, academic and professional functioning, adaptive functioning, neurocognitive functioning, physical health, and healthcare service use.

Methods

Sample

In total, 133 participants with childhood-diagnosed ADHD were recruited from a longitudinal cohort study initiated as part of the Dutch branch of the International Multicenter ADHD Genetics (IMAGE) study [58], of which the current study is an 18-year follow-up (as described in van der Plas et al. [127]). Inclusion criteria at baseline were: aged 5-19 years, Caucasian descent, IQ ≥ 70, and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, or known genetic disorders [58]. Recruited participants were children with ADHD combined type, and (where relevant) their siblings with ADHD combined type. In the current follow-up (2021-2024), all participants who had previously participated were invited [58, 59]. The current study thus only included adults with a childhood ADHD diagnosis at baseline.

For an attrition analysis testing the representativeness of the retained childhood ADHD group compared to the initial baseline childhood ADHD group, see van der Plas et al. [127]. Briefly, the retained childhood ADHD group did not differ from the initial childhood ADHD group at baseline in terms of sex, age, estimated TIQ, parental education level, oppositional defiant disorder symptoms, anxious/shy symptoms, and behavioral and emotional difficulties, except for ADHD symptom severity, where the retained childhood ADHD group showed higher ADHD symptom severity at baseline than the initial childhood ADHD group (Wald χ^2 = 4.72, p = .030; initial M = 75.29, SD = 9.80; retained M = 77.25, SD = 9.26, Table S7.1).

Childhood predictors

Twenty-one predictors were selected from the baseline assessment. Predictor selection was based on data availability (missing ≤ 20%) and known associations between the predictor and included outcome domains based on previous literature. The childhood predictors included measures in the following domains: 1) ADHD symptoms and treatment, 2) other psychopathology, 3) somatic characteristics, 4) cognition, 5) ADHD PRS (for details on how the PRS was calculated, see Supplementary Method 1), and 6) parental demographics and psychopathology. See Table S7.2 for a description of all instruments and variables used. For an overview of all instruments assessed at baseline see the Open Science Framework (OSF) https://doi.org/10.17605/OSF.IO/5Y29Q.

Procedure

Baseline (study entry / predictors)

The procedure at baseline (Dutch part of the IMAGE consortium) followed the standard procedures of the IMAGE study, as described elsewhere [58, 248]. In

short, assessments included (screening) questionnaires, a diagnostic interview, and neurocognitive testing. The Parental Account of Children's Symptoms (PACS) [249] was used as diagnostic interview. It is a semi-structured, standardized, investigator-based interview, assessing main DSM-4 diagnoses. Testing was done at the Vrije Universiteit Amsterdam or at the Radboud University Nijmegen Medical Center. The study was approved by the local medical ethics committees. All data was pseudo anonymized, and families were financially compensated for participation.

Follow-up wave (outcomes)

Detailed description of the procedures of the follow-up can be found in van der Plas et al [127]. Briefly, assessments comprised self-reported online questionnaires, other-reported online questionnaires, and two video calls, see Table S2.1. During the first video call the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 Disorders (SCID-5) was administered by certified researchers. The SCID-5 was used to assess the DSM-5 diagnosis of ADHD, and also of MDD, antisocial personality disorder (ASPD), anxiety, or SUD in participants with a positive screening. During the second video call, assessment of the cognitive tests took place, which was done by trained researchers according to a standardized protocol. If participants were unwilling to participate in the video calls, they were allowed to only complete the online questionnaires to increase participant retention. All data was pseudo-anonymized, and participants received 25 euros after completion of the questionnaires or the questionnaires and video calls. The study was approved by the local medical ethics committee of the Amsterdam Medical Center (AUMC; NL77520.029.21).

Adult outcome at follow-up: ADHD persistence

Persistence of ADHD was identified using the ADHD module of the Dutch version of the SCID-5 [99, 100] and coded either as persistent ADHD or remitted ADHD.

Data preprocessing

Imputation

Multivariate imputation by chained equations (MICE) was used to impute both missing predictor and outcome data together with no more than 20% missing, to maintain reliable estimates based on robust estimation of MICE [250]. Percentage of missingness across all predictors varied between 0–20%, and across all outcomes between 0-10%. PRS scores (9% missing) were also imputed, and an additional variable was created coding for imputation of the PRS score (yes/no). This variable was used to control for imputation of the PRS scores in the analyses. The parcel summary scores of all predictors and outcomes were constructed per

participant and together used to impute the missing values. Based on the recommendation to impute as many datasets as the percentage of participants with any missing data [71], we imputed 20 datasets using R (v4.3.0), using the mice package [84, 228].

Adult outcome at follow-up: Functioning

A total of 41 long-term outcome measures were assessed at follow-up, tapping into 7 domains of functioning (see Table S2.1). These domains included psychiatric status, behavioral and emotional problems, academic and professional functioning, adaptive functioning, cognitive functioning, physical health, and healthcare service use. To reduce the number of measures of functioning, outcomes were standardized using z-scores and subjected to K-means clustering to form groups of participants showing similar functioning across the outcomes. The number of clusters was based on the elbow and silhouette method [251].

Cross-validation

Training and test data were separated with stratified Grouped K-Fold Cross-validation with 5-folds to ensure enough cases were present in each fold. Siblings were grouped in the same training or test fold to account for familial dependency. See Figure S7.1 for a description of the pipeline within the cross-validation folds.

Generative adversarial network

Given the relatively limited data availability, a generative adversarial network (GAN) was used to generate synthetic training samples, in order to increase the effective training sample size and reduce overfitting [252]. The standard GAN architecture was selected as it is suitable for augmenting data resembling the distribution samples with limited data [252]. The GAN was trained on the training data within each cross-validation fold. Each training fold contained approximately 106 unique participants, reflecting 80% of the total sample due to the use of group-based cross-validation, ensuring siblings were never split across training and test sets. The GAN consisted of a generator, which attempts to produce synthetic data, and a discriminator, which attempts to distinguish between the original and produced synthetic data. Both used LeakyReLu activation to improve stability and were optimized using the basic settings, including the Adam optimizer (learning rate = 0.0002, β_1 = 0.50, β_2 = 0.999) for 100 epochs with a batch size of 64 [253]. The generator included three fully connected Dense layers (256, 512, and 1024 units, respectively) and BatchNormalization (momentum = 0.80), thereby providing an optimal number of layers to have both sufficient depth to learn (due to not too few layers), while avoiding instability (due to too many layers). The output layer of the generator employed a tanh activation function. The discriminator included two Dense layers (512, and 1024 units, respectively), a Dropout layer (rate = 0.30), and an output layer with sigmoid activation. To

maintain training stability, the discriminator was updated twice per batch, and label smoothing was applied by setting real labels to 0.90.

Before combining GAN data with the real data, synthetic data quality was validated within each cross-validation fold, comparing variable distributions between real and synthetic data, using the Kruskal–Wallis test for continuous variables and a chi-squared test for binomial variables. A synthetic dataset was accepted when no more than 20% of measures exhibited significant distributional differences between synthetic and original data to balance data fidelity and practical feasibility. If this threshold was not met, GAN training was cumulatively repeated up to five times per fold. The dataset with the least significant distributional differences was used if the cumulative training was futile.

The GAN generated 212 synthetic samples which were added to the 106 real observations per cross-validation fold. The resulting final training set per fold contained approximately 318 samples (2:1 ratio of synthetic to real samples). GAN was trained on each of the 20 imputed datasets separately.

Model development and evaluation

Several machine learning models were developed in Python (version 3.9.21) using Scikit-learn [254] for the two binary outcome measures: ADHD persistence and functioning. In addition to the predictors, PRS imputation (yes/no) was included as a covariate to assess whether imputation of the PRS significantly influenced the model. The covariate was excluded from the final models if it did not influence model development, which was tested by comparing the mean differences in AUC across the 20 different imputed datasets between the best performing model with and without covariate using paired t-tests with $\alpha = .05$. The developed models for classification included high-performing algorithms: 1) logistic regression (baseline model), 2) logistic regression with ridge regularization, 3) support vector machine (SVM), 4) random forest (RF), and 5) extreme gradient boosting (XGB). Models were tested with hyperparameter tuning using randomized search (Table S7.3). All models and predictions were run 20 times per imputed dataset, and performance measures were averaged across runs to obtain stable performance estimates.

To investigate the added value of the machine learning models, all models were compared to a baseline model: the conventional logistic regression without regularization. Models were evaluated using the area under the curve (AUC) with scores closer to 1 showing a greater fit. To statistically compare the pooled models, differences in AUC were calculated by subtracting the AUC of the machine learning model from the baseline model. Then, the mean differences in AUC across the 20 different imputed datasets were compared using paired t-tests with $\alpha = .05$. The best performing model was further described in terms of its average sensitivity (correctly identified true positives), specificity (correctly identified true

negatives), positive predictive value (PPV), and negative predictive value (NPV). To investigate which predictors were most important for model development, the relative contributions of the predictors were investigated with a SHapley Additive exPlanations (SHAP) analysis [255] for the best performing pooled model (either the baseline model or a more complex model).

Results

Sample description

The sample included 133 participants with childhood ADHD (M_{age}= 29.53, SD_{age} = 2.83, 75% male), see van der Plas et al. [127] for a full description of follow-up measures. Of all participants, 61 (47%) had a persistent ADHD diagnosis at follow-up. See Table 7.1 for a description of the age and sex distribution. No significant differences were found between the persistent ADHD and remittent ADHD group or between clustering groups on baseline or follow-up age or sex.

Table 7.1. *Age and Sex Distribution*

	Persistent ADHD (n = 61)	Remittent ADHD (n = 72)	Group differences persistent versus remitted ADHD[a]	Less favorable functioning cluster (n = 48)	More favorable functioning cluster (n = 85)	Group differences less versus more favorable cluster[a]	Total sample (N = 133)
Age at baseline, *M* (*SD*)	11.28 (2.73)	10.96 (2.88)	Wald χ^2 = 0.33, p = .565	11.71 (2.78)	10.76 (2.78)	Wald χ^2 = 3.66, p = .056	11.11 (2.81)
Age at follow-up, *M* (*SD*)	29.66 (2.61)	29.42 (3.01)	Wald χ^2 = 0.18, p = .670	30.06 (2.84)	29.22 (2.79)	Wald χ^2 = 2.75, p = .097	29.53 (2.83)
Male sex, *n* (%)	44 (72%)	56 (78%)	Wald χ^2 = 0.49, p = .485	32 (67%)	68 (80%)	Wald χ^2 = 2.58, p = .108	100 (75%)

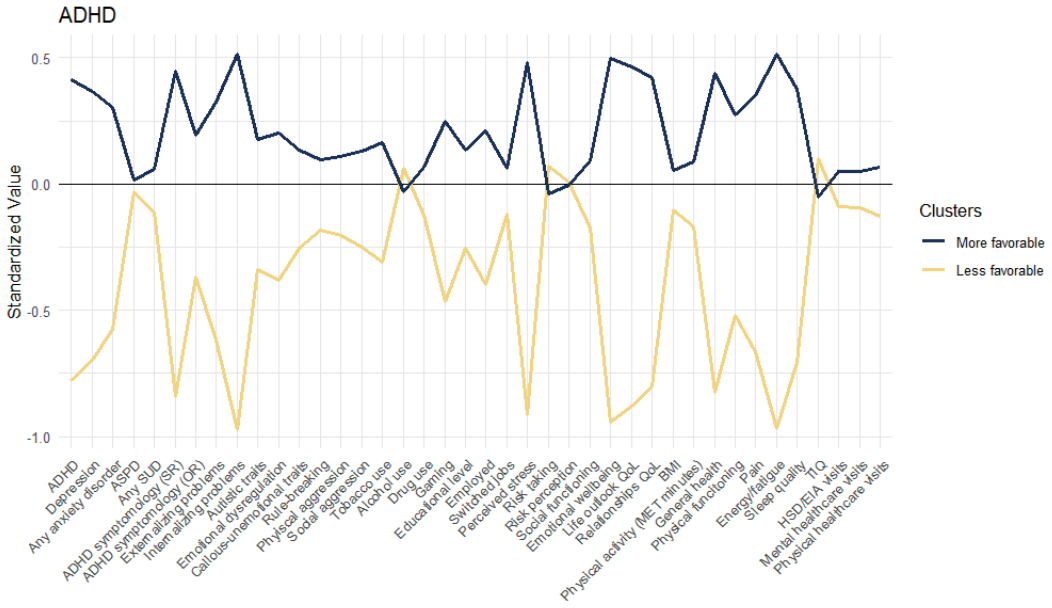
Note. ADHD = attention-deficit/hyperactivity disorder.
[a] Group differences were tested using Generalized Estimating Equations with an exchangeable correlation structure to account for familial dependency.

Data preprocessing

Functioning clustering

K-means clustering was used to identify groups of participants showing similar functioning across the outcomes, and both the elbow and silhouette plot indicated two clusters (Figure S7.2 and S7.3). Cluster quality was modest (silhouette score = 0.16, Davies-Bouldin Index = 1.70), but clusters showed clear interpretability. Based on their standardized centroid values, one cluster was interpreted as containing subjects with 'less favorable' functioning and the other as containing participants with 'more favorable' functioning, see Figure 7.1 for a visualization of the clusters' characteristics. See Table S7.4 for a description of long-term outcomes assessed at follow-up but excluded from the K-means clustering with the accompanying reasons (e.g., current ADHD medication use, as data was missing for more than 20% of the participants). Overall, the less favorable cluster of participants (n = 48, 36%) showed higher scores on negative outcomes and lower scores on positive outcomes, whereas the opposite was observed for the cluster of participants with more favorable functioning (n = 85, 64%). There were a few outcomes on which the two clusters showed hardly any differences (i.e., antisocial personality disorder, being employed) or where the more favorable cluster had a lower score on the positive outcomes and vice versa (i.e., alcohol use, risk taking behavior, and TIQ).

Figure 7.1. *Visualization of characteristics of the more and less favorable functioning cluster based on standardized scores on outcomes at follow-up*



Note. The figure shows the standardized z-scores on outcomes at follow-up of the two participant clusters. Higher scores indicate more favorable outcomes.
ADHD = attention-deficit/hyperactivity disorder, ASPD = antisocial personality disorder, BMI = body mass index, EIA = employee insurance agency, HSD = health and safety doctors, OR = other-report, QOL = quality of life, SR = self-report, SUD = substance use disorder, TIQ = total intelligence quotient.

Generative adversarial network

All synthetic datasets were accepted within 5 attempts, where each dataset had a maximum of 15% significant distributional differences of measures between synthetic and original data. The synthetic data differed from the real data on all folds for the binomial predictor stimulant use in the synthetic dataset used for predicting adult functioning.

Model development and evaluation

Predictors were not strongly intercorrelated (r's < 0.57), indicating predictors were likely not multicollinear.

Prediction of ADHD persistence

Table 7.2 shows the performance of all models and their comparison to the baseline logistic regression model. The baseline logistic regression model was the

best performing model for predicting ADHD persistence, with an AUC of .56 (95% CI .46-.65, sensitivity = 69%, specificity = 58%, PPV = 65%, NPV = 74%).

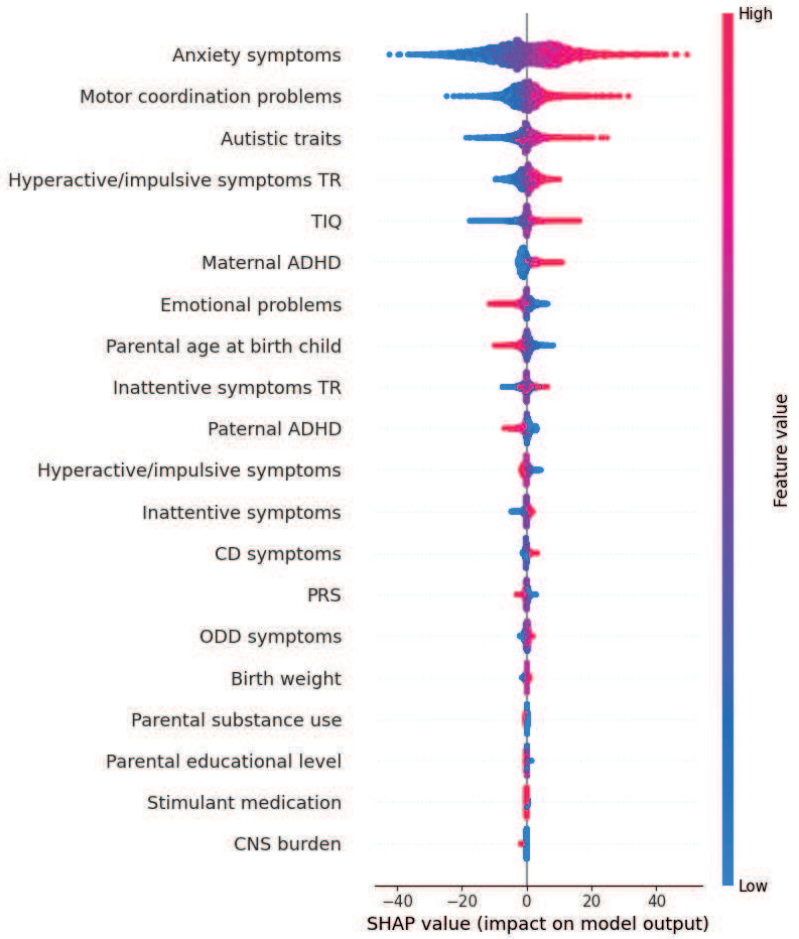
The top-5 most influential predictors of ADHD persistence, as indicated by SHAP of the best performing model, were anxiety symptoms, motor coordination problems, autistic traits, teacher-rated hyperactive-impulsive symptoms, and TIQ, with higher values contributing to a higher likelihood of ADHD persistence (Figure 7.2). The covariate PRS imputation negatively influenced model performance ($t(19) = -15.75$, $p < .001$), suggesting that accounting for imputation of PRS scores did not change the signal, i.e. that imputation did not bias the outcomes. Therefore, it was suitable to run the model without the PRS-imputation covariate.

Table 7.2. *Performance of models predicting ADHD persistence using childhood predictors and comparison with baseline model*

	AUC training-set	AUC test-set (95% CI)	*t*(19)
Real data (imputed)			
Logistic regression	0.78	0.56 (0.46-0.65)	Reference
Logistic regression, ridge regularization	0.78	0.56 (0.45-0.65)	-8.61***
Support vector machine	0.79	0.52 (0.44-0.59)	-5.25***
Random forest	1.00	0.56 (0.50-0.64)	.03
Extreme gradient boosting	0.99	0.54 (0.46-0.61)	-1.82
Real + GAN data			
Logistic regression	0.76	0.56 (0.46-0.65)	-4.56***
Logistic regression, ridge regularization	0.76	0.51 (0.42-0.61)	-4.59***
Support vector machine	0.83	0.50 (0.41-0.59)	-5.71***
Random forest	0.99	0.53 (0.46-0.60)	-3.17**
Extreme gradient boosting	0.95	0.51 (0.43-0.59)	-4.20**

Note. All models, except the baseline model, were trained using hyperparameter tuning. Performance of other models was compared with performance of the baseline reference model (conventional logistic regression) across the 20 different imputed datasets, using a paired t-test.
ADHD = attention-deficit/hyperactivity disorder, AUC = area under the curve, CI = confidence interval, GAN = generative adversarial network.
**p<.01, ***p<.001.

Figure 7.2. *SHAP plot of the baseline logistic regression model for ADHD persistence*



Note. Predictors were ranked by model importance based on their average absolute SHAP value. Colors indicate the value of the predictors, with red indicating higher values and blue indicating lower values. A higher SHAP value indicates a stronger influence on ADHD persistence (e.g., more anxiety symptoms predict ADHD being persistent). The individual dots represent individual participants; in some participants a predictor might have a stronger influence than in others. The SHAP plot is based on the pooled SHAP values across all 20 imputed datasets.
ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder, CNS = central nervous system, DSM = diagnostic and statistical manual of mental disorders, GAN = generative adversarial network, ODD = oppositional defiant disorder, PRS = polygenic risk score, SHAP = SHapley Additive exPlanations, TIQ = total intelligence quotient, TR = teacher-rated.

Prediction of Adult Functioning

Table 7.3 shows the performance of all models and their comparison to the baseline model. The baseline logistic regression model was the best performing model for predicting functioning, with an AUC of .59 (95% CI .50-.68, sensitivity = 61%, specificity = 70%, PPV = 58%, NPV = 77%).

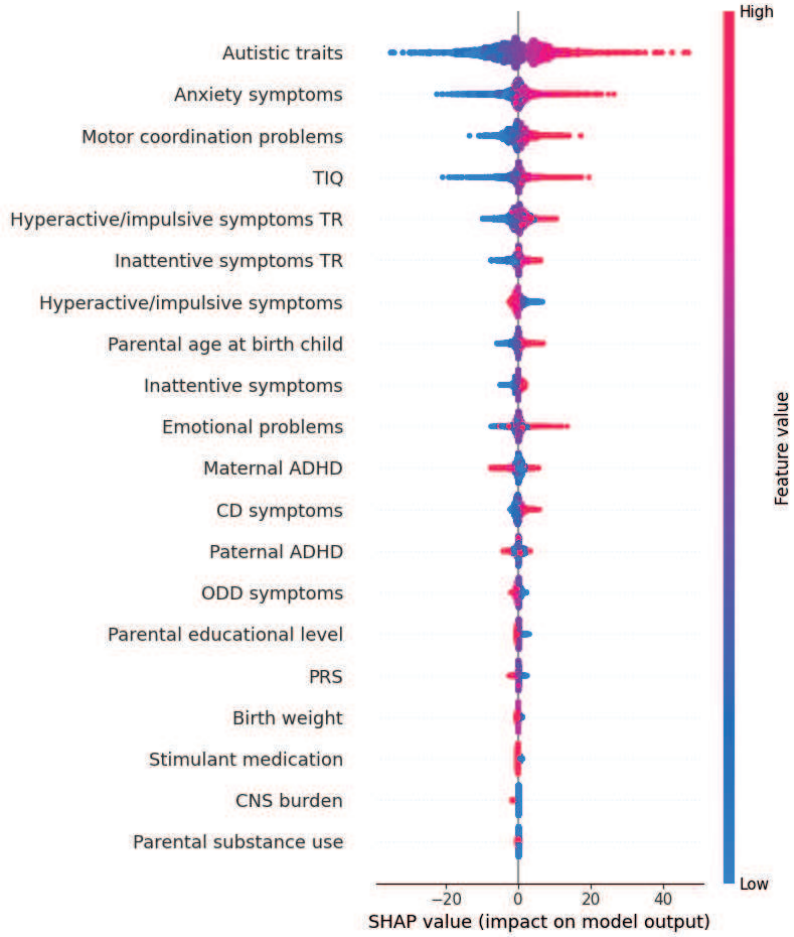
SHAP indicated that the top-5 most influential predictors of functioning in the best performing model were autistic traits, anxiety symptoms, motor coordination problems, TIQ, and teacher-rated hyperactive-impulsive symptoms, with higher values contributing to a higher likelihood of less favorable adult functioning (Figure 7.3). As the covariate PRS imputation again negatively influenced model performance ($t(19) = -12.80$, $p < .001$), the models reported in the results were run without the covariate.

Table 7.3. *Performance of models predicting more favorable adult functioning using childhood predictors and comparison with baseline model*

	AUC training-set	AUC test-set (95% CI)	$t(19)$
Real data (imputed)			
Logistic regression	0.76	0.59 (0.50-0.68)	Reference
Logistic regression, ridge regularization	0.76	0.59 (0.50-0.68)	-3.64**
Support vector machine	0.58	0.51 (0.41-0.60)	-7.44***
Random forest	1.00	0.47 (0.41-0.54)	-17.64***
Extreme gradient boosting	0.97	0.49 (0.41-0.56)	-11.57***
Real + GAN data			
Logistic regression	0.78	0.59 (0.51-0.68)	-1.86
Logistic regression, ridge regularization	0.78	0.58 (0.49-0.66)	-1.80
Support vector machine	0.84	0.56 (0.47-0.65)	-3.10**
Random forest	0.99	0.52 (0.44-0.61)	-5.73***
Extreme gradient boosting	0.94	0.52 (0.44-0.60)	-5.26***

Note. All models, except the baseline model, were trained using hyperparameter tuning. Performance of other models was compared with performance of the baseline reference model (conventional logistic regression) across the 20 different imputed datasets, using a paired t-test.
AUC = area under the curve, CI = confidence interval, GAN = generative adversarial network.
*$p<.05$, ***$p<.001$.

Figure 7.3. *SHAP plot of the baseline logistic regression model for more favorable adult functioning*



Note. Predictors were ranked by model importance based on their average absolute SHAP value. Colors indicate the value of the predictors, with red indicating higher values and blue indicating lower values. A higher SHAP value indicates a stronger influence on the functioning outcome (e.g., more autistic traits predict belonging to the worse functioning cluster). The individual dots represent individual participants; in some participants a predictor might have a stronger influence than in others. The SHAP plot is based on the pooled SHAP values across all 20 imputed datasets.
ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder, CNS = central nervous system, DSM = diagnostic and statistical manual of mental disorders, GAN = generative adversarial network, ODD = oppositional defiant disorder, PRS = polygenic risk score, SHAP = SHapley Additive exPlanations, TIQ = total intelligence quotient, TR = teacher-rated.

Discussion

This study is the first to explore the added value of using advanced machine learning techniques compared to conventional logistic regression in predicting long-term outcomes (18 years later), especially ADHD persistence and long-term functioning, of adults with childhood-diagnosed ADHD. K-means clustering was used to identify groups of participants showing similar functioning across 41 adult outcome measures within seven domains of functioning; it revealed a group of subjects with 'less favorable' functioning and a group of participants with 'more favorable' functioning. For the prediction models we used 20 variables measured in childhood. The best performing models were a logistic regression for both ADHD persistence (AUC = .56) and long-term functioning (AUC = .59), which, despite their poor fit, outperformed the more complex machine learning models. Also, the models including additional synthetic data did not outperform the conventional logistic regression.

Our prediction models were unable to distinguish between outcome status on ADHD persistence and functioning, just slightly outperforming chance. However, our models did show potential with acceptable NPV for ADHD persistence (74%) and acceptable specificity and NPV for functioning (≥ 70%), which can be relevant in early identification of a group with higher likelihood of remittent ADHD or favorable functioning. Performances of ADHD prediction models in previous studies are highly variable, with AUCs ranging from 0.50 to 0.99 [51], but those models mainly predicted a diagnosis in childhood versus controls or treatment response rather than long-term prognostic risk estimation. Two previous prognostic risk estimation models, predicting adult outcomes based on lifetime predictors (from birth up to one year before adult outcome), only reached acceptable predictive ability, using logistic regression to predict methylphenidate-related psychiatric symptoms (e.g., psychiatric effects of methylphenidate use, AUC = .75) and random forest to predict development of an SUD (AUC = .73), using larger sample sizes (N = 2,639 and 19,787, respectively) compared to our study [54, 55]. Overall, very few studies investigated prognostic risk estimation models for adult outcomes, none reached high predictive ability, and none investigated ADHD persistence or functioning in adults with childhood-diagnosed ADHD. Our study is the first to develop prediction models for these outcomes and shows potential for early identification of those individuals with a low risk for unfavorable outcomes; however, it corroborates the previous findings showing difficulties in developing good prognostic risk estimation models.

The insufficient model performance likely reflects that outcomes in adults with childhood ADHD are difficult to predict. There are a few possible explanations for our findings. First, outcomes may potentially be influenced by many risk factors with small effect sizes. A larger sample size and the assessment of an even larger number of risk factors than in the current study might be necessary to identify

relevant predictors and build effective prediction models, similar to genome-wide association studies, which are increasingly able to identify genetic risk loci for psychiatric disorders with their small effects. Establishing consortia or individual patient data meta-analysis (IPDMA) can support this endeavor, preferably having defined a core set of predictors. Second, we might have missed important childhood predictors, such as neuroimaging, environmental, and social factors. Third, our functioning outcome was determined by K-means clustering, as we aimed to capture a complete profile of functioning across several domains. Clusters had clear interpretability and differed on several important measures, e.g. the less favorable cluster had 1 standard deviation worse externalizing problems, social functioning, and energy/fatigue compared to the mean scores on those outcome measures. However, cluster quality was modest with a small distance between clusters, suggesting that some participants in the two clusters might have been close in functioning, undermining effective prediction. Development of a weighted sum score of functioning, incorporating measures across several domains, could increase generalizability. Fourth, deep learning models (neural networks) can likely obtain higher predictive accuracy, but these models are very complex with yet low interpretability [256]. As interpretability is desirable in clinical practice to guarantee usability, it is necessary that transparency of deep learning models increases, potentially through explainable artificial intelligence [257, 258].

Despite our low model performance, SHAP identified predictors with the highest influence on model performance, hinting towards several relevant predictors for ADHD persistence and functioning. In previous ADHD prediction models, performance was highest using clinical predictors, such as behavioral symptoms [51]. Our findings also showed clinical measures in the top-5 most influential predictors for both outcomes, including higher levels of anxiety symptoms, autistic traits, motor coordination problems, teacher-rated hyperactivity/impulsivity, and TIQ. Anxiety disorder and hyperactive-impulsive symptoms have previously been implicated as possible predictors for persistent ADHD [63], but autistic traits and motor coordination problems seem to be a novel potential predictor for ADHD persistence. For IQ, our findings were counterintuitive, given that higher IQ was related to ADHD persistence. A potential explanation for this finding could be that children with a higher IQ are better able to use compensatory strategies in childhood, therefore receiving less help for their ADHD, which eventually results in increased difficulties in adulthood when external structure disappears and demands for independence increase [259]. However, our SHAP-identified predictors were based on models with suboptimal performances, which also influences the reliability of predictors. Therefore, replication and external validation are essential to identify predictors with greater predictive value.

Our study should be viewed in the context of some strengths and limitations. The long follow-up period of 18 years with prospectively collected outcome data is a

strength of the current study and we included many variables that are often available in clinical practice, increasing the practical utility of the study. Missing data was appropriately handled with multiple imputation, maintaining the integrity of the data, which may be an issue in previous prediction studies in ADHD [51]. Despite the current study's strengths, the findings should be interpreted in light of the limitations. Our sample size was limited which resulted in overfitting in the training set, but, since rule of thumb for determining a minimum sample size and number of predictors are inconsistent, we purposefully used an exploratory approach in selecting the number of predictors [260]. To obtain a larger sample size, synthetic data were generated with GAN, a suitable technique even in datasets with a small sample size [252]. While in all GAN datasets less than 20% of all measures deviated from the real data, suggesting adequate data generation, GAN struggled synthetizing the binomial predictor stimulant medication, and the models including GAN data still overfitted in the training data, limiting generalizability. Finally, the test set outcomes were imputed together with the predictors, which could have artificially increased the relationship between predictors and outcomes. However, it is likely that this inflation remained confined, as missing outcome data was limited (max 10%), and the functioning outcome was based on 41 different measures.

To conclude, advanced machine learning techniques did not outperform conventional logistic regression models, and model fit was poor (AUCs between .56 and .59) for ADHD persistence and adult functioning, respectively. However, our acceptable NPVs (≥ 74%) show potential for early identification of a group that might need less monitoring in childhood. Including additional synthetic data did not improve findings. Currently, conventional models seem to remain an appropriate choice when analyzing outcomes in studies with relatively limited samples; however, studies should additionally opt for multivariate analysis to explore influences of multiple predictors together. Larger sample sizes and potentially additional/alternative measures may be needed to detect small effects and reflect the complexity of predicting long-term outcomes of ADHD.

Supplementary Method 7.1. *Polygenic liability scores calculation*

Polygenic liability scores were calculated using PRS-CS [261], which leverages linkage disequilibrium (LD) structure from GWAS summary statistics to estimate posterior effect size for each variant in a Bayesian framework. Specifically, PRS-CS uses a continuous shrinkage prior to regularize noisy SNP effects, thereby improving estimation accuracy compared to traditional (P + T) approaches.

We applied a maximum of 1500 Markov Chain Monte Carlo (MCMC) iterations and set the seed of the random number generator to 42. The remaining settings were the default settings. As a reference we used the 1KG panel provided by PRS-CS. We evaluated PRS-CS performance using both the automatic shrinkage parameter estimation (PRS-CSauto) and fixed shrinkage parameters (φ = $1e^{-2}$, $1e^{-4}$, $1e^{-6}$). Note that this parameter comparison was conducted within the same sample used for PRS calculation (NeuroIMAGE), which represents a form of overfitting. This analysis was performed solely to identify optimal parameter settings rather than to assess true predictive validity, which would require independent validation samples.

Based on this comparison, we found that PRS-CSauto performed best, albeit with a slim margin (R^2_{auto} = 0.096; $R^2_{1e\text{-}2}$ = 0.090; $R^2_{1e\text{-}4}$ = 0.090; $R^2_{1e\text{-}6}$ = 0.046). Therefore, PRS-CSauto derived PRS were used as predictors in the present analysis.

Table S7.1. *Comparison of successfully retained participants with childhood ADHD to the initial baseline sample*

M (*SD*)	Retained (*n* = 133)	Initial sample (*n* = 510)	Retained vs initial sample
Age in years (*SD*)	11.09 (2.79)	10.95 (2.80)	Wald χ^2 = 0.26
Male, *n* (%)	100 (75%)	400 (78%)	Wald χ^2 = 0.75
Estimated TIQ	100.74 (12.41)	98.88 (11.99)	Wald χ^2 = 1.67
Parental education level	5.24 (0.81)	5.19 (0.74)	Wald χ^2 = 0.13
ADHD symptoms	77.25 (9.26)	75.29 (9.80)	Wald χ^2 = 4.72*
ODD symptoms	65.05 (12.30)	66.09 (12.37)	Wald χ^2 = 0.01
Anxious/shy behavior	57.09 (13.43)	58.01 (13.74)	Wald χ^2 = 0.47
Behavioral and emotional difficulties	18.85 (5.71)	18.92 (6.18)	Wald χ^2 = 0.04

Note. ADHD = attention-deficit/hyperactivity disorder, ODD = oppositional defiance disorder, TIQ = total intelligence quotient.
*p<.05.

Table S7.2. *Description of predictors and their measurement*

Predictor	Measure	Dependent variable and range of possible scores	Description
Domain: ADHD symptoms and treatment			
DSM-4 hyperactive/impulsive symptoms (*parent-report*)	Hyperactive and impulsive module of PACS [249]	Number of DSM-4 hyperactive/impulsive symptoms of ADHD (range = 0 – 9)	Structured interview based on parent report assessing presence of symptoms of DSM-4 ADHD
DSM-4 inattentive symptoms (*parent-report*)	Inattentive and disorganization module of PACS [249]	Number of DSM-4 inattentive symptoms of ADHD (range = 0 – 9)	Structured interview based on parent report assessing presence of symptoms of DSM-4 ADHD
DSM-4 hyperactive/impulsive symptoms (*teacher-report*)	CTRS (Long Version) [262]	Severity of DSM-4 hyperactive/impulsive symptoms (range = 0 - 27)	Teacher-report questionnaire assessing DSM-related ADHD symptoms
DSM-4 inattentive symptoms (*teacher-report*)	CTRS (Long Version) [262]	Severity of DSM-4 inattentive symptoms (range = 0 - 27)	Teacher-report questionnaire assessing DSM-related ADHD symptoms
Stimulant medication	Custom made question	Presence of stimulant medication use	Parent-report question assessing use of

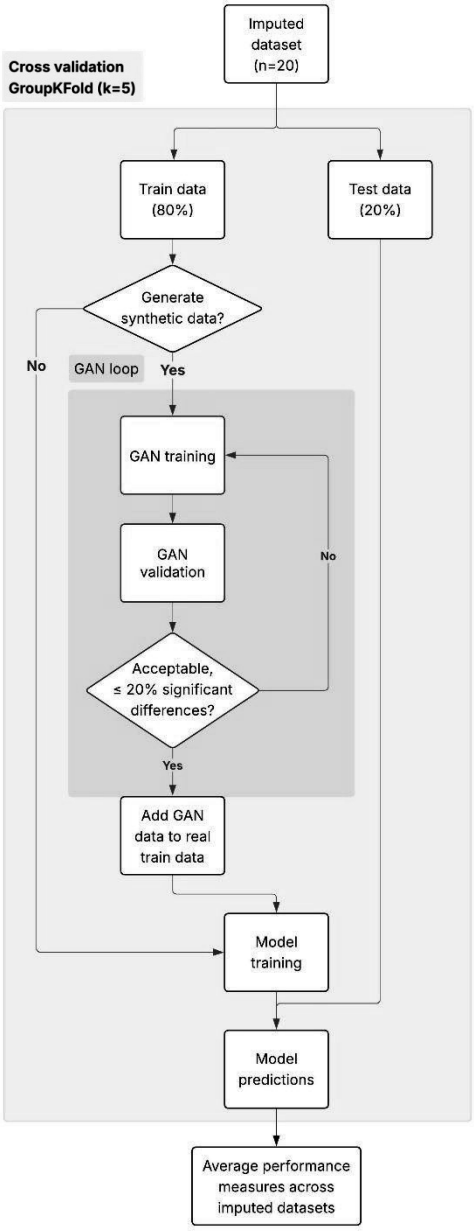
Predictor	Measure	Dependent variable and range of possible scores	Description
			methylphenidate, Ritalin or Concerta
Domain: Other psychopathology			
DSM-4 emotional problems	Emotional problems module of PACS [249]	Severity of DSM-4 depression and anxiety disorder symptoms (range = 0 – 48)	Structured interview based on parent report assessing presence of DSM-4 mood/anxiety symptoms
Anxiety symptoms	MASC [263]	Severity of anxiety symptoms (range = 0 – 117)	Self-reported questionnaire assessing anxiety
DSM-4 CD symptoms	CD module of PACS [249]	Number of DSM-4 CD symptoms of ADHD (range = 0 – 14)	Structured interview based on parent report assessing presence of symptoms of DSM-4 CD
DSM-4 ODD symptoms	ODD module of PACS [249]	Number of DSM-4 ODD symptoms of ADHD (range = 0 – 8)	Structured interview based on parent report assessing presence of symptoms of DSM-4 ODD
Autistic traits	CSBQ [264]	Severity of autistic traits (range = 0 – 98)	Parent-rated questionnaire assessing autistic traits
Domain: Somatic characteristics			
Birth weight	Custom made question	Birth weight (< 5 pounds - > 7 pounds)	Parent report question assessing birth weight
CNS burden	Custom made questions	Presence of a CNS burden	Parent report questions assessing past presence of meningitis, hospitalization due to trauma to the skull/concussion, and presence of epilepsy

Predictor	Measure	Dependent variable and range of possible scores	Description
Domain: Cognition			
Estimated TIQ	WISC-III or WAIS-III [76, 77]	Estimated Total IQ (range = 50 - 135)	Four-subtest short form to estimate total IQ.
Domain: ADHD PRS			
ADHD PRS	PRS	Genetic risk of ADHD	Genetic risk score based on risk alleles identified in the most recent ADHD GWAS [265]
Domain: Parental demographics and psychopathology			
Parental age at birth child	Custom made question	Mean age of parents at birth of child	Parental age at time of birth of child
Parental educational level[a]	Dutch Verhage scale [80]	Dutch Verhage score (range = 1 – 7)	Classification of highest level of completed education level based on the Dutch Verhage categories.
Maternal ADHD	Custom made questions	Severity of maternal DSM-4 ADHD symptoms in adulthood (range = 0 – 69)	Maternal-report questionnaire assessing their own DSM-4 ADHD symptoms in adulthood
Paternal ADHD	Custom made questions	Severity of parental DSM-4 ADHD symptoms in adulthood (range = 0 – 69)	Paternal-report questionnaire assessing their own DSM-4 ADHD symptoms in adulthood
Parental substance use	Custom made questions	Presence of parental substance use	Parental-report questions assessing their own use of cigarettes (> 5 per day), alcohol (> 5 units per day), cocaine, ecstasy, or heroin

Note. ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder, CNS = central nervous system, CSBQ = children's social behavior questionnaire, CTRS = conners' parent

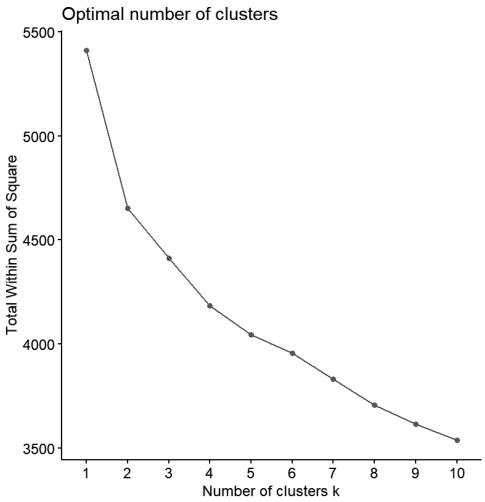
rating scale, DCDQ = developmental coordination disorder questionnaire, DSM = diagnostic and statistical manual of mental disorders, MASC = multidimensional anxiety scale for children, ODD = oppositional defiant disorder, PACS = parental account of children's symptoms, PRS = polygenic risk score, TIQ = total intelligence quotient, WAIS = Wechsler adult intelligence scale, WISC = Wechsler intelligence scale for children.
[a] Parental educational level based on the was based on the assessment in wave II as this was not assessed at wave I, assuming these levels did not differ between waves I and II (wave II was 5.60 years after wave I).

Figure S7.1. *Overview of the pipeline within the cross-validation folds*



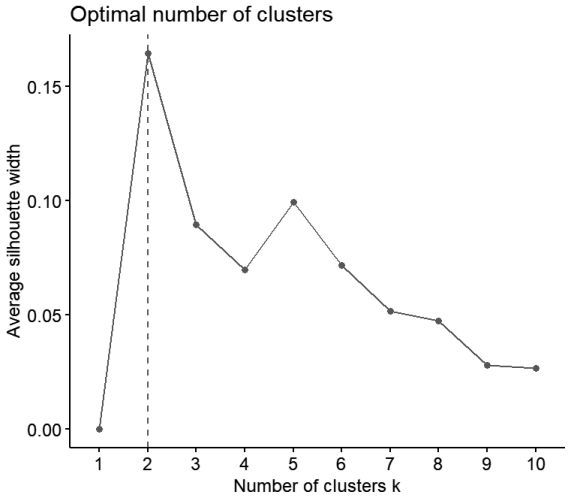
Note. All models were trained both on a dataset including only real data and on a dataset including real and synthetic (GAN) data.
GAN = generative adversarial network.

Figure S7.2. *Elbow plot for identification of number of clusters of functioning using K-means clustering*



Note. The elbow plot identified k = 2 as an optimal number of clusters of functioning based on 41 outcome measures.

Fig S7.3. *Plot of the silhouette score for identification of number of clusters of functioning using K-means*



Note. The silhouette score identified k = 2 as the optimal number of clusters of functioning based on 41 outcome measures.

Table S7.3. *Hyperparameter tuning*

Model	Hyperparameters grid search
Logistic regression with ridge regularization	C (0.001, 0.01, 0.1, 1, 10, 100) solver (lbfgs)
Support vector machine	C = (0.1, 1.0, 10) kernel = (rbf, linear)
Random forest	n_estimators = (100, 200, 300} max_depth = (5, 10, 15}
Extreme gradient boosting	n_estimators = (50, 100) max_depth = (3, 6, 10) learning_rate = (0.01, 0.1, 0.3)

Table S7.4. *Description of outcomes excluded from K-means clustering to identify groups with similar adult functioning*

Outcome	Measure	Description	Reason for exclusion
Demographics			
Age	Age	Self-reported question	No long-term outcome of ADHD
Family status	Family status	Self-reported question	Measure is dependent on age (e.g., single at age 20 is not a negative outcome, whereas it might indicate a negative outcome at age 35)
Number of children	Number of children	Self-reported question	Measure is dependent on age
Gender	TMF [145]	Self-report questionnaire assessing self perceived masculinity/femineity	No long-term outcome of ADHD, but a stable or predictive measure
Adaptive functioning			
Number of significant life events after age 16	Long-term Difficulties Questionnaire [112]	Self-report questionnaire assessing number of significant life events after age 16	No long-term outcome of ADHD, but a stable or predictive measure
Creativity	CAQ [113]	Self-report questionnaire assessing presence of 10 domains of creative achievements	No long-term outcome of ADHD, but a stable or predictive measure
Neurocognitive functioning			

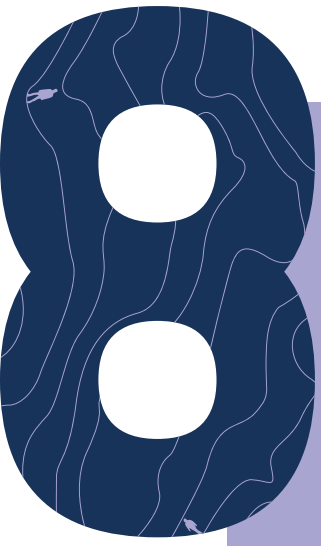
Short-term memory – digits	WAIS-IV [114, 118]	Total raw score of the Digit Span Forwards subtask from the Digit Span module. Higher scores indicate a better short-term memory	No long-term outcome of ADHD, but a stable or predictive measure
Short-term memory – verbal	15WT [117]	Test assessing short-term memory, based on total number of correct short-term retention with 15 auditory presented words 5 times. Higher scores indicate a better short-term memory	No long-term outcome of ADHD, but a stable or predictive measure
Working memory	WAIS-IV [114, 118]	Raw score of the Digit Backwards and Digit Span Sequencing subtask from the Digit Span module. Higher scores indicate a better working memory	No long-term outcome of ADHD, but a stable or predictive measure
Long-term memory	15WT [117]	Test assessing long-term memory, based on total number of correct words retained after 20 minutes. Higher scores indicate a better long-term memory	No long-term outcome of ADHD, but a stable or predictive measure
Cognitive fluency	Dutch version of the COWAT [86]	Test assessing letter fluency, based on total number of correct words produced across 3 letters (D, A, T). Higher scores indicate better letter fluency	No long-term outcome of ADHD, but a stable or predictive measure
Physical health			
Role limitation due	Role limitation due to	Self-report questionnaire assessing limitations	No variance in the responses

to physical problems	physical problems subscale of SF-36 [109, 110]	in usual role activities because of physical health problems. Higher scores indicate a more favorable health state	
Role limitation due to emotional problems	Role limitation due to emotional problems subscale of SF-36 [109, 110]	Self-report questionnaire assessing limitations in usual role activities because of emotional problems. Higher scores indicate a more favorable health state	No variance in the responses
Healthcare service use			
Current ADHD medication use	Pharmacy dispensing records	Based on the presence of at least one prescription of dexamphetamine, methylphenidate, or atomoxetine in the previous year	Missing for > 20% of participants
Current general medication use	Pharmacy dispensing records	Based on summing the total number of different ATC codes prescribed in the previous year	Missing for > 20% of participants
Other			
Coping through religion	Coping through religion	Self-report questionnaire assessing perceived support from religion and religious communities.	Missing data, as it was assessed in a subset of participants: those who belong to a religious group
Use of effective disciplinary practices	PPI [266-268]	Self-report questionnaire for parents assessing parents' use of effective disciplinary practices.	Missing data, as it was assessed in a subset of participants: participants with children.
Use of positive parenting	PPI [266-268]	Self-report questionnaire for parents assessing parents' use of positive disciplinary practices.	Missing data, as it was assessed in a subset of participants: participants with children.

Use of harsh discipline	PPI [266-268]	Self-report questionnaire for parents assessing parents' use of harsh disciplinary practices	Missing data, as it was assessed in a subset of participants: participants with children.

Note. ATC = anatomical therapeutic chemical, CAQ = creative achievement questionnaire, COWAT = controlled oral word association test, PPI = parenting practice interview, SF-36 = short form health survey, WAIS-IV = Wechsler adult intelligence scale, 15T = Dutch verbal learning test.

7



CHAPTER 8

Summary and general discussion

Summary of main findings

The aims of this thesis were to map the nature and severity of the long-term outcomes of adults who received an ADHD diagnosis in childhood and identify predictors for these long-term outcomes. Such results can support a reliable prognosis for adulthood outcomes of children with ADHD and may suggest possible targets for early prevention strategies to ameliorate negative outcomes. This is of importance as ADHD has a highly heterogeneous trajectory from childhood into adulthood, with potentially negative long-term outcomes. However, studies so far do not provide a comprehensive understanding of the full range of long-term outcomes of childhood ADHD, and predictors of long-term outcomes remain understudied and poorly understood. To tackle these issues, we first studied the long-term outcomes of adults with childhood ADHD looking at an extensive set of outcomes across seven domains of functioning (**Part I, Chapter 2-4**). Thereafter, predictors of these long-term outcomes were investigated (**Part II, Chapter 5-7**). Most of our studies, except the systematic review and meta-analysis (**Chapter 5**), used data from the 18-year follow-up study of the IMAGE/NeuroIMAGE cohort. This follow-up successfully included 421 participants, among which adults (M_{age} = 28.84) with childhood ADHD (n = 154), their siblings (n = 138), and controls (n = 129). Outcomes collected at follow-up included 51 measures across 7 domains of functioning, including psychiatric status, behavioral and emotional problems, academic and professional functioning, adaptive functioning, neurocognitive functioning, physical health, and healthcare service use. See Table 8.1 for an overview of the main findings per chapter. In the current chapter, the results of the studies pertaining to the two thesis aims are summarized and discussed. Subsequently, the limitations of this thesis and future directions for research, and the implications of our findings are addressed.

Part I - Long-term outcomes of childhood ADHD

In **Chapter 2**, we investigated differences between adults with childhood ADHD (n = 154), their siblings (n = 138), and controls (n = 129) on the 51 long-term outcomes across 7 domains of functioning (i.e., psychiatric status, behavioral and emotional problems, academic and professional functioning, adaptive functioning, neurocognitive functioning, physical health, and healthcare service use). Compared to their siblings and controls, adults with childhood ADHD showed worse long-term outcomes on more than 60% of the outcomes across the 7 domains of functioning, while their other outcomes were similar. The 3 most affected domains were behavioral and emotional functioning, with group differences on 86% of the 14 measures; adaptive functioning, with group differences on 56% of the 9 measures; and neurocognitive functioning, with group differences on all 5 measures. Most identified differences translated into small-sized effects, but several identified differences translated into moderate or large-

sized effects. Most notable negative long-term outcomes, with moderate or large effects, included both psychiatric and behavioral and emotional outcomes (i.e., a DSM-5 diagnosis of ADHD or major depressive disorder [MDD], and higher levels of ADHD symptoms, externalizing problems, autistic traits, mood dysregulation, and physical and social aggression) and one academic outcome (i.e., a lower educational level). Furthermore, we found moderate or large differences on neurocognitive outcomes (i.e., worse cognitive fluency and worse working memory), and one physical health outcomes (i.e., less adherence to the Dutch recommended diet).

On the one hand, despite significant group differences, group averages of the childhood ADHD group were similar to normative means reported in validation studies (within 1 SD) or fell below clinical thresholds indicative of problem levels. This suggests that the childhood ADHD group was not impaired on ADHD symptoms, externalizing problems, physical and social aggression, perceived stress, quality of life, and general health perceptions. On the other hand, group averages of the childhood ADHD group reflected clinical problems and difficulties with daily life functioning (deviating 1 SD from the defined normative range and above clinical thresholds indicative of problem levels). This was the case for a MDD diagnosis, autistic traits, tobacco use, sleep, and overweight. Importantly, the long-term negative outcomes of childhood ADHD were largely independent of a current ADHD diagnosis, as both the persistent and remittent ADHD groups differed from controls on 51% of the long-term outcomes. However, effect sizes of the differences were larger for the persistent ADHD group compared to the remittent ADHD group. This implies that additional factors other than a current ADHD status explain heterogeneity in adult functioning.

Furthermore, we specifically investigated if the siblings of adults with childhood ADHD (without childhood ADHD themselves) were at an increased risk for negative long-term outcomes, as siblings share half of their genetic material and part of their childhood environment. Therefore, these siblings might also be at an increased risk of negative long-term outcomes. Nonetheless, we found that siblings were not at an increased risk of negative long-term outcomes, as they did not differ from controls on most long-term outcomes, except some small-sized effects, including higher levels of ADHD symptoms and autistic traits, higher BMI, and worse diet.

Chapter 3 served as an in-depth analysis of healthcare service use where pharmacy dispensing records of medication for ADHD, other psychotropic medication, and somatic medication of the last year were compared between adults with childhood ADHD (n = 125), their siblings (n = 109), and controls (n = 101). We found that adults with a childhood ADHD diagnosis had elevated medication use, which might indicate a long-term health burden. Of the childhood ADHD group, only 26% used ADHD medication as adults; they were 6 to 8 times more likely to use ADHD

medication and were prescribed more different ADHD medications compared to both their siblings and controls. Fourteen percent of the childhood ADHD group used psychotropic medication that was not prescribed for ADHD, which they were 4 times more likely to be on, and a larger number of different psychotropic medications were prescribed to this group, compared to controls but not the siblings. Finally, 58% of the adults with a childhood ADHD diagnosis used somatic medication and were 3 to 7 times more likely to take neurological medications, specifically analgesics (usually prescribed for pain relief) and non-steroidal anti-inflammatory drugs (NSAIDs; usually prescribed to treat inflammation and rheumatic conditions), compared to both siblings and controls. For most specific somatic medication subgroups, use did not differ between groups. Differences in adult medication use were influenced by presence of current ADHD or MDD, as the childhood ADHD group no longer differed on psychotropic medication use, neurological medications, and analgesics after controlling for current ADHD and MDD. Also, similar to **Chapter 2**, there were no differences between siblings of adults with childhood ADHD and controls regarding adult medication use, reiterating that these siblings were not at an increased risk for negative long-term outcomes.

To follow-up on the findings from **Chapter 2**, in **Chapter 4** we investigated whether males or females with childhood ADHD were more at risk of specific long-term outcomes, as the sex differences in the general population might be more pronounced within ADHD. We investigated moderations of sex in ADHD (n_{males} = 104, $n_{females}$ = 50) compared to controls (n_{males} = 52, $n_{females}$ = 77) and found that, generally, sex did not have a more pronounced effect in ADHD than in controls on the 51 long-term outcomes. A moderating effect was found only for social functioning, where males with childhood ADHD had difficulties in social functioning, but females with childhood ADHD and controls (males and females) did not. Additionally, we aimed to explore the moderating role of gender. However, due to high overlap between sex and gender-expression, potential effects of gender could not be explored. Thus, sex differences in ADHD were similar to the sex differences present in the general population, meaning we found no double-burden of sex in ADHD regarding long-term outcomes.

Part II - Predictors of long-term outcomes of childhood ADHD

As the previous chapters indicated heterogeneity in the long-term outcomes of childhood ADHD, with some adults showing typical functioning, and others showing functioning indicative of remaining difficulties in daily life functioning, we attempted to identify factors predicting long-term outcomes.

First, in **Chapter 5**, we summarized the current literature on childhood predictors of prevalent psychiatric outcomes of adults with a childhood ADHD diagnosis, including ADHD persistence, substance use disorder (SUD), conduct disorder (CD),

antisocial personality disorder (ASPD), MDD, and anxiety disorders, by conducting a systematic review and meta-analysis. We included 36 studies encompassing 119 predictors, with 10 predictors eligible for meta-analysis. The meta-analyses showed that adults with childhood ADHD who had a history of childhood stimulant treatment were twice as likely to have persistent ADHD. Also, children with a higher childhood IQ were slightly less likely to have persistent ADHD (OR = 0.99), but when looking at fair and good quality studies only, childhood IQ was no longer related to ADHD persistence. Furthermore, we found that adults with persistent ADHD were two to three times more likely to have a SUD or MDD in adulthood. Narratively reviewed predictors from studies with fair and good study quality suggested several potential predictors for an increased risk of ADHD persistence, including having childhood ADHD combined type, hyperactive/impulsive symptoms, anxiety disorders, externalizing problems, social dysfunctioning, and lower socioeconomic status. No narrative predictors were identified based on fair and good quality studies for the other psychiatric outcomes. To conclude, we could only identify few predictors, partly because our study was hampered by methodological shortcomings of the available literature (e.g., clinical and methodological heterogeneity, poor study quality), highlighting the need for conducting more comprehensive studies.

Thereafter, in **Chapter 6**, we used data from the 18-year follow-up of the IMAGE/NeuroIMAGE sample to study whether stimulant treatment in childhood could be predictive of a broad range of long-term outcomes. For this specific study, we used stimulant treatment data available from birth until wave II (M_{age} = 16.14), with the long-term outcomes measured 12 years after wave II. Using K-means clustering, two childhood stimulant treatment trajectory groups were identified amongst the 324 children with ADHD and available wave II stimulant treatment data. The wave II stimulant treatment data included age at initiation, treatment duration, total dose, maximum dose, variability of dose, and stop age. Only a subset of the wave II children participated in the 18-year follow-up, so, from the 143 participants reassessed at the 18-year follow-up, 48 adults were part of the group characterized by early-and-intense use and 63 adults were assigned to the group characterized by late-and-moderate use. These groups were compared to a stimulant-naïve group (n = 34).

The three groups did not differ on most adult outcomes in the domains of psychiatric status, behavioral and emotional problems, academic and professional functioning, adaptive functioning, neurocognitive functioning, physical health, and healthcare service use. We found differences for only 3 out of a total of 51 outcome measures. Specifically, early-and-intense use was related to (trend effects) the most favorable mean scores on risk perception (domain adaptive functioning), cognitive flexibility (domain neurocognitive functioning), and sleep quality (domain physical health), as compared to the stimulant naïve and late-and-moderate group. Moreover, both groups who used stimulant medication in

childhood (i.e., the early-and-intense and late-and-moderate group) had more favorable mean scores (trend effects) on cognitive flexibility and sleep quality compared to the group without stimulant medication use in childhood. Notably, the differences in mean scores between the three groups were not clinically relevant, such as that all three groups had sleep problems. Despite few trend effects without clinical relevance, our results showed that stimulant medication use in childhood is not associated with risks or benefits for most adult outcomes

Finally, in **Chapter 7**, we investigated the potential of machine learning in identifying predictors for a) ADHD persistence and b) adult functioning, both assessed 18 years later, by comparing a conventional logistic regression approach to more advanced machine learning approaches (i.e., ridge regression, support vector machine, random forest, and extreme gradient boosting). Predictors included a range of childhood factors (i.e., ADHD symptoms and treatment, other psychopathology, ADHD polygenic risk score [PRS], cognition, somatic characteristics, and parental demographics and psychopathology). First, using K-means clustering, we identified 2 groups of participants showing similar functioning across 41 adult outcome measures within 7 domains of functioning: a group of subjects with 'less favorable' functioning (n = 48) and a group of participants with 'more favorable' functioning (n = 85). Then we developed prediction models and compared the performance of a conventional logistic regression model to more advanced machine learning models. The best performing models were the conventional logistic regression for both ADHD persistence (AUC = .56) and long-term functioning (AUC = .59), showing that the more complex machine learning models did not outperform conventional logistic regression. Additionally, synthetic data was generated to increase the sample size, but this did not improve the models. Although all models showed a suboptimal performance, which influenced the reliability of the predictors, several possibly relevant predictors were suggested including anxiety symptoms, autistic traits, and motor coordination problems. These predictors might be especially relevant in early identification of a group with low risk for negative adult outcomes, given that the conventional logistic regression models reached an acceptable negative predictive value (≥ 74%). Despite the advanced machine learning models being able to handle complex relationships, they were unable, at least in our sample, to capture the expected complex relationships between predictors and outcomes. Thus, the advanced machine learning models did not increase model performance, not even after additional synthetic data were added.

Table 8.1. Main findings

Chapter	Aim	Participants	Measures	Main findings	Conclusions
2	Investigate long-term outcomes of childhood ADHD.	154 A 138 S 129 C	Outcomes • 51 measures across 7 domains of functioning[a]	• ADHD in childhood posed risks for adult functioning, as adults with childhood ADHD showed worse long-term outcomes on 60% of the outcomes across the seven domains compared to their siblings and controls, although most of the identified group differences translated into small-sized effects. • Adults with both persistent and remittent childhood ADHD were at risk for negative long-term outcomes. Both groups had worse outcomes compared to controls, with larger effect sizes for the persistent ADHD group. • No specific risks were identified for siblings.	• Childhood ADHD is a risk condition for long-term difficulties in daily life functioning. • However, adults with childhood ADHD also show typical functioning across several outcomes. • The elevated risk for negative outcomes in adults with childhood ADHD is not merely explained by shared familial factors but seems attributable to unique genetic, environmental, and phenotypic factors, as well as unique gene-environment interactions and correlations.
3	Investigate adult medication use, including ADHD, other psychotropic, and somatic medication.	125 A 109 S 101 C	Outcomes • ADHD, other psychotropic, and somatic medication use • Subgroups of other psychotropic and somatic medications	• Childhood ADHD was linked to elevated medication use in adulthood, including ADHD medication and some somatic medication subgroups (i.e., NSAIDs and neurological medications, specifically other analgesics) compared to their siblings and controls. Compared to controls, childhood ADHD was linked to	• Childhood ADHD is associated with a long-term burden as measured by medication use. • The elevated medication use is not merely explained by shared familial factors, but seems attributable to unique genetic, environmental, and phenotypic factors, as well

Chapter	Aim	Participants	Measures	Main findings	Conclusions
				elevated psychotropic medication use. • The elevated medication use in childhood ADHD was partly attributable to current psychiatric status, as several group differences were no longer significant after controlling for current ADHD and MDD. However, after controlling for current ADHD and MDD the childhood ADHD group still had an increased risk for ADHD medication use, NSAIDs use, and more different psychotropic medication prescriptions. • Siblings did not have elevated adult medication use.	as unique gene-environment interactions and correlations.
4	Investigate the moderating role of sex in the association between ADHD and its long-term outcomes, and additionally explore the moderating role of gender.	50 AF 104 AM 77 CF 52 CM	Outcomes • 51 measures across 7 domains of functioning[a]	• There was no moderation of sex on most outcomes. • Males with childhood ADHD had difficulties in social functioning, while females with childhood ADHD and controls (males and females) did not. • Sex and gender-expression were highly correlated.	• Generally, sex did not have a more pronounced effect in ADHD compared to controls on long-term outcomes. • Gender-expression could not be studied in our predominantly cis-gendered sample.
5	Aggregate existing longitudinal studies focusing on childhood predictors for the development of the most prevalent psychiatric	Review & meta-analysis of 36 studies including	Outcomes • ADHD persistence • Any SUD • CD • ASPD • MDD	Fair/good quality studies showed: • History of stimulant treatment was associated with increased risk of ADHD persistence.	• Few predictors have been identified thus far. • The available literature is hampered by methodological shortcomings.

Chapter	Aim	Participants	Measures	Main findings	Conclusions
	outcomes of adults diagnosed with childhood ADHD.	119 predictors	• Any anxiety disorder	• ADHD persistence was associated with increased risk of adult SUDs and MDD. • Narratively reviewed predictors of potential predictors for ADHD persistence included ADHD combined type, hyperactive/impulsive symptoms, anxiety disorders, externalizing problems, social dysfunctioning, and socioeconomic status)	
6	Explore childhood stimulant treatment trajectories as potential prediction profiles for long-term outcomes of childhood ADHD.	48 EI 63 LM 34 SN	Outcomes • 51 measures across 7 domains of functioning[a]	• K-means identified two stimulant treatment trajectory groups (i.e., EI and LM) that were compared to a SN group. • Long-term outcomes generally did not differ between stimulant treatment trajectories (48 out of 51 measures not significant). • Stimulant treatment trajectories might influence risk perception, cognitive flexibility, and sleep quality, with most favorable outcomes for EI use.	• Overall, childhood stimulant treatment does not predict long-term functional outcomes.
7	Explore the added value of using advanced machine learning techniques compared to conventional logistic regression in predicting long-term outcomes of childhood ADHD.	133 A	Childhood predictors: • ADHD symptoms and treatment • Other psychopathology • Cognition • Somatic characteristics	• K-means identified two groups of childhood ADHD, each showing similar adult functioning. • Models were unable to accurately predict ADHD persistence and adult functioning.	• Adults with childhood ADHD can be divided into different groups of functioning. • Predicting long-term outcomes of ADHD is complex.

Chapter	Aim	Participants	Measures	Main findings	Conclusions
			• ADHD polygenic risk score • Parental demographics and psychopathology Outcomes: • ADHD persistence • Adult functioning, based on 41 outcome measures	• No machine learning model outperformed the conventional logistic regression model. • The logistic regression models reached acceptable negative predictive values (≥ 74%). • Although models had suboptimal performances, several relevant predictors were suggested: anxiety symptoms, autistic traits, and motor coordination problems.	• The models show potential for early identification of a group who might need less monitoring in childhood.

Note. A = adults with childhood ADHD, ADHD = attention-deficit/hyperactivity disorder, AF = females with childhood ADHD, AM = males with childhood ADHD, ASPD = antisocial personality disorder, C = controls, CD = conduct disorder, CF = female controls, CM = male controls, EI = early-and-intense stimulant treatment, LM = late-and-moderate stimulant treatment, MDD = major depressive disorder, NSAIDs = non-steroidal anti-inflammatory drugs, S = siblings of adults with childhood ADHD, SN = stimulant-naïve, SUD = substance use disorder.

[a] the seven domains of functioning include psychiatric status, behavioral and emotional problems, academic and professional functioning, adaptive functioning, neurocognitive functioning, physical health, and healthcare service use.

General discussion

Part I - Long-term outcomes of childhood ADHD

The first aim of this thesis was to identify long-term outcomes of childhood ADHD by comparing a broad set of outcomes between adults with childhood ADHD, their siblings, and controls, to support a reliable prognosis for adulthood outcomes of children with ADHD. We showed that adults with childhood ADHD are indeed at an increased risk of negative long-term outcomes across several domains of adult functioning (**Chapter 2** and **Chapter 3**). However, these outcomes should be viewed in a broader context to approximate the severity of these long-term outcomes.

Importantly, despite significant group differences on long-term outcomes, adults with childhood ADHD seem to have comparable functioning to the general population on several measures. Most adults were employed (88%) and had completed an education at least at a middle level (i.e., finished average-level secondary education, high level education, or a university degree; 94%) [80]. Also, more than half (55%) did not have an ADHD diagnosis in adulthood, reflecting remittance of at least some of their childhood symptoms in most adults with childhood ADHD. Furthermore, potentially due to most of the group having remittent ADHD, group averages of ADHD symptoms, externalizing problems, physical and social aggression, perceived stress, quality of life, and general health perceptions were similar to normative means reported in validation studies (within 1 SD) or fell below clinical thresholds indicative of problem levels [78, 101, 104, 109, 111, 269], suggesting typical functioning in these outcomes.

Additionally, while a SUD has previously been suggested as a long-term outcome of childhood ADHD [16], this was not the case in our sample, given we found no increased risk for a SUD. However, increased risk for a SUD was found for the early-and-intense group in the adolescent follow-up of the same cohort (12 years before the current adult follow-up) [44]. Although it may be that some of these individuals were lost to follow-up, the finding that our cohort no longer had an increased risk for a SUD as adults may also reflect effects of receiving proper treatment and/or a natural decline in substance use with age [270, 271]. Finally, current medication use was relatively low. Few adults with childhood ADHD currently use ADHD medication (26%) and other psychotropic medication (14%). Also, adults with childhood ADHD used, on average, less than two different somatic medications. Additionally, most of the group who had used ADHD medication in childhood no longer used ADHD medication in adulthood (72%). In total, 66% used at least one medication, which is comparable to medication use in the general population (64%) [272].

Despite the similarities with the general population, childhood ADHD was still linked to a range of mental, physical, and lifestyle risks in our study. Notably,

adults with childhood ADHD had an increased risk for a higher level of autistic traits (β = 0.78 – 1.06, large group differences) with average group scores indicative of clinical impairment. They also had a higher likelihood of an MDD diagnosis (OR = 3 – 4) and were more often prescribed specific medications (OR = 3 – 7). Despite small effects, average group scores of the adults with childhood ADHD reflected difficulties (deviating 1 SD from the defined normative range) with social functioning, and were above clinical thresholds indicative of problem levels on tobacco use, sleep, and overweight (β range = 0.30 – 0.44, small group differences) [69, 109, 120, 273, 274]. While some group differences are subtle in effect size (for example on the domains of adaptive functioning, neurocognitive functioning, and physical health), these differences may indicate the starting point for subsequent somatic disease and neurological disorders due to an additive effect of persistent detrimental habits (e.g., stress, unhealthy lifestyle) [25, 122]. Thus, the presence of negative long-term outcomes with small-to-large differences points to a heterogenous prognosis with difficulties in daily life functioning, albeit with limited clinical problems.

Although both adults with remittent and persistent childhood ADHD are at an increased risk of negative long-term outcomes, the outcomes of the persistent ADHD group are even worse with larger effect sizes on the long-term outcomes. Only the persistent group had a heightened risk for a MDD diagnosis compared to controls. Furthermore, their average group scores were higher compared to both controls and the remittent ADHD group and deviated from the defined normative range (> 2 SD) or above clinical thresholds indicative of problem levels on ADHD symptoms, autistic traits, internalizing problems, tobacco use, and sleep problems, suggesting the persistent ADHD group experiences more impairment. Additionally, their average group scores deviated from the defined normative range (between 1 SD and 1.5 SD) on quality of life, social functioning, and emotional wellbeing, suggesting difficulties on these outcomes. Similarly, elevated medication use was attributable to current psychiatric status (ADHD and MDD), as several group differences no longer were significant after controlling for current ADHD and MDD. These findings suggest that the heightened risk for negative long-term outcomes is partly attributable to ADHD persistence.

Yet, a current ADHD status (persistent ADHD) is not the only factor underlying differences in adult functioning. Using K-means clustering analysis, we were able to identify two groups of participants with different patterns of adult functioning across long-term outcomes: one with more favorable functioning and another with less favorable functioning (**Chapter 7**). See Figure 8.1 for a visual depiction of the heterogeneity in outcomes of adults with childhood ADHD in terms of standardized scores while distinguishing between persistent and remittent childhood ADHD and favorable and less favorable adult functioning. The less favorable adult functioning group consisted primarily of adults with persistent childhood ADHD (83%), but the more favorable adult functioning group also

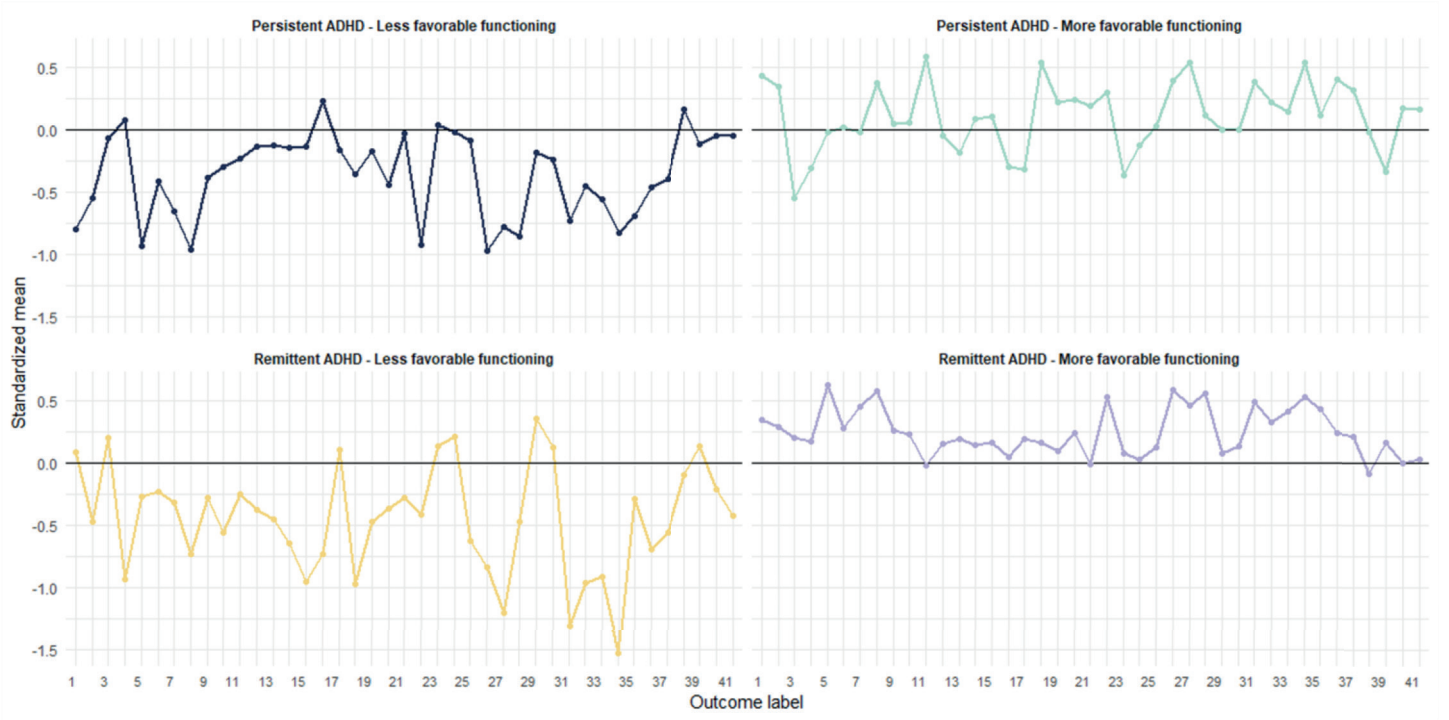
comprised adults with persistent childhood ADHD (25%). Furthermore, adults with an internalizing psychiatric disorder (MDD, any anxiety disorder) were generally part of the less favorable adult functioning group, while other externalizing disorders (any SUD, ASPD) were equally distributed between groups. The average scores of the less favorable adult functioning group indicated impairment, with group averages deviating (above 2 SD) from the defined normative range or above clinical thresholds indicative of problem levels (i.e., ADHD symptoms, autistic traits, internalizing problems, tobacco use, BMI, and sleep problems), and difficulties, with group averages deviating (between 1 and 2 SD) from the defined normative range (i.e., social functioning, life outlook - part of quality of life, emotional wellbeing, and general health). Most of the average scores of the more favorable adult functioning group reflected typical functioning, with group averages mostly similar (within 1 SD) to normative means reported in validation studies or below clinical thresholds indicative of problem levels. However, average scores of the more favorable adult functioning group did deviate (between 1 and 2 SD) from the defined normative range or fell above clinical thresholds indicative of problems on autistic traits, tobacco use, and BMI. Outcomes which contributed most (i.e., were most useful to discriminate between groups) to the distinct groups of adult functioning were internalizing problems, wellbeing, energy, perceived stress, quality of life, ADHD symptoms, general health, and a persistent ADHD diagnosis. These findings reiterate that adults with childhood ADHD can be divided into different groups of functioning, reflecting heterogeneity within individuals with childhood ADHD.

Another potential factor which might introduce heterogeneity in long-term outcomes of ADHD is sex. However, we did not find a double burden of sex and ADHD, as we did not observe greater sex differences in ADHD than in the general population (**Chapter 4**). While other studies suggested sex differences in long-term outcomes of childhood ADHD [5, 6, 30, 31, 151], those studies did not investigate specific moderating effects of sex. This suggests previously identified differences between males and females with ADHD are similar to those found in the general population and thus independent of a childhood diagnosis of ADHD. Interestingly, social functioning was the exception, as males with childhood ADHD experienced difficulties in social functioning, while females with childhood ADHD had comparable social functioning to males and females without childhood ADHD. However, as we were interested in long-term outcomes of childhood ADHD, our study did not include adults with ADHD diagnosed (relatively) late in life (i.e., in adolescence or adulthood). Especially many females with ADHD receive a diagnosis later in life and potentially are at the highest risk of negative outcomes, such as lower self-esteem, worse mental health, and overall lower wellbeing [6, 139, 152]. This heightened risk of negative outcomes for late-diagnosed females might be caused by misdiagnosis, inadequate or untimely support, and high levels of masking [5, 153]. This might additionally explain why cross-sectional studies

identified sex differences which were not observed in the current study, as these previous studies are based on adult samples with current ADHD that potentially include late-diagnosed females. In short, while the prognosis of males and females with childhood ADHD in our sample showed similar outcomes, later diagnosed individuals may face different risks.

To conclude, there is heterogeneity in long-term outcomes of the childhood ADHD group, with some individuals showing comparable functioning to the general population, and others showing difficulties in daily life functioning. So far, we found that this heterogeneity does not seem to be driven by ADHD-specific sex differences but may partly be due to persistent ADHD. As persistent ADHD does not explain all differences in adult functioning, we also need to explore potentially relevant childhood factors.

Figure 8.1. Visualization of outcomes of the ADHD persistence and functioning groups based on standardized scores



Note. Higher scores indicate more favorable outcomes. Scores were standardized within the childhood ADHD group, with x = 0 showing the mean group average of the childhood ADHD group. The four plots show the standardized scores on 41 outcomes, as detailed in Table 2.1, for the adults with persistent childhood ADHD and less favorable functioning (n = 40) and more favorable functioning (n = 21), and adults with remittent childhood ADHD and less favorable functioning (n = 8) and more favorable functioning (n = 64).

Part II - Predictors of long-term outcomes of childhood ADHD

The second aim of this thesis was to identify predictors of the long-term outcomes of childhood ADHD, thereby suggesting potential targets for the prevention of possible negative outcomes to improve the prognosis of childhood ADHD. Although there is heterogeneity within the childhood ADHD group in long-term outcomes (see Figure 8.1), our findings show it is difficult to identify predictors of these outcomes (**Chapters 5-7**). More specifically, we found stimulant treatment trajectories generally did not predict long-term outcomes (**Chapter 6**). Also, our prediction models achieved suboptimal model performance, albeit showing some evidence for childhood predictors anxiety symptoms, autistic traits, and motor coordination problems (**Chapter 7**). Moreover, previous studies have also been unable to successfully identify predictors of long-term outcomes (**Chapter 5)**.

While our meta-analysis (**Chapter 5**), showed that those with a childhood history of stimulant treatment were more likely to have persistent ADHD, we failed to find evidence that childhood stimulant treatment was related to long-term adult outcomes (**Chapter 6**). Previous studies may have identified stimulant treatment as a predictor of ADHD persistence because, in their samples, stimulant treatment use was potentially confounded by ADHD severity (i.e., the most affected children receiving stimulant treatment) which inflated the association between childhood stimulant treatment and ADHD persistence [200]. In contrast, this confounding was possibly absent in our study. Our sample was likely more homogenous in terms of ADHD severity and medication use (yes/no) compared to other samples. This homogeneity may have resulted in less differences in long-term outcomes. Indeed, our three stimulant treatment trajectory groups did not differ in childhood ADHD symptoms. We might have included a more homogeneous sample of ADHD severity due to the inclusion of children with ADHD combined type only (at the first wave), while other studies likely included a more heterogeneous sample with more variation in type of symptoms (including children with other subtypes) [178-181]. Also, our sample was more homogenous in terms of having used stimulants (yes/no), as the majority of our sample had used medication in childhood (75%), while other studies had a larger group without a history of childhood stimulant treatment (average of 57%) [178-181].

Furthermore, we did not replicate the previously reported positive outcomes of childhood stimulant use on mood, depression, anxiety, and SUDs. However, the majority of the studies reporting positive outcomes of childhood stimulant use had a follow-up period of ≤ 3 years in contrast to our follow-up period of 12 years [42]. It might be that stimulant use has a beneficial effect for some years after use, but the 'lasting' effects decline with time and eventually disappear after a long (> 10 years) period. Importantly, while our lack of long-term differences contrasts with studies reporting positive short-term outcomes, it aligns with several other studies with larger samples or longer follow-ups. These other studies on stimulant

use include a large registry study showing no long-term effects on comorbidities despite initial protective effects [275], a review study showing beneficial effects on childhood outcomes but less on adult outcomes [220], and the large MTA study showing no lasting long-term effects despite beneficial short-term effects [229, 276]. However, stimulant use may still influence other long-term outcomes not assessed in our study, such as a lower risk of crime, self-harm, unintentional injury, traffic crashes, and all-cause mortality [231, 232]. Overall, despite beneficial short-term effects, it is likely that childhood stimulant treatment may not have lasting effects on many long-term (> 10 years) functional outcomes, although it might still have a lasting effect on several other outcomes not included in the current study.

Moreover, while using machine learning approaches seems to be a promising avenue for identification of early life predictors for long-term outcomes of ADHD, our findings reflect the complexity of predicting long-term outcomes of ADHD. Both conventional logistic regression and machine learning models in **Chapter 7** were unable to adequately predict ADHD persistence and adult functioning. There are several potential explanations for the lack of positive findings. First, outcomes may have been influenced by the inclusion of many risk factors with small effect sizes and our relatively small sample size. Larger sample sizes and assessment of an even larger number of risk factors might be necessary for building effective prediction models, similar to genome-wide association studies with very large sample sizes which are increasingly able to identify risk loci with small effects. Very large research groups or collaborations are necessary to enable this endeavor, preferably with a broad core set of predictors, potentially through consortia or individual patient data meta-analysis (IPDMA). Second, potentially relevant childhood predictors might have been left out of previous and current studies, complicating accurate prediction of long-term outcomes of ADHD. Potentially relevant environmental predictors missed include early life factors (e.g., peri- and prenatal environment), exposure to environmental toxins, parental factors (e.g., parental psychopathology, parenting style), and social support [204, 212, 213, 277, 278]. However, we did include a large number of supposedly important predictors, encompassing measures across domains of ADHD symptoms and treatment, other psychopathology, cognition, somatic characteristics (e.g., the perinatal factor birth weight), the genetic ADHD PRS, and parental demographics and psychopathology (i.e., parental age at childbirth, and current educational level, ADHD symptoms, and substance use). Including both genetic and additional environmental measures in prediction models may improve predictive accuracy, as gene-environment interactions and correlations seem particularly relevant for understanding heterogeneity in ADHD, and machine learning models are suitable for modelling complex interplays between predictors [46, 279].

Third, although classification has clinical relevance, binary grouping can mask substantial variability within each group and potential similarities between

groups, which can undermine effective prediction. For example, the clusters of adult functioning had clear interpretability and differed on several important measures, but cluster quality was modest with a small distance between clusters, suggesting that some participants in the two clusters might have been close in functioning. Also, up to 60% of all adults with childhood ADHD experience a fluctuating ADHD status throughout adulthood [11]. Thus, for instance, individuals with subthreshold ADHD (remittent ADHD) at one point in time might have a persistent ADHD diagnosis at another point in time and vice versa, while this temporal instability might dilute the binary distinction. Prediction of continuous outcomes (e.g., a weighted sum score of functioning across several domains or number of ADHD symptoms) and taking multiple moments of measurement into account (investigating trajectories) might yield more accurate prediction. Finally, it might be the case that early-life characteristics may not be sufficiently predictive of adult outcomes. This might explain why siblings are not at an increased risk of negative long-term outcomes, despite sharing their genetic material as well as part of their childhood environment, and why the most consistently identified factors associated with adult functioning are more recent factors (e.g., behavioral symptoms, short-term/current medication use).

Despite our low model performances in predicting ADHD persistence and adult functioning, the most influential predictors for both outcomes included anxiety symptoms, autistic traits, and motor coordination problems. Anxiety disorder has previously been implicated as a possible predictor for persistent ADHD through narrative review of fair and good quality studies (**Chapter 5**). However, autistic traits and motor coordination problems seem novel potential predictors for ADHD persistence. Autistic traits/autism spectrum disorder and motor coordination problems/developmental coordination disorder have almost never been included in previous studies as potential predictors for ADHD persistence (**Chapter 5**), despite high overlap between ADHD and these disorders [280, 281]. These predictors should be replicated and externally validated in future studies.

Lastly, investigation of the long-term outcomes of siblings of children with an ADHD diagnosis, who did not receive an ADHD diagnosis in childhood themselves, can provide insight into the role of shared genetics and childhood environment. These siblings typically share half of their genetic material as well as part of their childhood environment [14]. Notably, despite partly shared genetics and a rearing environment, the siblings of children with an ADHD diagnosis (without an ADHD diagnosis in childhood themselves) have little risk of long-term negative outcomes (**Chapter 2** and **Chapter 3**). The siblings included in our follow-up had a higher IQ and less anxiety symptoms compared to the initial sample of siblings at study entry, leaving the possibility that some siblings with the highest risk of negative long-term outcomes have been lost to follow-up. Nonetheless, a potential explanation for the absent risk for negative long-term outcomes in siblings is that, beyond shared familial factors, unique genetic, environmental, and

phenotypic factors, as well as unique gene-environment interactions and correlations influence adult functioning. We did not find evidence for an effect of the common genetic variants underlying ADHD on prediction of long-term outcomes of our ADHD group, as the ADHD PRS had a very small contribution to our prediction models (**Chapter 8**). However, our findings do not rule out unique genetic effects, as the PRS captures only part of the genetic liability [282]. For instance, combining ADHD PRS with the gene sets related phenotypes PRS improved prediction in previous studies, highlighting additional genetic influences beyond ADHD PRS [283]. Beyond additive genetic effects, gene-environment interplay likely contributes to heterogeneity in outcomes, with unaffected siblings being less susceptible to impairment or having more protective factors [94]. Twin studies support the role of unique environmental factors and gene–environment interplay [95, 96]. For example, evocative gene–environment correlations were found where higher ADHD PRS predicted more ADHD symptoms, which in turn predicted worse parenting behaviors, while siblings with less ADHD symptoms may be less likely to evoke these parenting behaviors [92]. This reciprocity between child and parental behavior may result in a negative spiral that can influence future behavioral expressions or functioning. Importantly, gene-environment interactions and correlations remain largely underexplored with respect to long-term outcomes of childhood ADHD, underscoring the need for future research.

Limitations and future directions

The studies included in this thesis provide an extensive overview of the long-term outcomes of adults with childhood ADHD, and currently known predictors thereof. Five out of six chapters were empirical studies using the 18-year follow-up of a cohort study with unique extensive coverage of outcome domains, including the scarcely investigated domains of neurocognitive functioning and physical health. As our cohort study included both males and females, we were able to investigate a double burden of sex and ADHD on the long-term outcomes. Also, we were the first to investigate objectively assessed (i.e., through pharmacy dispensing records) adult medication use and to compare the performance of conventional logistic regression models to advanced machine learning models for prognostic risk estimation in ADHD, which has not been done before in a prospective cohort study of ADHD. Furthermore, our unique design including siblings of adults with childhood ADHD allowed for investigation of long-term outcomes of a group potentially at risk, and hint towards the potential contribution of shared genetic and childhood environmental factors to long-term outcomes. However, the findings of this thesis should be interpreted in the light of some limitations.

Importantly, the findings from the empirical studies are limited in generalizability in terms of diversity, subtype, attrition, and scope. The sample included Caucasian, predominantly cisgendered individuals, while long-term outcomes might differ

for more diverse samples due to differences in healthcare access and cultural and social factors [284, 285]. Also, although successive follow-ups and inclusion of new participants allowed for any type of ADHD, the first inclusion wave of the cohort allowed only for children with combined type ADHD. Few of the newly included children with ADHD in the successive follow-ups had inattentive type ADHD, therefore our results might not apply to adults with childhood inattentive type ADHD given a generally delayed diagnosis and treatment for the inattentive type ADHD which may influence long-term outcomes [8]. Furthermore, as is common in longitudinal studies, attrition was substantial, but selective attrition seems limited, implying the results are mostly generalizable to the initial cohort. The retained childhood ADHD group had worse childhood ADHD severity compared to the initial ADHD group, suggesting the current outcomes bear particular relevance for children with more severe ADHD. Still, the retained groups were similar to the initial cohort in important demographic and behavioral characteristics, suggesting limited selective attrition (see **Chapter 2-4** and **Chapter 6-7**). Also, findings from our sample do not inform on late onset of ADHD, while this group is potentially at highest risk of negative outcomes (Attoe & Climie, 2023; Martin et al., 2025). However, the prospective longitudinal design granted good investigation of the development of ADHD and represented both males and females. To obtain an even more comprehensive overview of long-term outcomes of ADHD, future studies should assess whether outcomes differ across ethnicity, gender, ADHD subtypes, and late-onset ADHD.

Finally, it is important to remark that the findings in this thesis are based on group averages and do not inform on causality. Although the longitudinal design can hint towards a sequence of events, it cannot infer causation and cannot rule out influences of potential moderations and mediators. Similarly, group averages are very useful in identification of overall trends, but these averages mask heterogeneity within the groups (e.g., there was considerable variation in several outcomes with large standard deviations relative to the average scores). Ideally, clinical practice can eventually be informed by individual risk predictions. To achieve individual risk prediction, larger samples are necessary. This can be achieved via the design of a golden standard for studies, including a broad core set of predictors, outcomes, and covariates, while leaving enough room to explore specific outcomes and covariates in individual studies. Individual studies should join consortia and IPDMAs to increase sample size and advance understanding of long-term outcomes of childhood ADHD and its predictors.

Implications

The comprehensive overview of a broad range of long-term outcomes of childhood ADHD and (potential) predictors (**Chapter 2-7**) can inform clinicians on what to communicate concerning adult outcomes of childhood ADHD. Primarily, clinicians should communicate that the development of ADHD into adulthood is

heterogeneous and difficult to predict, but that it is likely the child with ADHD will show typical functioning in adulthood (**Chapter 2** and **Chapter 3**). However, about 36% to 46% of all children with ADHD will show difficulties, with some impairments, in adult functioning, especially in psychiatric status (i.e., a persistent ADHD and MDD diagnosis) and behavioral and emotional problems (e.g., autistic traits) (**Chapter 2** and **Chapter 7**). Clinicians can also inform the siblings of a child with ADHD (who do not have ADHD themselves) that they are generally not at an increased risk for impairments in adult functioning (**Chapter 2** and **Chapter 3**).

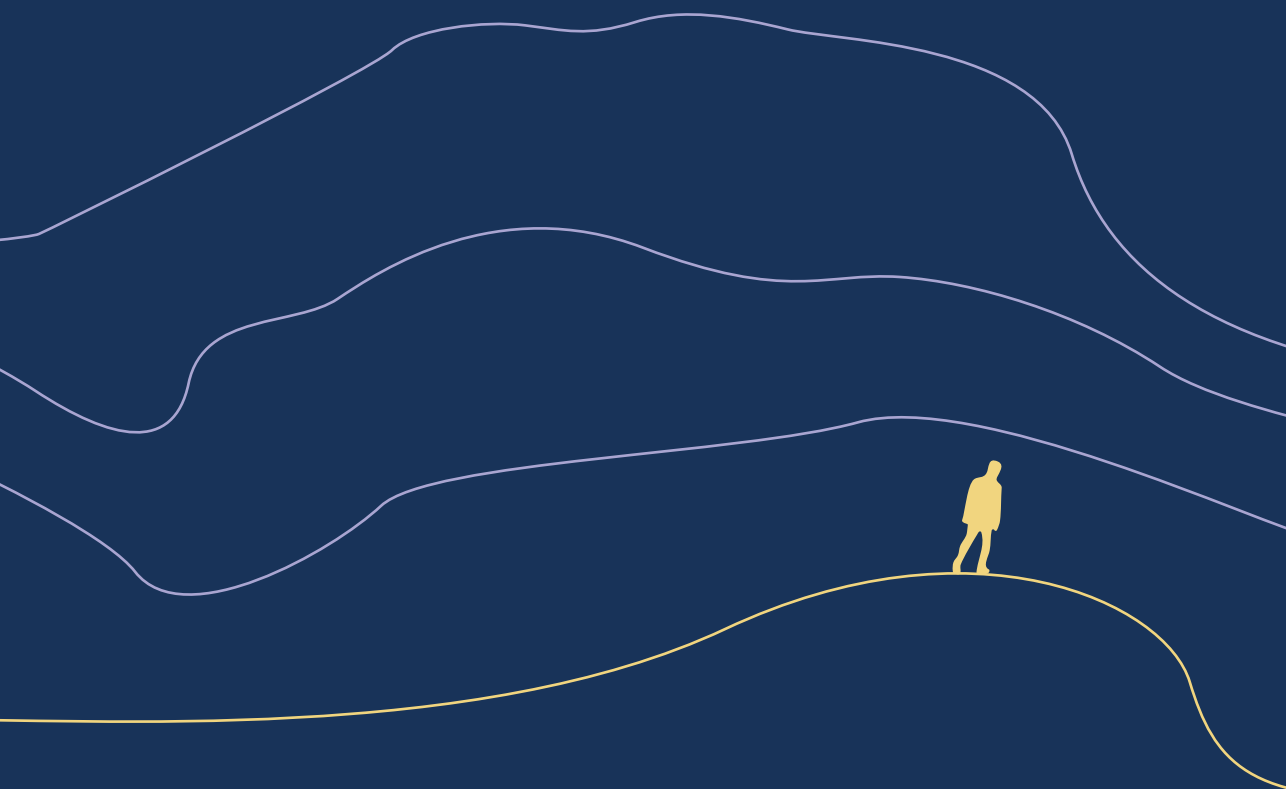
In addition, our findings suggest specific measures for clinicians to consider in the initial assessment, as this can guide prevention and early intervention. We recommend that clinicians should assess levels of anxiety symptoms, autistic traits, and motor coordination problems (**Chapter 7**), persistent ADHD (**Chapter 3** and **Chapter 5**), and MDD (**Chapter 3**), as these measures seem to be related to the largest risks of negative long-term outcomes. Furthermore, social functioning should be assessed, specifically in boys with ADHD, to potentially prevent difficulties in adulthood in social functioning (**Chapter 4**). Our recommendations support current guidelines emphasizing comprehensive initial assessments (i.e., assessments of additional difficulties) and ongoing monitoring of problems [286, 287]. Additionally, future improvements and external validation of prediction models showing acceptable negative predictive value (**Chapter 7**) can potentially be used to identify a group of children that is not at risk of negative long-term outcomes. These models may eventually help guide efficient allocation of resources.

Lastly, our findings, taken together with previous studies, suggest childhood medication use is generally unrelated to long-term functional outcomes (**Chapter 6**). Current guidelines do not address long-term effects of stimulant treatment [286, 287], however, they may include that clinicians need to set clear expectations that stimulant medication is effective in treating current symptoms, including ADHD symptoms and associated behavioral symptoms (e.g., oppositional behavior, aggression), but the evidence regarding sustained benefits on future functioning is inconclusive. Despite beneficial effects up to 3 years, for example on SUD [44], there currently is little evidence of longer (> 10 years) lasting effects of stimulant use.

Key findings and conclusions

- Childhood ADHD is a risk condition for long-term difficulties in daily life functioning, but clinical problems in adulthood are limited.
- While adults with remittent childhood ADHD are still at risk for difficulties in daily life functioning, the risk for difficulties in daily life functioning are higher for adults with persistent childhood ADHD. Furthermore, adults with childhood ADHD can be divided into different groups of functioning, which shows there is heterogeneity in the long-term outcomes of childhood ADHD.
- Generally, siblings of adults with an ADHD diagnosis in childhood, without an ADHD diagnosis in childhood themselves, do not have an increased risk for negative long-term outcomes.
- The elevated risk for negative outcomes in adults with childhood ADHD is not merely explained by shared familial factors but seems attributable to unique genetic, environmental, and phenotypic factors, as well as unique gene-environment interactions and correlations.
- Generally, the sex differences in long-term outcomes of ADHD are not more pronounced in adults with childhood ADHD compared to the general population.
- Only few predictors for long-term outcomes of ADHD were identified in our studies. Our meta-analyses showed that history of stimulant treatment was associated with increased risk of ADHD persistence. In turn, ADHD persistence was associated with increased risk of adult MDD and SUD. Despite low model performance, our prediction models showed that higher levels of anxiety symptoms, autistic traits and motor coordination problems in childhood might be associated with negative long-term outcomes.
- Predicting long-term outcomes of ADHD is complex, but there is potential for early identification of children who are not at risk for negative long-term outcomes via prediction models with acceptable negative predictive values.
- Childhood stimulant treatment is unrelated to functional long-term (>10 years) outcomes in our sample.

APPENDICES



Achtergrond

Langetermijnuitkomsten van ADHD in de kindertijd

Aandachtsdeficiëntie-/hyperactiviteitsstoornis (*attention-deficit/hyperactivity disorder*, ADHD) is een neurologische ontwikkelingsstoornis die vaak begint in de kindertijd. Van de schoolgaande kinderen heeft ongeveer 5.3% ADHD [1, 2]. Echter, ADHD is niet gelimiteerd tot de kindertijd. De ontwikkeling van de stoornis vanuit kindertijd tot de volwassenheid heeft uiteenlopende trajecten [3, 4]. Deze trajecten kunnen variëren van volledige remissie (geen last meer van ADHD) tot persistentie van ADHD met ongunstige gevolgen.

ADHD in de kindertijd lijkt geassocieerd te zijn met negatieve langetermijnuitkomsten op verschillende domeinen, waaronder mentale, sociale en fysieke problemen [16, 17, 28]. Deze negatieve langetermijnuitkomsten hebben een nadelige invloed op de kwaliteit van leven en het dagelijks functioneren. De studies naar de langetermijnuitkomsten van ADHD hebben veelal gekeken naar een beperkt aantal uitkomsten, terwijl het belangrijk is om naar een breed scala aan uitkomsten te kijken om een volledig beeld te kunnen vormen. Ook waren de eerdere studies vaak gebaseerd op steekproeven van voornamelijk mannen uit de Verenigde Staten. Mogelijk verschillen mannen en vrouwen met ADHD in hun langetermijnuitkomsten [5, 6, 30, 31]. Hierdoor is het belangrijk om ook vrouwen te betrekken.

Daarnaast hebben eerdere studies niet gekeken naar de langetermijnuitkomsten van de broers en zussen van kinderen met ADHD. Juist deze groep kan ook een verhoogd risico hebben op negatieve langetermijnuitkomsten. Dit kan komen doordat broers en zussen de helft van hun genetisch materiaal en een deel van de omgeving waarin ze opgroeien delen met elkaar. In de hebben de broers en zussen (zonder ADHD-diagnose) meer ADHD-gerelateerde kenmerken vergeleken met kinderen zonder broer of zus met een ADHD-diagnose [14, 15]. Door naar de langetermijnuitkomsten in deze groep te kijken kunnen we onderzoeken of deze broers en zussen inderdaad een verhoogd risico lopen op negatieve langetermijnuitkomsten. Dit kan wijzen op de mogelijke bijdrage van het gedeelde genetisch materiaal en de omgeving waarin ze opgroeien aan de langetermijnuitkomsten van ADHD.

Voorspellers langetermijnuitkomsten van ADHD in de kindertijd

Tot op heden is informatie over betrouwbare (vroege) voorspellers voor langetermijnuitkomsten van ADHD in de kindertijd schaars. Eén meta-analyse naar de specifieke langetermijnuitkomsten ADHD (symptoom) persistentie liet

zien dat een hogere ADHD-ernst, een farmacologische behandeling voor ADHD, een comorbide gedragsstoornis en depressie in de kindertijd voorspellend waren voor ADHD-persistentie [33]. Er is weinig onderzoek gedaan naar andere mogelijke voorspellers en andere langetermijnuitkomsten dan ADHD-persistentie. Verder waren de studies die wel voorspellers onderzochten qua opzet en resultaten beperkt. Het is belangrijk om voorspellers uit de kindertijd te vinden, omdat deze kunnen bijdragen aan het verlichten van de negatieve langetermijnuitkomsten door het sturen van tijdige preventie en monitoring.

Een mogelijke relevante voorspeller voor de langetermijnuitkomsten van ADHD is een medicamenteuze behandeling met stimulantia in de kindertijd. De behandeling met stimulantia is namelijk de eerstelijns farmacologische behandelingsoptie voor ADHD. Tussen 0,76 en 3,13% van alle kinderen wereldwijd gebruiken stimulantia [35]. Stimulantia is zeer effectief in korte termijn vermindering van ADHD-symptomen, oppositioneel gedrag, agressie, angst en het risico op zelfmoord [38-40, 123]. Hoewel kortetermijneffecten vaak zijn onderzocht, blijven de langetermijneffecten (>10 jaar) onduidelijk [41].

Een andere beperking in de gelimiteerde studies naar voorspellers van langetermijnuitkomsten van ADHD is dat de voorspeller vaak afzonderlijk wordt onderzocht. Hierdoor worden de additieve effecten van meerdere voorspellers samen buiten beschouwing gelaten. Bovendien hebben de meeste onderzoeken conventionele statistische modellen gebruikt, waarbij wordt uitgegaan van lineariteit tussen voorspellers en uitkomsten. Het is juist waarschijnlijk dat uitkomsten bij ADHD moeilijk te voorspellen zijn vanwege de complexe relaties tussen voorspellers en uitkomsten en de interacties tussen voorspellers. In tegenstelling tot conventionele statistische modellen lijken *machine learning* modellen een veelbelovende aanpak om goed te voorspellen. Deze modellen kunnen namelijk wel op passende wijze omgaan met niet-lineaire relaties en interacties [46]. Daarom is het wenselijk om modellen te ontwikkelen die meerdere voorspellers tegelijk meenemen en gebruikmaken van *machine learning* om niet-lineaire relaties en interacties te onderzoeken.

Onderzoeksontwerp

Het doel van dit proefschrift is om meer inzicht te krijgen in de langetermijnuitkomsten van ADHD. Om dat doel te bereiken, is het belangrijk om een breed scala aan uitkomsten te bestuderen (**Deel I, Hoofdstuk 2-4)** en zowel risico- als beschermende factoren van de uitkomsten te identificeren (**Deel II, Hoofdstuk 5-7**). Kennis over de langetermijnuitkomsten kan een goede prognose ondersteunen voor het functioneren op volwassen leeftijd van kinderen met ADHD. Ook kan kennis over risico- en beschermende factoren helpen bij het sturen van vroege preventie- en interventiestrategieën. Op deze manier kunnen we gerichte ondersteuning bieden om negatieve uitkomsten te verlichten.

De studies in dit proefschrift (behalve de systematische review en meta-analyse in **Hoofdstuk 5**) zijn gebaseerd op deelnemers uit de meest recente opvolging van het Nederlandse ADHD-cohort ($M_{leeftijd}$ = 28.84), waarbij de oorspronkelijke groep kinderen ongeveer 18 jaar na de start opnieuw is onderzocht. Zowel ADHD- als controlefamilies deden mee aan het onderzoek. ADHD-families hadden ten minste één kind met ADHD. Daarentegen hadden controlegezinnen ten minste één kind en geen directe familieleden met ADHD. Voor de huidige vervolgmeting in volwassenheid (2022-2024) zijn alle deelnemers van het cohort opnieuw uitgenodigd. We hebben gegevens verzameld via online vragenlijsten en twee videogesprekken. Deze gesprekken bestonden uit een diagnostisch interview en neurocognitieve tests. Daarnaast waren de apotheekafgiftegegevens van de deelnemers opgevraagd bij de apotheken. In totaal zijn er bij de huidige vervolgmeting 51 maten verzameld over 7 domeinen van functioneren: psychiatrische status, gedrags- en emotionele problemen, academisch en professioneel functioneren, adaptief functioneren, neurocognitief functioneren, lichamelijke gezondheid en zorggebruik.

De deelnemers zijn in dit proefschrift ingedeeld in één van de drie groepen gebaseerd op hun ADHD status en familie op moment van instroom in het cohort. De groep met ADHD in de kindertijd bestond uit kinderen met een ADHD-diagnose op het moment van instroom (n = 154). De groep broers en zussen bestond uit kinderen zonder ADHD op het moment van instroom, terwijl ze wel een broer of zus hadden met ADHD (n = 138). Deelnemers in de controlegroep (n = 129) hadden geen ADHD op het moment van instroom, noch broers en zussen met ADHD.

Belangrijkste resultaten

Deel I: Langetermijnuitkomsten van ADHD in de kindertijd

In **Hoofdstuk 2** onderzochten we 51 langetermijnuitkomsten (verdeeld over de 7 domeinen) van kinderen met ADHD, hun broers/zussen zonder ADHD, en controles. Volwassenen met ADHD in de kindertijd scoorden slechter op meer dan 60% van de uitkomsten vergeleken met hun broers/zussen en de controles. De meeste groepsverschillen waren in de domeinen gedrags- en emotionele problemen, adaptief functioneren en neurocognitieve functies. Over het algemeen waren de verschillen klein, met enkele matige en grote verschillen. De matig en grote verschillen betroffen hogere niveaus van ADHD-symptomen, stemmingsproblemen en agressie, een lager opleidingsniveau, slechtere cognitieve functies en een minder gezond dieet bij de groep met ADHD in de kindertijd. De negatieve uitkomsten bleken grotendeels onafhankelijk van een huidige ADHD-diagnose, omdat zowel de groep met een persistente ADHD-diagnose als de groep met een remitterend ADHD-diagnose verschilde van de controles op het merendeel van de uitkomsten. Toch waren de verschillen groter tussen de groep met een persistente ADHD-diagnose en controles dan de groep met een remitterend

ADHD-diagnose. Dat wil zeggen dat de uitkomsten van de groep met persisterende ADHD nadeliger zijn dan voor de groep met remitterende ADHD. De broers en zussen hadden geen verhoogd risico op negatieve uitkomsten, op enkele kleine verschillen na (ADHD-symptomen, BMI, dieet).

Daarna analyseerden we in **Hoofdstuk 3** specifiek medicatiegebruik in de volwassenheid, zoals ADHD-medicatie, andere psychotrope medicatie en somatische medicatie. Van de volwassenen met ADHD in de kindertijd gebruikte slechts 26% ADHD-medicatie als volwassene; hadden 6 tot 8 keer meer kans om ADHD-medicatie te gebruiken en kregen meer verschillende ADHD-medicijnen voorgeschreven vergeleken met zowel hun broers en zussen als de controles. Daarnaast gebruikte 14% van de volwassenen met ADHD in de kindertijd psychotrope medicatie (anders dan ADHD-medicatie). Zij hadden 4 keer zoveel kans om deze medicatie te gebruiken en kregen bovendien meer verschillende soorten psychotrope medicijnen voorgeschreven dan de controlegroep. Ten slotte gebruikte 58% van de volwassenen met ADHD in de kindertijd somatische medicatie. De kans was 3 tot 7 keer groter dat ze neurologische medicijnen gebruikten, met name analgetica (meestal voorgeschreven voor pijnverlichting) en NSAID's (meestal voorgeschreven om ontstekingen en reumatische aandoeningen te behandelen), vergeleken met zowel broers en zussen als controles. De verschillen in medicatiegebruik verdwenen grotendeels na correctie voor een huidige ADHD-diagnose of depressie. Ook hier verschilden medicatiegebruik van de broers en zussen niet van controles.

Om de bevindingen uit **Hoofdstuk 2** op te volgen onderzochten we in **Hoofdstuk 4** of er in de langetermijnuitkomsten verschillen waren tussen mannen en vrouwen met ADHD, of dat deze verschillen vergelijkbaar waren met die in de algemene bevolking. Over het algemeen waren de verschillen tussen mannen en vrouwen vergelijkbaar met verschillen tussen mannen en vrouwen in de algemene populatie; er was geen sprake van een 'dubbele last' van sekse bij ADHD. Dat wil zeggen dat er geen extra nadelige invloed was van sekse boven op een ADHD-diagnose. Deze 'dubbele last' werd alleen gevonden voor sociaal functioneren: mannen met ADHD in de kindertijd hadden problemen in het sociaal functioneren, terwijl vrouwen met ADHD in de kindertijd en controles (mannen en vrouwen) dat niet hadden.

Deel II: Voorspellers van langetermijnuitkomsten van ADHD in de kindertijd

Omdat eerdere hoofdstukken lieten zien dat volwassenen met ADHD in de kindertijd sterk uiteenlopende uitkomsten hebben, variërend van normaal functioneren tot moeilijkheden en beperkingen in het dagelijks leven, hebben we geprobeerd voorspellers uit de kindertijd voor deze uitkomsten te identificeren.

Om eerst in kaart te brengen wat er al bekend was over voorspellers voerden we in **Hoofdstuk 5** een systematische review en meta-analyse uit naar voorspellers van psychiatrische uitkomsten bij volwassenen met ADHD in de kindertijd. De psychiatrische uitkomsten waren ADHD-persistentie, middelenmisbruik, antisociale persoonlijkheidsstoornis, depressie en angststoornissen. We includeerden 36 studies met 119 voorspellers. Hiervan waren 10 voorspellers geschikt voor meta-analyse. Via de meta-analyse vonden we dat stimulantiagebruik in de kindertijd de kans op ADHD-persistentie verdubbelde. Verder hadden volwassenen met persisterende ADHD 2 tot 3 keer meer risico op middelenmisbruik en depressie. Uiteindelijk waren er weinig robuuste voorspellers te vinden, mede door beperkingen in de literatuur, zoals klinische en methodologische heterogeniteit en slechte studie kwaliteit. Deze bevindingen benadrukken de noodzaak voor meer studies naar voorspellers.

Daarna onderzochten we in **Hoofdstuk 6** zelf of stimulantiagebruik in de kindertijd samenhing met de uitkomsten op volwassenheid. Er was van 324 kinderen informatie beschikbaar over het stimulantiagebruik vanaf hun geboorte tot de tweede vervolgmeting van het cohort (12 jaar geleden, $M_{leeftijd}$ = 16.14). Deze informatie bevatte leeftijd van starten met de medicatie, behandelingsduur, totale dosis, maximale dosis, variabiliteit van dosis en leeftijd van stoppen met de medicatie. Door middel van *K-means clustering* konden we drie groepen van medicatiegebruik in de kindertijd identificeren. Er deed maar een deel van de kinderen van de tweede vervolgmeting ook mee aan de vervolgmeting in volwassenheid, dus de drie groepen van medicatiegebruik waren uiteindelijk: vroeg en intensief stimulantia gebruik (n = 48), laat en matig stimulantia gebruik (n = 63) en stimulantia-naïef (n = 34). De drie groepen verschilden nauwelijks op de 51 uitkomstmaten; alleen enkele trendverschillen werden gevonden voor risicoperceptie, cognitieve flexibiliteit en slaapkwaliteit. De groep met vroeg en intensief stimulantia gebruik had de beste gemiddelde groepsscores op risicoperceptie, cognitieve flexibiliteit en slaapkwaliteit. Echter, de verschillen in de groepsgemiddelden hadden geen klinische betekenis. Dit laat zien dat stimulantiagebruik in de kindertijd geen duidelijke risico's of voordelen lijkt te hebben voor het functioneren in volwassenheid.

Als laatste ontwikkelde we in **Hoofdstuk 7** onze eigen voorspellingsmodellen en vergeleken we conventionele logistische regressie met geavanceerde *machine learning* modellen (*ridge regression, support vector machine, random forest, extreme gradient boosting*) om ADHD-persistentie en functioneren in volwassenheid te voorspellen. Om de uitkomsten te voorspellen gebruikten we 21 factoren uit de kindertijd, waaronder ADHD-symptomen en behandeling, comorbiditeit, de polygenetische risicoscore van ADHD, cognitie, somatische kenmerken en informatie over de ouders (bijvoorbeeld opleidingsniveau en ADHD-symptomen). De prestaties van alle modellen waren suboptimaal, maar de conventionele logistische regressie modellen presteerde het beste (AUC .56–.59). Ook het

toevoegen van synthetische data verbeterde de prestaties van de modellen niet. De modellen lieten wel een acceptabele prestatie zien als het gaat om het identificeren van een groep met laag risico op de negatieve uitkomsten. Ondanks dat de prestaties suboptimaal waren werden er een aantal mogelijk relevante voorspellers gesuggereerd, namelijk angstsymptomen, autistische trekken en motorische coördinatieproblemen in de kindertijd. Hogere mate van angstsymptomen, autistische trekken en motorische coördinatieproblemen in de kindertijd hingen samen met een grotere kans op persisterende ADHD en minder gunstig functioneren. Onze bevindingen laten zien dat de geavanceerde *machine learning* modellen de langetermijnuitkomsten van ADHD niet beter konden voorspellen dan de conventionele logistische regressie, zelfs niet met additioneel synthetische data.

Discussie

Allereerst laten onze bevindingen zien dat volwassenen die een diagnose ADHD hebben gekregen in de kindertijd een verhoogd risico hebben op negatieve langetermijnuitkomsten, maar dat hun functioneren ook op veel gebieden vergelijkbaar is met de algemene bevolking (**Hoofdstuk 2** en **Hoofdstuk 3**). Zo was 88% werkzaam, behaalde 94% minimaal een middelbaar opleidingsniveau en had 55% geen ADHD-diagnose meer. De gemiddelde scores van de volwassenen met een ADHD-diagnose in de kindertijd waren vergelijkbaar met de gemiddelde scores van de algemene populatie of onder klinische drempelwaarden die wijzen op probleemniveaus op ADHD-symptomen, externaliserende problemen, middelenmisbruik en stress. Ook medicatiegebruik was laag en vergelijkbaar met de algemene populatie.

Toch kwamen enkele duidelijke risico's naar voren: meer autistische trekken, een verhoogde kans op depressie, en meer gebruik van specifieke subgroepen van medicatie. Daarnaast rapporteerden de volwassenen met ADHD in de kindertijd een lagere kwaliteit van leven, lager sociaal functioneren, meer roken, slechtere slaap en een hogere BMI.

De groep met een persisterende ADHD-diagnose had meer moeilijkheden dan de groep met een remitterende ADHD-diagnose. Zo had de groep met een persisterende ADHD-diagnose onder andere hogere scores op ADHD-symptomen, autistische trekken, internaliserende en externaliserende problemen, roken, stress, kwaliteit van leven, sociaal functioneren en slaapproblemen vergeleken met de groep met een remitterende ADHD-diagnose. Daarnaast konden we met behulp van clusteranalyses twee groepen van functioneren identificeren: één met gunstig functioneren en één met minder gunstig functioneren (**Hoofdstuk 7**). Persisterende ADHD kwam vaker voor in de minder gunstige groep, maar ook in de gunstige groep waren volwassenen met persisterende ADHD aanwezig. Dit laat zien dat er naast een persisterende ADHD-diagnose nog meer factoren van belang

zijn als het gaat om heterogeniteit in de uitkomsten. Aangezien de verschillen tussen mannen en vrouwen met ADHD vergelijkbaar waren met die in de algemene populatie lijkt het er niet op dat sekse een factor onderliggend aan de heterogeniteit (**Hoofdstuk 4**).

Ondanks de deels gedeelde genetische en omgevingsfactoren van de broers en zussen van kinderen met ADHD in de kindertijd had deze groep over het algemeen geen verhoogd risico op negatieve langetermijnuitkomsten (**Hoofdstuk 2** en **Hoofdstuk 3**). Een mogelijke verklaring hiervoor is dat het verhoogde risico op negatieve uitkomsten bij volwassenen met ADHD in de kindertijd niet verklaard lijkt te worden door de gedeelde familiale factoren, maar wellicht toe te schrijven is aan unieke genetische, omgevings- en fenotypische factoren, evenals aan unieke gen-omgevingsinteracties en correlaties.

Als laatste bleek het complex om (unieke) vroege voorspellende factoren te identificeren (**Hoofdstuk 5-7**). Stimulantiagebruik in de kindertijd was niet gerelateerd aan langetermijnuitkomsten (**Hoofdstuk 6**) en onze voorspellingsmodellen waren niet goed in staat om de langetermijnuitkomsten te voorspellen (**Hoofdstuk 7**). Desalniettemin hebben onze voorspellingsmodellen enige aanwijzingen gevonden voor een aantal mogelijk belangrijke voorspellers, namelijk angstsymptomen, autistische trekken en motor coördinatieproblemen in de kindertijd.

Implicaties

Onze bevindingen hebben verschillende implicaties voor de klinische praktijk. Het uitgebreide overzicht van een breed scala aan langetermijnuitkomsten van ADHD bij kinderen en potentiële voorspellers hiervan kan clinici informeren over wat ze kunnen communiceren over de langetermijnuitkomsten van ADHD. De belangrijkste boodschap is dat de ontwikkeling naar volwassenheid heterogeen is en moeilijk te voorspellen. Dit wil zeggen dat er een groep is die in de volwassenheid gemiddeld zullen functioneren (**Hoofdstuk 2** en **Hoofdstuk 3**). Wel is er verhoogd risico op blijvende moeilijkheden, vooral psychiatrische stoornissen (persistente ADHD, een depressieve stoornis) en gedrags- en emotionele problemen (zoals autistische trekken). Broers en zussen zonder ADHD lopen doorgaans geen extra risico op problemen in het functioneren als volwassene.

We adviseren dat clinici extra aandacht hebben voor angstsymptomen, autistische trekken, motorische problemen, persisterende ADHD, depressie en sociale problemen (vooral bij jongens; **Hoofdstuk 2-5, Hoofdstuk 7**) tijdens de eerste beoordeling. Ook is eventuele monitoring van deze problemen gewenst om preventie en vroege interventies te sturen. Deze aanbevelingen sluiten aan bij bestaande richtlijnen [286, 287].

Ten slotte suggereren onze bevindingen, samen met eerdere studies, dat medicijngebruik tijdens de kindertijd over het algemeen niet samenhangt met functionele langetermijnuitkomsten (**Hoofdstuk 6**). De huidige richtlijnen gaan niet in op de langetermijneffecten van behandeling met stimulerende middelen [286, 287]. Ons advies is om in de ADHD-behandelrichtlijnen op te nemen dat clinici duidelijke verwachtingen moeten scheppen over stimulantiagebruik zoals methylfenidaat, waarbij evidentie is dat stimulantia effectief kan zijn binnen de behandeling van ADHD voor het doen afnemen van ADHD-symptomen, maar dat het bewijs voor blijvende voordelen op toekomstig functioneren (> 10 jaar) niet eenduidig is.

Kernbevindingen van dit proefschrift

- ADHD in de kindertijd is gerelateerd aan een verhoogd risico op langdurige functionele problemen, maar klinische problemen op volwassen leeftijd blijven meestal beperkt.
- Hoewel volwassenen met een remitterende ADHD-diagnose ook risico lopen op moeilijkheden bij het functioneren in het dagelijks leven, is het risico op moeilijkheden bij het functioneren in het dagelijks leven groter voor volwassenen met een persisterende ADHD-diagnose. Bovendien kunnen volwassenen met ADHD in de kindertijd worden onderverdeeld in verschillende groepen van functioneren, wat laat zien dat er heterogeniteit bestaat in de langetermijnuitkomsten van ADHD in de kindertijd.
- Over het algemeen lopen de broers en zussen (zonder ADHD in de kindertijd) van volwassenen met ADHD in de kindertijd geen verhoogd risico op negatieve langetermijnuitkomsten.
- Het verhoogde risico op negatieve uitkomsten bij volwassenen met ADHD in de kindertijd lijkt niet verklaard te worden door gedeelde familiale factoren, maar lijkt toe te schrijven aan unieke genetische, omgevings- en fenotypische factoren, evenals aan unieke gen-omgevingsinteracties en correlaties.
- Over het algemeen zijn de sekseverschillen in de langetermijnuitkomsten van ADHD niet meer uitgesproken bij volwassenen met ADHD in de kindertijd dan bij de algemene bevolking.
- Er zijn slechts enkele voorspellers voor de langetermijnuitkomsten van ADHD geïdentificeerd. Uit onze meta-analyses bleek dat een voorgeschiedenis van stimulantiagebruik geassocieerd was met een verhoogd risico op ADHD-persistentie. Daarnaast werd ADHD-persistentie geassocieerd met een verhoogd risico op depressie en verslaving. Ondanks de suboptimale modelprestaties lieten onze voorspellingsmodellen zien dat hogere niveaus van angstsymptomen, autistische kenmerken en motorische coördinatieproblemen in de kindertijd geassocieerd kunnen zijn met negatieve langetermijnuitkomsten.
- Het voorspellen van de langetermijnuitkomsten van ADHD is complex, maar er lijkt potentie voor vroege identificatie van kinderen die geen risico lopen op negatieve langetermijnuitkomsten op basis van voorspellingsmodellen met aanvaardbare negatieve voorspellende waarden.
- Stimulantiagebruik in de kindertijd is in onze steekproef niet gerelateerd aan functionele langetermijnuitkomsten (>10 jaar later).

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Author contributions

Chapter 2	**Growing up with ADHD: findings from an 18-year longitudinal follow-up study of adults with childhood ADHD, their siblings, and controls**
Authors involved:	NE van der Plas (NP), SDS Noordermeer (SN), B Franke (BF), CA Hartman (CH), PJ Hoekstra (PH), NNJ Rommelse (NR), E Sprooten (ES), M Luman (ML), J Oosterlaan (JO)
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Chapter 3	**Psychotropic and somatic medication use in adults with childhood ADHD, their siblings, and controls: a prospective long-term longitudinal study**
Authors involved:	NE van der Plas (NP), SDS Noordermeer (SN), B Franke (BF), CA Hartman (CH), PJ Hoekstra (PH), NNJ Rommelse (NR), E Sprooten (ES), PM Bet (PB), M Luman (ML), J Oosterlaan (JO)
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Chapter 4	**Differences between males and females in long-term outcomes of ADHD**
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	Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.
Chapter 5	**Systematic review and meta-analysis: predictors of adult psychiatric outcomes of childhood ADHD**
Authors involved:	NE van der Plas (NP), SDS Noordermeer (SN), J Oosterlaan (JO), M Luman (ML)
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Chapter 6	**Long-term outcomes of childhood ADHD stimulant use trajectories**
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Chapter 7	**From childhood to adulthood: an attempt to model long-term outcomes of ADHD using machine learning**
Authors involved:	NE van der Plas (NP), FC Bennis (FB), B Franke (BF), CA Hartman (CH), PJ Hoekstra (PH), A Nijmeijers (AN), LA Oblong (LO), NNJ Rommelse (NR), E Sprooten (ES), M Luman (ML), J Oosterlaan (JO), SDS Noordermeer (SN)
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About the author

Noa van der Plas was born on April 9, 1998 in Evanston (the United States). In 2016 she completed her bilingual atheneum education ('Tweetalig Onderwijs', TTO) at Visser 't Hooft Lyceum in Leiden. As she was very interested in human behavior and determinants thereof, she completed the bachelor Psychology, with a minor in Genes, Brain, and Behaviour (Vrije Universiteit Amsterdam, 2019). She became intrigued with scientific research and biological psychology and enrolled in the Research Master Genes in Behaviour and Health (Vrije Universiteit Amsterdam).

For her first research internship, she investigated the biological mechanisms of aggression by evaluating genetic correlations of aggression, subcortical brain volumes, and metabolites (Biological Psychology, Vrije Universiteit Amsterdam). In her second research internship, she conducted an exposome-wide association study on depression, using data from the UK Biobank (Epidemiology, University of Oxford). Additionally, she worked as a research assistant at the Netherlands Twin Registry, where she helped with data collection of DNA material and disseminated scientific publications to the research participants. Throughout her master's degree, Noa developed a passion for using rich datasets and advanced statistical techniques to investigate human behavior and mental disorders and obtained her Research Master's degree in 2021 (cum laude).



Thereafter, she started as a PhD candidate at the department of Clinical Neuropsychology (Vrije Universiteit Amsterdam). Within this project she coordinated a follow-up of a large cohort study (NeuroIMAGE), aiming to investigate the long-term outcomes of adults with ADHD diagnosed in childhood, their siblings, and controls, and predictors thereof. Currently, Noa works as a postdoctoral researcher at the department of Molecular Epidemiology at the LUMC. At the LUMC she is investigating the mechanisms of how partnership into long-lived families is associated with healthy aging, using longitudinally collected data from the Leiden Longevity Study and data from Statistics Netherlands.

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