Örebro Studies in Medicine 283

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Attention-Deficit/Hyperactivity Disorder (ADHD) beyond the Young Age

Investigation of the Prevalence of ADHD in Older Adults and the Risk of Age-related Disorders

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Title: Attention-Deficit/Hyperactivity Disorder (ADHD) beyond the Young Age, Investigation of the Prevalence of ADHD in Older Adults and the Risk of Age-related Disorders

Publisher: Örebro University, 2023
www.oru.se/publikationer

Print: Örebro University, Repro, September 2023
ISSN: 1652-4063
ISBN: 978-91-7529-512-1 (print)
ISBN: 978-91-7529-513-8 (pdf)

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by impairing levels of inattention and/or hyperactivity-impulsivity. Symptoms of ADHD, which typically emerge in childhood, may persist until older age with a substantial adverse impact on health and functionality. Yet there is a notable knowledge gap in research on ADHD in older age and the potential associations of adult ADHD with disorders that are common in older age (i.e., age-related disorders). Thus, this thesis aimed to investigate the prevalence rates of ADHD in older age and whether ADHD in adulthood is associated with an increased risk of age-related disorders.

Study I, a systematic review and meta-analysis, suggests that a considerable number of older adults report elevated levels of ADHD symptoms, while the prevalence of treated ADHD is less than half of the prevalence of clinically diagnosed ADHD. In Studies II, III, and IV, we used data from Swedish population registers. We found that ADHD is associated with an increased risk of dementia and mild cognitive impairment (Study II), which substantially attenuates after controlling for psychiatric comorbidity. Further, ADHD symptoms in adulthood are associated with an increased risk of subsequent cardiometabolic disorders (Study III). The associations attenuate after controlling for educational attainment, psychiatric comorbidity, and lifestyle factors, and they are confounded by genetic factors. Finally, the prediction of cardiovascular risk in adults initiating pharmacological treatment for ADHD may improve by considering novel risk factors (i.e., psychiatric comorbidity and use of other psychotropic medications) in addition to traditional predictors (Study IV).

Overall, the findings indicate that a substantial number of older adults have increased levels of ADHD symptoms and that ADHD in adults is associated with an increased risk of age-related disorders. Further longitudinal studies, based on both community samples and epidemiological data, are needed to explore the risk of age-related disorders in ADHD, and the underlying mechanisms, until a more advanced older age.

Keywords: ADHD, prevalence, comorbidity, functional impairments, older adults, age-related disorders, dementia, mild cognitive impairment, cardiometabolic disorders, prediction model

“Ne mogu ja - kaže - dobri čovječe, ozdraviti, jer ja i nisam bolestan, nego sam ovakav, a od sebe se ne može ozdraviti.”

- Ivo Andrić, Prokleta avlija

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List of Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ICD	International Statistical Classification of Diseases and Related Health Problems
WHO	World Health Organization
DSM	Diagnostic and Statistical Manual of Mental Disorders
APA	American Psychiatric Association
EPA	European Psychiatric Association
ASRS	Adult ADHD Self-Report Scale
DIVA	Diagnostic Interview for ADHD in adults
CBT	Cognitive behavioral therapy
GWAS	Genome-wide association study
MCI	Mild cognitive impairment
CVD	Cardiovascular disease
AD	Alzheimer's disease
DLB	Dementia with Lewy bodies
IHD	Ischemic heart disease
ECG	Electrocardiogram
NICE	National Institute for Health and Care Excellence
T2D	Type 2 Diabetes Mellitus
PIN	Personal Identity Number
TPR	Total Population Register
NPR	National Patient register
NBHW	National Board of Health and Welfare

CDR	Cause of Death Register
PDR	Prescribed Drug Register
ATC	Anatomical Therapeutic Classification
LISA	Longitudinal integration database for health insurance and labour market studies register
MGR	Multigenerational Register
STR	Swedish Twin Registry
STAGE	Study of Twin Adults: Genes and Environment
SD	Standard deviation
BMI	Body Mass Index
HR	Hazard ratio
CI	Confidence interval
AUC	Area under the curve
ROC	Receiver operating characteristic curve
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
PPV	Positive predictive value
NPR	Negative predictive value
NRI	Net Reclassification Index
IDI	Integrated Discrimination Improvement Index
GDPR	General Data Protection Regulations
RCT	Randomized controlled clinical trial

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Dobrosavljevic, M., Solares, C., Cortese, S., Andershed, H. & Larsson, H. (2020). Prevalence of attention-deficit/hyperactivity disorder in older adults: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, 118, 282-289. doi: 10.1016/j.neubiorev.2020.07.042.

II. Dobrosavljevic, M., Zhang, L., Garcia-Argibay, M., Du Rietz, E., Andershed, H., Chang, Z., Faraone, S. & Larsson, H. (2021). Attention-deficit/hyperactivity disorder as a risk factor for dementia and mild cognitive impairment: a population-based register study. *European psychiatry*, 65 (1), 1-19. doi: 10.1192/j.eurpsy.2021.2261

III. Dobrosavljevic, M., Larsson, H., Kuja-Halkola, R., Brikell, I., Li, L., Chang, Z. & Du Rietz, E. Attention-deficit/hyperactivity disorder symptoms and subsequent cardiometabolic disorders in adults: investigating underlying mechanisms using a longitudinal twin study. (Submitted)

IV. Dobrosavljevic, M., Fazel, S., Du Rietz, E., Li, L., Zhang, L., Chang, Z., Jernberg, T., Faraone, S. V., Jendle, J., Chen, Q., Brikell, I. & Larsson, H. (2022). Risk prediction model for cardiovascular diseases in adults initiating pharmacological treatment for attention-deficit/hyperactivity disorder. *Evidence-Based Mental Health*, 25, 185-190. doi:10.1136/ebmental-2022-300492.

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Related publications

(Not included in the thesis)

I. Solares, C., Dobrosavljevic, M., Larsson, H., Cortese, S. & Andershed, H. (2020). The mental and physical health of older offenders: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, 118, 440-450. doi: 10.1016/j.neubiorev.2020.07.043.

II. Zhang, L., Du Rietz, E., Kuja-Halkola, R., Dobrosavljevic, M., Johnell, K., Pedersen, N. L., Larsson, H. & Chang, Z. (2022). Attention-deficit/hyperactivity disorder and Alzheimer's disease and any dementia: A multi-generation cohort study in Sweden. *Alzheimer's & Dementia*, 18 (6), 1155-1163. doi:10.1002/alz.12462.

III. Li, L., Chang, Z., Sun, J., Garcia-Argibay, M., Du Rietz, E., Dobrosavljevic, M., Brikell, I., Jernberg, T., Solmi, M., Cortese, S. & Larsson, H. (2022). Attention-deficit/hyperactivity disorder as a risk factor for cardiovascular diseases: a nationwide population-based cohort study. *World Psychiatry*, 21 (3), 452-459. doi: 10.1002/wps.21020.

IV. Solares, C., Garcia-Argibay, M., Chang, Z., Dobrosavljevic, M., Larsson, H. & Andershed, H. (2023). Risk of dementia and mild cognitive impairment in older adults with a criminal background: a population-based register study in Sweden. *Scientific Reports*, 13 (1). doi: 10.1038/s41598-023-28962-w

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset neurodevelopmental disorder characterized by impairing and age-inappropriate levels of inattention and/or hyperactivity-impulsivity (Faraone et al., 2015). ADHD is a highly heritable condition, with a heritability in adults as high as 70-80%, with one third of heritability being due to a polygenic component (Brikell, Kuja-Halkola, & Larsson, 2015; Faraone & Larsson, 2019). Despite genetic factors playing a major role in the etiology of ADHD, environmental factors and gene-environment interactions may increase the risk of developing ADHD as well (Banerjee, Middleton, & Faraone, 2007).

It is estimated that ADHD affects about 5% of children and adolescents, and about 2.5% of adults worldwide (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). Although it is estimated that ADHD symptoms persist until adulthood in a substantial number of affected individuals, ADHD is far less studied in older adults (Torgersen, Gjervan, Lensing, & Rasmussen, 2016). If left untreated, ADHD can have major and long-lasting negative social, educational, and occupational outcomes (Fayyad et al., 2017). Additionally, a substantial number of psychiatric comorbidities in ADHD (e.g., substance use disorder, depression, anxiety disorders., etc.) have been well documented both in children and adults (Faraone et al., 2021; Fayyad et al., 2017; Sobanski, 2006). It has also been well documented that ADHD is associated with several non-psychiatric health issues, such as obesity, sleep disorders and asthma (Instanes, Klungsøyr, Halmøy, Fasmer, & Haavik, 2018). Furthermore, emerging research has suggested that ADHD is associated with an increased risk of developing age-related disorders, such as dementia (Fluegge & Fluegge, 2018; Golimstok et al., 2011; Tzeng et al., 2019) and cardiometabolic disorders (e.g., hypertension, ischemic heart disease, heart failure, type 2 diabetes, etc.) (M.-H. Chen et al., 2018; Q. Chen et al., 2018; Du Rietz et al., 2021). However, relevant studies are notably scarce and have mixed findings.

With a continuing rise of the proportion of older aged individuals globally (He, Goodkind, & Kowal, 2016), and the increasing impact of age-

related disorders (Nichols et al., 2022; Roth et al., 2020), more research on the potential risk factors underlying the development of these disorders in ADHD is warranted. The current thesis aimed to expand the knowledge on the prevalence of ADHD in older adults and the potential increased risk of developing age-related disorders in adults with ADHD. This was done via a systematic review and meta-analysis (Study I) and by using large-scale population-based data from Sweden (Studies II, III and IV). The acquired knowledge can provide useful insights to clinicians in relation to proper health care of ADHD in older adults, and on developing corresponding prevention programs for age-related disorders earlier in life.

Background

Diagnostic assessment of ADHD

Although the contemporary concept of ADHD, as defined by current diagnostic systems, is relatively new, the typical features of ADHD of inattention, excessive motor activity and impulsiveness, have been described and recognized in medical and scientific literature since the late 18th century (Faraone et al., 2021). Currently, a diagnosis of ADHD can be established according to two classification systems, the International Statistical Classification of Diseases and Related Health Problems (ICD), issued by the World Health Organization (WHO), commonly used in Europe and other regions outside of the USA, and the Diagnostic and Statistical Manual of Mental Disorders (DSM), issued by the American Psychiatric Association (APA), predominantly used in the USA.

According to the latest, 11th revision of the ICD (ICD-11), published in 2019, ADHD is classified under Neurodevelopmental disorders, and referred to as Attention deficit hyperactivity disorder, while in the previous version, ICD-10, it was classified under: "Behavioural and emotional disorders with onset usually occurring in childhood and adolescence", under Hyperkinetic disorders (World Health Organization [WHO], 2019). The ICD-11 requires symptoms of inattention and/or hyperactivity-impulsivity to be persistent (i.e., last at least 6 months), with an impairing effect on academic, social, or occupational functioning, and across multiple settings (e.g., school, home, work, etc.), and it requires evidence of significant symptoms before age 12, while earlier versions of ICD required an early onset of symptoms, usually in the first five years of life. The ICD-11 recognizes three presentation categories of ADHD: (i) ADHD with the predominantly inattentive presentation, (ii) ADHD with the predominantly hyperactive-impulsive presentation, and (iii) combined presentation.

According to the latest, fifth version of DSM (DSM 5) (American Psychiatric Association [APA], 2013), ADHD is, as in the ICD 11, classified under Neurodevelopmental disorders, and it is defined as a persistent pattern (i.e., symptoms lasting at least 6 months) of inattention and/or

hyperactivity-impulsivity, which interferes with development or functioning in at least two settings (i.e., social, occupation or educational). This definition of ADHD requires at least 6 symptoms of inattention and/or hyperactive/impulsive behavior to be present in children and younger adolescents, or at least 5 symptoms of either or both domains to be present in individuals aged 17 and older, with several inattentive or hyperactive-impulsive symptoms to be present before age 12. In contrast, the DSM-IV required onset of symptoms and impairment by the age 7, and at least 6 symptoms to be present in older adolescents and adults. According to both ICD and DSM criteria, diagnoses of other psychiatric disorders and/or use of a substance/medication need to be excluded as potential causes of the symptoms. With the latest versions of DSM and ICD, there has been a shift in diagnostic criteria towards more recognition and inclusivity of adults and older adults who experience impairing levels of symptoms of ADHD and who are in need of health care, but do not fulfill the criteria based on the earlier versions of these classification systems (Doernberg & Hollander, 2016; Epstein & Loren, 2013). Additionally, ICD-11 or DSM 5 no longer consider autism spectrum disorders (ASD) as an exclusionary diagnosis (APA, 2013; Doernberg & Hollander, 2016; Epstein & Loren, 2013; WHO, 2019).

Symptoms of inattention are manifested as difficulty concentrating and sustaining attention without immediate rewards, forgetfulness, difficulties in planning activities, and being easily distracted; while symptoms of hyperactivity/impulsivity are commonly manifested as excessive motor activity, talking too much, interrupting others and a tendency to act without thinking. However, the clinical presentation of ADHD may change with age, and it may differ between men and women. For instance, symptoms of hyperactivity may decrease with age, and instead, feelings of restlessness and inattentiveness may become prevalent. Further, ADHD is more prevalent in males than females, with a roughly two-to-one male to female ratio in youth (Willcutt, 2012). Clinical presentation of ADHD in girls and women is more commonly characterized by internalizing symptoms (i.e., inattention) than externalizing symptoms (i.e., hyperactivity and impulsivity), and it is more often considered a "subthreshold" by clinicians (Quinn & Madhoo, 2014). Furthermore, it has been suggested that females with

ADHD may develop coping strategies, which mask the symptoms of ADHD and their functional impact (Quinn & Madhoo, 2014). Additionally, in some women with ADHD clinicians may fail to establish a diagnosis of ADHD due to frequent comorbid symptoms of anxiety and depression.

The diagnosis of ADHD is established through a comprehensive diagnostic assessment within specialist healthcare services in Sweden (National Board of Health and Welfare [NBHW], 2022). In general, diagnostic assessment is based on information from self-report, parents/relatives/spouses, and teachers, and sometimes, documents/school records (National Institute for Health and Care Excellence [NICE], 2019). The Updated European Consensus Statement on diagnosis and treatment of adult ADHD (Kooij et al., 2019) issued by the European Psychiatric Association (EPA), has provided guidelines in relation to clinical presentation, proper diagnosis, and treatment of ADHD in adults. They recommend screening for ADHD in adults with a history of inattentiveness, hyperactivity/impulsivity, and emotion dysregulation; adults with family members with a diagnosis of ADHD; and in those with a history of other mental health disorders, behavioral problems, and/or criminality.

A screening tool, with 18 or 6 self-report items, has been developed to assess ADHD symptoms in adults, in accordance with the DSM-IV criteria: Adult ADHD Self-Report Scale (ASRS) (Kessler et al., 2005), and updated according to the DSM-5 criteria (Ustun et al., 2017). For the diagnostic assessment of ADHD in adults, several instruments are recommended: the Diagnostic Interview for ADHD in adults (DIVA), based on the DSM-IV-TR and DSM-5 criteria (Kooij, Francken, Bron, & Wynchank, 2010), and the Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAADID), according to the DSM-IV criteria (Ramos-Quiroga et al., 2012). Among ADHD screening tools and diagnostic interviews for adults, only a screening list with nine questions developed by Barkley and Murphy (Barkley, Murphy, & Fischer, 2010) has been validated in older adults (aged 60 to 94 years) against a structured diagnostic interview (DIVA 2.0) (Kooij, Michielsen, Kruithof, & Bijlenga, 2016). The screening list has shown good sensitivity (0.80)

and specificity (0.77), but only a moderate test-retest validity with an intraclass correlation of 0.56.

A full medical and family history of other psychiatric and somatic disorders needs to be taken, with collateral information from a spouse or other family member (Kooij et al., 2019). Functional impairment in at least two settings (i.e., relationships, school, work, etc.) and confirmation of childhood-onset of the symptoms are also required. Nevertheless, some authors argue that the validity of the age-of-onset criterion in older adults needs to be investigated (Sharma, Lavoie, & Callahan, 2021). Firstly, there may be substantial issues with the retrospective assessment of childhood symptoms at a later age due to unreliable memory linked to aging or ADHD, more specifically. Secondly, symptoms of ADHD may remain undetected or not fully manifested in some individuals during their earlier life due to compensative cognitive/behavioral strategies, low socio-economic status and poor access to health care, or in some instances, protective family/educational/occupation environments which are well structured or flexible enough to mask the symptoms of ADHD. Increasing functional demands in social or work conditions during adulthood or older age may lead to experiencing impairing levels of ADHD symptoms in these individuals, when they would seek professional help (Sharma et al., 2021). Finally, with ADHD being a relatively new clinical concept, it is possible that symptoms were not recognized in older adults during their childhood, which may impede establishing a diagnosis in adulthood and allowing proper healthcare to these individuals.

Prevalence of ADHD across the lifespan

Based on the findings of systematic reviews and meta-analyses, pooled worldwide prevalence estimates of ADHD have been estimated at 5.3% (95% Confidence intervals (CI) = 5.0, 5.6) (Polanczyk et al., 2007) to 7.2% (95% CI = 6.7, 7.8) in children and adolescents (Thomas, Sanders, Doust, Beller, & Glasziou, 2015) and 2.5% (95% CI = 2.1, 3.1) in adults (Simon et al., 2009). The prevalence estimates are highly heterogeneous, mostly due to methodological differences of included studies, such as: (i) applied diagnostic criteria, with lower prevalence estimates based on ICD-10 and DSM-III compared to DSM-IV criteria, (ii) application of

impairment criterion, with lower prevalence estimates when impairment criterion was used, and (iii) source of information, with self-reports substantially underestimating the persistence of ADHD compared to parent reports in young adults (Barkley, Fischer, Smallish, & Fletcher, 2002; Polanczyk et al., 2007; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Persistence rates of ADHD from childhood to adulthood, based on prospective studies, vary substantially as well, ranging from 5 to 76% of affected individuals (Caye et al., 2016). The striking variability in persistence rates of ADHD from childhood to adulthood comes from methodological differences across studies, and these are, for instance, changes in diagnostic criteria over time, differences in durations of follow-up and age at follow-up, and whether criteria of functional impairment and childhood onset of symptoms were applied (Caye et al., 2016).

Furthermore, most of the studies on ADHD do not include adults aged 50 and older. One of the potential reasons for not considering or excluding this age group is the risk of recall bias of childhood symptoms (Kessler et al., 2005) or misclassification as mild cognitive impairment (MCI), which is common in older age and similar to ADHD in its clinical presentation (Goodman, Mitchell, Rhodewalt, & Surman, 2016; Pollak, 2012). A systematic review that investigated the prevalence of ADHD in adults aged 50 and older (Torgersen et al., 2016) identified only four relevant studies that reported a prevalence ranging from 1.0% to 6.2%. However, these findings have not been properly synthesized (i.e., by applying a meta-analysis). Furthermore, included studies were not restricted to those aged 50 and older, and they were limited to research diagnosis of ADHD symptoms (i.e., by using validated scales to assess symptoms of ADHD in community samples), while the prevalence of ADHD clinical diagnosis or treatment has not been considered. The authors (Torgersen et al., 2016) concluded that, although there are indications that the prevalence of ADHD decreases with age, the overall health problems and ADHD medication side effects may become more serious after the age of 65. This may indicate that even though the number and severity of symptoms may decrease with age, their effects remain significant. More research is needed to identify relevant studies on the prevalence of ADHD in older adults (i.e., adults aged 50 and older), considering different assessment methods of ADHD.

Additionally, the results of these studies need to be properly synthesized through a meta-analysis to provide pooled prevalence estimates of ADHD in this age group.

Treatment of ADHD

The Updated European Consensus Statement on diagnosis and treatment of adult ADHD recommends a multimodal and multidisciplinary approach to the treatment of ADHD, consisting of psychoeducation to increase knowledge on ADHD as a first step, followed by pharmacotherapy and psychotherapy (Kooij et al., 2019). Psychotherapy (e.g., cognitive behavioral therapy (CBT)) is recommended as adjacent to pharmacotherapy (Kooij et al., 2019). Additionally, treatment seeking in adults with ADHD is usually targeted towards comorbid conditions rather than ADHD itself (Fayyad et al., 2017); thus, comorbid conditions and symptoms should be addressed as part of a comprehensive treatment and management of ADHD. Pharmacological treatment usually consists of treatment with central nervous system stimulants (e.g., amphetamine ATC code N06BA01, dexamphetamine ATC code N06BA02, and methylphenidate ATC code N06BA04) and non-stimulant medication (e.g., atomoxetine, ATC code N06BA09). In Sweden, the most commonly prescribed ADHD medication is methylphenidate, followed by atomoxetine, while amphetamine and dexamphetamine are less commonly prescribed (Zetterqvist, Asherson, Halldner, Långström, & Larsson, 2013a). Both stimulants and atomoxetine have been shown to be effective in ADHD symptom reduction and may have long-term benefits (Faraone & Glatt, 2009).

The most common adverse effects of ADHD medication in all age groups are sleep problems, reduced appetite, and increased heart rate and blood pressure, although more serious cardiovascular events, such as stroke or ischemic heart disease (IHD), are rare (Cooper et al., 2011; Kooij et al., 2019). Additionally, a recent meta-analysis has found no statistically significant associations between ADHD medication use and cardiovascular diseases (Zhang, Yao, et al., 2022). Nonetheless, certain clinical precautions are recommended when it comes to ADHD medication prescriptions, particularly in older adults, due to the high comorbidity of ADHD with other psychiatric and physical disorders,

and potential interactions with other medications (Brod, Schmitt, Goodwin, Hodgkins, & Niebler, 2012; Goodman, Mitchell, Rhodewalt, & Surman, 2016; Kooij et al., 2019; Lensing, Zeiner, Sandvik, & Opjordsmoen, 2015). Upon initiating ADHD pharmacological treatment, a comprehensive physical assessment is recommended, with the assessment of height, weight, pulse, blood pressure, and cardiovascular assessment and obtaining a medical history of conditions/medication use, which may increase cardiovascular risk (NICE, 2019). Electrocardiogram (ECG) is recommended only in those with a medical history of cardiovascular disorders, a family history of sudden death in a first-degree relative before age 40 suggesting a cardiac disease, in those with a comorbid condition treated with medication associated with an increased cardiac risk (NICE, 2019) and in people older than 50 years of age (Kooij et al., 2016). Additionally, it is recommended to monitor relevant measures at least twice a year during treatment (Kooij et al., 2019).

Current evidence on the safety and efficacy of ADHD medication in older adults is scarce. Although several observational studies have indicated that pharmacological treatment may be safe and effective in treating ADHD in this age group (Brod et al., 2012; Lensing et al., 2015; Manor, Rozen, Zemishlani, Weizman, & Zalsman, 2011; Michielsen et al., 2021), more studies, and randomized control trials (RCTs) in particular, are needed.

Etiology of ADHD

In most individuals with ADHD, both genetic and environmental factors may play a role in the etiology of the disorder (Faraone et al., 2021). Firstly, ADHD is a highly heritable disorder. Twin studies have shown a high heritability of about 70-80% in children (Brikell et al., 2015). In adults, initial reports from twin studies have suggested the heritability of ADHD of approximately 30 to 40%. However, these studies were mostly based on the self-rating of ADHD symptoms, while studies in children and adolescents have mostly used one informant (either parent or teacher) to rate both twins (Brikell et al., 2015). Studies that have used cross-informant data on ADHD symptoms in adults (i.e., combined parent- and self-rating or clinical diagnosis) have identified

heritability of about 70-80%, which is consistent with findings in children (Brikell et al., 2015). These estimates of heritability are comparable to the heritability of other psychiatric disorders, for instance, bipolar disorder or schizophrenia (Banerjee et al., 2007). Moreover, genome-wide association studies (GWAS) have found that about one-third of the heritability of ADHD is due to a polygenic component with many common variants of small effects (Faraone et al., 2005; Faraone & Larsson, 2019). Family-based studies have further confirmed the strong familial component in the etiology of ADHD, with a 2- to 8-fold increase in the risk for ADHD in parents and siblings of children with ADHD (Banerjee et al., 2007).

Environmental factors, present during the prenatal or early postnatal period may also play a role in the etiology of ADHD (Faraone et al., 2021). Some examples of environmental factors are early life exposure to toxicants (e.g., lead, maternal smoking, etc.) (Nilsen & Tulve, 2020) and nutrient deficiencies (e.g., blood levels of omega-3 PUFAs, maternal vitamin D levels, etc.) (Hawkey & Nigg, 2014; Sucksdorff et al., 2021); events during pregnancy and birth (e.g., premature birth, low birth weight, maternal hypertension) (Franz et al., 2018; Maher et al., 2018); pre- and postnatal deprivation, stress, infection, poverty, and trauma (Faraone et al., 2021). These factors are more likely to increase the risk of ADHD rather than play a causal role (Banerjee et al., 2007; Faraone et al., 2021), and exhibit their effects through gene-environment interactions, which would account for a large extent of ADHD etiology (Faraone & Larsson, 2019), and through epigenetic mechanisms (Walton et al., 2017). Finally, in some rare cases, it has been suggested that ADHD-like symptoms may be caused by a single genetic abnormality (Faraone & Larsson, 2019), early-life extreme institutional deprivation (Kennedy et al., 2016), or traumatic brain injury (Stojanovski et al., 2019).

Due to the high heritability of ADHD, further research is needed to investigate whether potential associations of ADHD with physical health issues are confounded by familial factors, i.e., shared environment and genetic factors.

ADHD and functional impairments and multimorbidity across the lifespan

Symptoms of ADHD may persist far beyond childhood and adolescence (Simon et al., 2009; Torgersen et al., 2016), and may significantly impact one's social, educational, and occupational functioning, as well as mental and physical health, throughout the lifespan (Fayyad et al., 2017; Instanes et al., 2018; Kittel-Schneider et al., 2022; Sobanski, 2006). Although the clinical presentation of ADHD can be heterogeneous, common features of ADHD have been linked to impairments in executive functions (e.g., response inhibition and working memory, issues with organization, sustained attention, and ability to perform complex tasks in school or at work), emotion dysregulation, mood issues and irritability (Franke et al., 2018; Nigg, 2013). Individuals with ADHD are also often diagnosed with other neurodevelopmental disorders, such as autism spectrum disorder, tic disorders, intellectual disability, learning difficulties, and language disorders (Franke et al., 2018). Further, ADHD has been associated with a reduction in quality of life across the lifespan (Lee et al., 2016; Thorell, Holst, & Sjöwall, 2019) and an increased risk for criminality (Mohr-Jensen, Müller Bisgaard, Boldsen, & Steinhausen, 2019). ADHD also carries a substantial individual, family, and societal economic burden (Du Rietz et al., 2020).

The patterns of psychiatric comorbidities in ADHD may change with age, with oppositional defiant disorder and conduct disorder being the most common comorbidity in childhood, while substance use disorder, mood, and anxiety disorders become more prevalent with age (Franke et al., 2018). Psychiatric comorbidity has been well documented in adults with ADHD, encompassing a broad range of psychiatric disorders, such as anxiety disorders, mood disorders, behavioral disorders, substance use disorder and sleep disorders (Fayyad et al., 2017; Sobanski, 2006). Between 65–89 % of all adults with ADHD are diagnosed with one or more additional psychiatric disorders (Sobanski, 2006), although ADHD is commonly reported as a temporally primary disorder in relation to other psychiatric disorders, given the early age of onset in ADHD (Fayyad et al., 2017; Sobanski, 2006).

Moreover, ADHD has been associated with an increased risk of physical multimorbidity (Stickley et al., 2017) and increased mortality rates,

mostly due to unnatural causes (e.g., accidents) (Dalsgaard, Østergaard, Leckman, Mortensen, & Pedersen, 2015). A recent narrative review of literature has indicated associations of ADHD with multiple physical disorders: neurological disorders (e.g., epilepsy, migraine, etc.), neurodegenerative disorders, diseases of the digestive and urinary system (e.g., elimination disorders, celiac disease, inflammatory bowel disease, etc.), endocrine and metabolic disorders (e.g., obesity, diabetes mellitus, disorders of the thyroid gland, etc.), cardiovascular diseases, and autoimmune and allergic diseases (e.g., atopic disorders and allergies) (Kittel-Schneider et al., 2022). Furthermore, genome-wide association studies (GWAS) have reported significant positive genetic correlations of ADHD with smoking, major depressive disorder, neuroticism, anorexia nervosa, migraine, obesity, insomnia, and mortality, and negative correlations with educational attainment and childhood IQ (Demontis et al., 2023; Demontis et al., 2019; Franke et al., 2018). Similarly, Swedish large-scale, family-based studies have suggested a significant sharing of underlying genetic factors between ADHD and comorbid psychiatric disorders (Pettersson, Larsson, & Lichtenstein, 2016), and a range of respiratory, musculoskeletal, and metabolic diseases, while the associations of ADHD with nervous system disorders were largely explained by non-shared environmental factors (Du Rietz et al., 2021). Additionally, the lifespan of adverse functional and socio-economic outcomes (e.g., low educational attainment, few employment opportunities, relationship issues, etc.) of ADHD may put individuals on a trajectory leading to an increased risk for both psychiatric and physical comorbidity in adult ADHD (Franke et al., 2018).

Finally, emerging research has suggested that individuals with ADHD are at higher risk of developing disorders which are common in older age, i.e., age-related disorders such as dementia, cardiovascular diseases (CVDs) (i.e., hypertension, cerebrovascular diseases, heart failure, etc.), and common metabolic disorders (i.e., obesity, type 2 diabetes, etc.) (M.-H. Chen et al., 2018; Du Rietz et al., 2021; Garcia-Argibay et al., 2022; Garcia-Argibay et al., 2023; Golimstok et al., 2011; Li et al., 2022; Li et al. 2023; Tzeng et al., 2019). It has been estimated that the prevalence and impact of age-related disorders will continue to rise and impose an increasing societal and economic burden globally (Nichols et al., 2022; Roth et al., 2020). However, available studies on the potential

associations of ADHD with age-related disorders and the underlying mechanisms are still scarce and have yielded mixed findings. Due to a substantial knowledge gap, it is of importance to improve our understanding of the increased risk of age-related disorders in individuals with ADHD. The acquired knowledge could inform public health policies and clinicians to provide timely and targeted health care to adults with ADHD and comorbid conditions to prevent or ameliorate the impact of age-related disorders.

ADHD in adults and the risk of age-related disorders

ADHD and dementia and mild cognitive impairment

Dementia is characterized by a progressive decline in cognition and behavior with significant functional impairments (WHO, 2020), and it is one of the leading causes of death and disability worldwide (GBD 2019 Collaborators, 2021). It has been forecasted that the prevalence of dementia will almost triple from 2020 by 2050 (Nichols et al., 2022). On the other hand, mild cognitive impairment (MCI) is defined by the presence of impairment in one or more cognitive domains but with preserved functional independence (Winblad et al., 2004b). The concept of MCI, although heterogeneous, can be useful both in clinical practice and research to denote individuals with a clinical syndrome which does not fulfill the diagnostic criteria for dementia but puts them at a higher risk of progressing to dementia (Winblad et al., 2004b). This may be of importance in relation to individuals with ADHD due to potential methodological limitations concerning the younger age of available study populations with ADHD, and with MCI having a younger age of onset than dementia (Winblad et al., 2004a). Considering the risk of MCI in addition to dementia may provide a more comprehensive understanding of abnormal cognitive aging in people with ADHD.

So far, only a few studies have investigated potential associations of ADHD with dementia/MCI, and these have shown mixed findings (Fluegge & Fluegge, 2018; Golimstok et al., 2011; Ivanchak et al., 2011; Tzeng et al., 2019). Several studies have identified an increased risk of dementia in individuals with ADHD (Du Rietz et al., 2021; Fluegge &

Fluegge, 2018; Golimstok et al., 2011; Tzeng et al., 2019), while a cross-sectional study from the U.S. found a significant association of childhood symptoms of ADHD with cognitive test profiles, but not with dementia or MCI. There are several important limitations of available studies that need to be addressed: (i) the use of inpatient data, which may limit the findings to most severe cases of dementia and ADHD since most individuals with ADHD are treated in outpatient care (Fluegge & Fluegge, 2018); (ii) over-representation of individuals between 18 and 54 years old and of males sex, which may not represent the population at risk (Tzeng et al., 2019) since dementia is less prevalent in men than women and it is rare before age 55 (Ruitenberg, Ott, van Swieten, Hofman, & Breteler, 2001); (iii) retrospective assessment of childhood symptoms in older individuals with cognitive impairment (Golimstok et al., 2011; Ivanchak et al., 2011), which may lead to recall bias and misclassification, and/or (iv) not considering the potential effects of ADHD-related comorbidities and functional impairments on the association with dementia (Du Rietz et al., 2021; Golimstok et al., 2011).

Several potential underlying mechanisms explaining the association of ADHD with dementia/MCI have been suggested (Callahan, Bierstone, Stuss, & Black, 2017). Common genetic or early life factors (e.g., fetal stress, low birth weight, early psychosocial adversity) may play a role in leading to brain abnormalities manifesting as ADHD in childhood, and in progressing to MCI, and eventually dementia in older age (Callahan et al., 2017). However, evidence on potential pathophysiological pathways is limited and may depend on the specific subtype of dementia (Alzheimer's disease (AD), Dementia with Lewy bodies (DLB), Vascular dementia, etc.) (Callahan et al., 2017). Some recent studies have indicated that ADHD is associated with AD within families (Zhang, Du Rietz, et al., 2022) and that genetic liability for ADHD is associated with the development of pathophysiology in AD (i.e., amyloid-β (Aβ) deposition) and cognitive deterioration (Leffa et al., 2023). On the other hand, a potential association between ADHD and DLB may stem from a common neurobiological disturbance in a hypodopaminergic and noradrenergic substrate in the brain (Golimstok et al., 2011). Furthermore, the risk for dementia might be increased in people with ADHD due to mediating factors, such as adverse health behaviors (i.e.,

risk-taking behaviors, head injuries, smoking, excessive drinking, lack of exercise, unhealthy diet, inadequate sleep, etc.), psychiatric and physical health comorbidities across the lifespan associated with both ADHD and dementia/MCI (Callahan et al., 2017). Finally, it has been suggested that ADHD, MCI, and dementia may display clinical presentations similar in nature, especially in older age, but ultimately with unrelated underlying mechanisms (Callahan et al., 2017; Callahan et al., 2022; Mendonca et al., 2021).

Further research is needed to elucidate the association of ADHD with dementia and MCI, and to what extent these associations are affected by potential mediating factors, such as educational attainment, common metabolic disorders (i.e., type 2 diabetes, obesity, hypertension, hyperlipidaemia), comorbid psychiatric disorders (i.e., anxiety, depression, substance use disorder, and bipolar disorder), head injuries, and sleep disorders.

ADHD and cardiometabolic disorders

Cardiovascular disorders (CVDs), primarily ischemic heart disease (IHD) and stroke, are the leading cause of mortality and a major cause of disability in adults globally (Roth et al., 2020). Further, the prevalence of metabolic disorders has been rising over the past decades and they have become a major healthcare concern worldwide (Khan et al., 2020; Seidell & Halberstadt, 2015).

The available research on the associations of ADHD with CVDs and metabolic diseases (i.e., cardiometabolic diseases) is sparse and has mixed findings. A systematic review from 2018 (Instanes et al., 2018) has reported strong evidence of a significant association between ADHD and obesity. On the other side, the same review found weak evidence for the associations of ADHD with CVDs and metabolic diseases other than obesity. Nevertheless, more recent studies have reported significant positive associations of ADHD with a range of CVDs and metabolic diseases in children (Akmatov, Ermakova, & Bätzing, 2021; Çöl, Gökçen, Kılıç, & Karadağ, 2019), and adults (M.-H. Chen et al., 2018; Q. Chen et al., 2018; Du Rietz et al., 2021; Garcia-Argibay et al., 2022; Garcia-Argibay et al., 2023; Li et al., 2022; Li et al. 2023; Porter, Henry, Halkett, & Hinshaw, 2022; Xu et al., 2022). However,

available, large-scale studies which have reported an increased risk of cardiometabolic disorders in adults with ADHD have used definitions of ADHD based on clinical diagnoses (M.-H. Chen et al., 2018; Q. Chen et al., 2018; Ebba Du Rietz et al., 2021; Li et al., 2022; Xu et al., 2022). The population of older adults diagnosed with ADHD may not cover all those affected by symptoms of ADHD (Goodman et al., 2016; Torgersen et al., 2016). This could be problematic when it comes to research on cardiometabolic disorders, which typically have adult onset, and their incidence peaks after the age of 60-65 (Kuk & Ardern, 2010; Yazdanyar & Newman, 2009). Moreover, it may be difficult to discern the risk of cardiometabolic disorders associated with ADHD itself from the risk associated with ADHD medication in clinical studies since clinical diagnosis might be confounded by medication. Additionally, only a few studies have applied a longitudinal study design investigating the associations between ADHD and cardiometabolic disorders, but these studies have had follow-up periods limited to young adulthood (M.-H. Chen et al., 2018; Fuemmeler, Østbye, Yang, McClernon, & Kollins, 2011; Porter et al., 2022).

Further, little is known on the underlying mechanisms of the proposed associations between ADHD and cardiometabolic disorders. Weak-to-moderate sharing of underlying genetic factors between ADHD and cardiometabolic disorders has been reported by family-based (Du Rietz et al., 2021) and genome-wide association studies (Demontis et al., 2022; Demontis et al., 2019). Furthermore, ADHD has been associated with a range of adverse life course outcomes, such as lower socioeconomic status, lifestyle factors (i.e., body mass index, physical activity, smoking, etc.), and comorbid psychiatric disorders (e.g., depression, alcohol dependence, anxiety disorders, etc.), which are cardiometabolic risk factors as well (Cannon, 2007; Nigg, 2013). It has been found that these life-course risk factors may partially mediate the association between ADHD (Garcia-Argibay et al., 2022; Li et al., 2022; Xu et al., 2022) and the risk of cardiometabolic disorders.

Finally, due to clinical concerns related to potential cardiovascular risks in connection with ADHD medication (Cooper et al., 2011; Kooij et al., 2016), it is of importance to identify individuals who are at high risk of developing CVDs. Currently available clinical guidelines and

prediction models of cardiovascular risk (e.g., Framingham risk score, QRISK, ASSIGN), developed to optimize preventative strategies for CVDs and to identify individuals who are at high risk, mostly rely on established, traditional cardiovascular risk factors, such as hypertension, diabetes mellitus, obesity, family history of cardiovascular disorders, smoking, and dyslipidemia (Kooij et al., 2019; Kooij et al., 2016; NICE, 2019; Siontis, Tzoulaki, Siontis, & Ioannidis, 2012). Potentially relevant novel cardiovascular risk factors associated with ADHD have mostly been overlooked by available prediction models (Siontis et al., 2012). Such novel risk factors have been suggested to increase cardiovascular risk and they can be found among psychiatric disorders that are highly comorbid with ADHD (i.e., anxiety, depression, bipolar disorder, schizophrenia, sleep disorders, substance use disorder), co-medication with psychotropic drugs other than ADHD medication (i.e., anxiolytics, antidepressants, hypnotics and sedatives, antiepileptics, mood stabilisers, antipsychotics and drugs used for addictive disorders), and adverse socio-economic outcomes of ADHD (i.e., low education attainment) (Cohen, Edmondson, & Kronish, 2015; Davy Vancampfort et al., 2013; Khaing, Vallibhakara, Attia, McEvoy, & Thakkinstian, 2020; Krantz et al., 2009; Roerecke & Rehm, 2014; Sofi et al., 2020).

Further research is needed to investigate the associations between ADHD and cardiometabolic disorders, and the underlying mechanisms of the potential associations. Additionally, it is necessary to investigate whether we can identify individuals with ADHD who are at high risk of developing CVDs.

Aim

Overarching aim

The present PhD project is concerned with investigating a significant knowledge gap in research on ADHD in older adults and associated adverse health outcomes, using different methodological approaches. Findings from the conducted studies have important clinical implications by drawing the attention of healthcare providers to: 1) facilitate adequate and timely assessment and treatment of older adults with ADHD; and 2) develop targeted prevention programs earlier in life to prevent the impact of age-related disorders.

Specific research questions and aims

Study I: Investigate a pooled prevalence estimate of ADHD in adults aged 50 and older via a systematic literature review and meta-analysis.

Study II: Investigate a potential association of ADHD with dementia and mild cognitive impairment (MCI) and whether this association is affected by educational attainment, comorbid metabolic disorders (i.e., hypertension, type 2 diabetes, and obesity), sleep disorders, head injuries, psychiatric disorders (i.e., depression, anxiety, substance use disorder, and bipolar disorder), other developmental disorders, and sex.

Study III: Investigate potential associations between ADHD symptoms in young and mid-adulthood, and subsequent cardiometabolic diseases, and the underlying mechanisms of the associations.

Study IV: Improve the predictive accuracy of traditional cardiovascular disease (CVD) risk factors for adults initiating pharmacological treatment of ADHD by considering novel CVD risk factors which have been associated with ADHD (i.e., comorbid psychiatric disorders, socio-demographic factors, and use of other psychotropic medication).

Methodology

Data sources

In the present PhD project, complementary methodological approaches and data sources have been implemented to gain a more comprehensive understanding of the research questions. Study I is a systematic review of literature and meta-analysis of relevant articles. Studies II, III, and IV are based on data linkages of several Swedish nationwide registers. Additionally, in Study III, we used questionnaire-based data from the Study of Twin Adults: Genes and Environment (STAGE).

Swedish National Registers

Sweden has a long history of reporting information on different aspects of life of its residents in national registers. All Swedish residents are assigned a unique personal identity number (PIN), which enables a linkage of these registers (Ludvigsson et al., 2016). Data from the following Swedish population-based registers were used in Studies II-IV:

The Total Population Register (**TPR**) is maintained by Statistics Sweden ("Registret över totalbefolkningen") and covers life events and demographic data (i.e., date of birth, sex, date of death, migration, country of origin) for all individuals residing in Sweden since 1968 (Ludvigsson et al., 2016).

The National Patient Register (**NPR**) is founded and maintained by the National Board of Health and Welfare (NBHW) (Socialstyrelsen) and it covers diagnoses from inpatient hospital admissions with complete national coverage since 1987 (the Swedish National Inpatient Register), and from the Outpatient register since 2001 (Ludvigsson et al., 2011). Diagnoses in the NPR are coded according to the International Classification of Diseases (ICD, ICD version 7 since 1964, ICD-8 since 1968, ICD-9 since 1987, and ICD-10 since 1997). Data from primary care are not reported to the NBHW on a national level.

The Cause of Death Register (**CDR**) contains information on all deaths in Sweden, and it has been available for electronic access since 1952 (Brooke et al., 2017). For the period between 1911 and 1993,

Statistics Sweden was responsible for the CDR, and since 1994, it has been under the responsibility of the NBHW. Diagnoses in the CDR are classified and coded according to the ICD versions 7/8/9/10.

The Prescribed Drug Register (**PDR**) contains information on all dispensed medications prescriptions since July 2005 coded according to the Anatomical Therapeutic Classification (ATC) system, as well as information on a date of prescription and dosage (Wettermark et al., 2007). The prescriptions are obtained from the outpatient and primary healthcare system. The PDR is maintained by the NBHW.

Longitudinal integration database for health insurance and labour market studies register (Longitudinell Integrationsdatabas för Sjukförsäkrings- och Arbetsmarknadsstudier, **LISA**) contains information on educational attainment, unemployment, social benefits, and family income, for all individuals aged ≥ 16 for each year since 1990 (Ludvigsson, Svedberg, Olén, Bruze, & Neovius, 2019). Data are obtained from social and educational services, as well as the labour market, with an update each year creating annual registers. Information on educational attainment from LISA (i.e., the highest educational level achieved) was used for Studies II and IV.

The Multi-Generation Register (**MGR**) is maintained by Statistic Sweden, and it is part of the TPR. It contains information on the biological and adoptive parents of all individuals who were born after 1932, and who were living in Sweden since 1961, except for those individuals whose parents died or emigrated from Sweden before 1947 (Ekbom, 2011). We used the MGR in Study IV to link all individuals of our study population with their first-degree relatives, to further extract information on family history of cardiovascular diseases from the NPR.

The Swedish Twin Registry and the Study of Twin Adults: Genes and Environment (STAGE)

The Swedish Twin Registry (STR) was established in the late 1950s, and it includes more than 170,000 twins who were born in Sweden since 1886 (Lichtenstein et al., 2006). The STR database is regularly updated with information from relevant healthcare registries on hospital

discharges, inpatient and cancer diagnoses, vital status, conditions during birth, and cause of death. Data have been collected through multiple data collection waves. For the purposes of Study III, we applied data from the Study of Twin Adults: Genes and Environment (STAGE) (Larsson, Asherson, et al., 2013; Lichtenstein et al., 2006). A total of 42,582 twins born between 1959 and 1985 in Sweden who survived their first birthday were identified from the population of the STR. Out of them, 25,364 (59.6%) individuals responded to either a telephone interview or a web-based questionnaire within the STAGE data collection between November 2005 and March 2006. Twins were sent invitation letters to participate in the study, with their personal login information for the study web page, and they could also choose to complete the questionnaire via telephone interview and to supplement the information on sensitive topics with a self-administered paper questionnaire. The questionnaire included 1300 items in 34 sections concerning physical and mental health, lifestyle, and socioeconomic/demographic data. Non-responders were sent up to three reminders.

In Study III, we used self-reported data on ADHD symptoms, lifestyle factors (smoking, body mass index, and physical activity level), and symptoms of major depression, generalized anxiety disorder, and alcohol dependence.

Main measurements

ADHD

In Study I, individuals with ADHD were defined as having: i) a research diagnosis of ADHD, i.e., meeting the threshold/cut-off levels on ADHD validated scales based on the DSM criteria (DSM III, IV, IV-TR, or DSM-5); ii) a clinical diagnosis according to the ICD (9 or 10) or DSM (III, IV, IV-TR, or 5) as reported in registers/medical files or self-reported medical history; or iii) pharmacological, and/or non-pharmacological treatment (e.g., psychoeducation or psychotherapy) for ADHD, as reported in registers/medical files or self-reported prescription.

In Study II, ADHD was identified based on a diagnosis established according to the ICD-9/10 from the NPR (ICD-9: 314, ICD-10: F90)

(Larsson, Rydén, et al., 2013), or a dispensed medication prescription for ADHD treatment (Zetterqvist et al., 2013a), according to the ATC codes from the PDR (N06BA01, N06BA02, N06BA04, N06BA09, 06BA12, C02AC02).

In Study III, the primary focus was on ADHD symptoms which were assessed within the STAGE interview/questionnaire via self-report on nine inattention items and nine hyperactivity/impulsivity items, in accordance with the DSM-IV diagnostic criteria for ADHD (Larsson, Chang, D'Onofrio, & Lichtenstein, 2014). Each item had a three-point answer format, with 0="No," 1="Yes, to some extent," and 2="Yes". The items were slightly modified to fit adults. We considered the total score (minimum score 0, maximum 36) in the main analysis, as well as scores on the two subscales for inattention, and hyperactivity/impulsivity (minimum 0, maximum 18) in the sensitivity analysis. Both subscales have shown good internal consistency with Cronbach α of 0.79 for inattention, and 0.77 for hyperactivity/impulsivity (Larsson, Asherson, et al., 2013). In Study III, we additionally considered the following definitions of ADHD within sensitivity analyses using: i) a clinical diagnosis of ADHD based on the ICD 9/10 and acquired from the NPR, and ii) a research diagnosis of ADHD established using the norm-based approach (Capusan, Bendtsen, Marteinsdottir, Kuja-Halkola, & Larsson, 2015). Using the norm-based approach, we considered that individuals had the primarily inattentive subtype if their scores were 2SD above the mean on the inattention subscale but not on the hyperactivity/impulsivity subscale. Likewise, those with scores 2SD above the mean for the hyperactivity/impulsivity subscale, but not for inattention, were considered as having the primarily hyperactive/impulsive subtype. Those with scores 2SD above the mean on both subscales were considered as having the combined subtype.

In Study IV, we included individuals prescribed stimulant medications: amphetamine (ATC code N06BA01), dexamphetamine (ATC code N06BA02) and methylphenidate (ATC code N06BA04), and non-stimulant medication: Atomoxetine (ATC code N06BA09). Prescriptions that were returned to pharmacies by patients after dispensation or that were prescribed for indications other than ADHD (i.e., narcolepsy, multiple sclerosis, idiopathic hypersomnia, pain, handicap, and

catalepsy) were removed from the data set using natural language processing models for free-text prescriptions from the PDR (Zhang, Lagerberg, et al., 2021).

Dementia and mild cognitive impairment

In Study II, the main outcomes were dementia and mild cognitive impairment (MCI). Dementia is characterized by significant decline in cognition and behavior, and significant impairments in daily functionality (WHO, 2020). We included individuals who received a diagnosis of one the following subtypes of dementia: Alzheimer's disease (AD), vascular dementia, and other dementias, with diagnostic codes according to the ICD-8/9/10 from the NPR and the CDR, or dispensed medication prescriptions for AD according to the ATC codes from the PDR (Table 1) (Eriksson et al., 2019). MCI was characterized by impairment in one or more cognitive domains without affecting a person's functional independence (Winblad et al., 2004b). Individuals with MCI were identified if they received a diagnosis with a diagnostic code F06.7, according to the ICD-10, and registered in the NPR.

Table 1. ICD and ATC codes for dementia subtypes.

	ICD-8	ICD-9	ICD-10	ATC
Alzheimer's disease (AD)	290	290A/B/X, 331A	F00, F03, G30	N06DA02-N06DA04, N06DX01
Vascular dementia	293.0-293.1	290E	F01	-
Other dementia	-	294B, 290W, 331B/C/X	F02, F02.1, F02.2, F02.3, F02.4, F02.8, F05.1, G31.1, G31.8	-

Cardiovascular and metabolic disorders

In Study III, the main outcomes were cardiovascular and metabolic disorders (i.e., cardiometabolic disorders). Cardiovascular disorders

included the following conditions: hypertension, ischemic heart disease, heart failure, cerebrovascular disease, venous thromboembolism, and tachyarrhythmias. The following metabolic disorders were included: type 2 diabetes, obesity, and hyperlipidaemia. These disorders were identified from the NPR using the ICD-10 codes, and dispensed medication prescriptions from the PDR using the ATC codes (Table 2). Twins were followed-up from the time they completed the STAGE questionnaire/interview by the time they either: acquired a diagnosis/dispensed medication prescription for a cardiometabolic disorder, died, or up to December 31st, 2018, whichever came first.

In Study IV, we identified individuals with a first diagnosis (i.e., primary or any secondary diagnosis) or dispensed medication prescription for any of the following cardiovascular diseases (CVDs): ischemic heart disease, cerebrovascular disease, venous thrombo-embolism, heart failure, and tachyarrhythmias. Diagnoses were coded according to the ICD-10 from the NPR and CDR, while medication prescriptions were coded per the ATC codes from the PDR (Table 2). Incident diagnoses were identified by December 31st, 2013.

We included the information on dispensed medication prescriptions in both Study III and IV, in addition to clinical diagnoses, to increase the coverage of cases. Cardiometabolic disorders are often diagnosed and followed-up in the primary care services and may not be captured in the NPR, which includes specialist healthcare services only.

Table 2. ICD and ATC codes for cardiovascular and metabolic disorders.

	ICD-10	ATC
Ischemic heart disease		
Acute myocardial infarction	I21-I23 (primary)	C01D
Acute myocardial infarction (also including secondary, type-2 myocardial infarction)	I21-I23 (primary or secondary)	
Acute coronary syndrome	I21-I23 or I20.0	
Any ischemic heart disease	I20-I25 (primary or secondary)	
Cerebrovascular disease		
Subarachnoidal bleeding	I60 (primary or secondary)	—
Hemorrhagic stroke	I61-I62 (primary or secondary)	
Ischemic stroke	I63-I64 (primary or secondary)	
Other cerebrovascular disease	I65-I69 (primary or secondary)	
Venous thrombo-embolism		
Deep vein thrombosis	I80 (primary or secondary)	—
Pulmonary emboli	I26 (primary or secondary)	
Heart failure		
Heart failure	I50 (primary diagnosis)	C01A
Heart failure	I50 (primary or secondary)	
Tachyarrhythmias		
Atrial fibrillation/fludder	I48 (primary or secondary)	C01A
Supraventricular tachycardia	I47.1 (primary or secondary)	

Ventricular tachycardia	I47.0, I47.2, I49.0, I49.8 (primary or secondary)	C01B
Cardiac arrest	I46 (primary or secondary)	—
Hypertension	I10-I13, I15	C02, C03, C07, C08, C09
Type 2 diabetes	E11	A10A, A10B
Obesity	E65-E66	-
Hyperlipidaemia	E78	C10

Covariates

The main analyses were adjusted for several covariates, relevant socioeconomic and lifestyle factors associated with ADHD, and psychiatric and physical comorbidities of ADHD (Fayyad et al., 2017; Nigg, 2013), which are also risk factors of dementia and mild cognitive impairment (Study II) (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014), and cardiometabolic disorders (Study III) (Cannon, 2007).

In Study II, data for covariates were extracted from Swedish national registers. The main analysis was firstly adjusted by 1) sex and age (data were extracted from the TPR), followed by adjustment for: 2) educational attainment/the highest level of education achieved by age 50, with the following categories: compulsory education ≤9 years, upper secondary, postsecondary and postgraduate education (data were extracted from LISA), 3) metabolic disorders: hypertension, type 2 diabetes, and obesity, 4) sleep disorders, 5) head injuries, 6) psychiatric disorders: depression, anxiety, substance use disorder, and bipolar disorder, and 7) other developmental disorders: autism spectrum disorder, learning disorders, intellectual disability and motor disorders. The first diagnosis of the included disorders was extracted from the NPR, and it was coded per the ICD-8/9/10. Please see Table 3 for the complete list of included ICD codes.

Table 3. ICD codes for covariates used in Study II.

Covariate	ICD-8	ICD-9	ICD-10
Hypertension	400 – 404	401 – 405	I10 – I13, I15
Type 2 diabetes mellitus	-	-	E11
Obesity	277.99	278A, 278B	E65-E66
Sleep disorders	347, 780.60	347, 780F	G47.0/1/2/3/4/8/9, F51
Head Injuries	800, 801, 803, 850 - 854	800, 801, 803, 850 - 854	S020, S021, S027 - S029, S060 - S071
Depression	296.00, 300.40	296B, 300E, 311	F32, F33
Anxiety	300 (except 300.4)	300 (except 300E)	F40, F41, F42, F44, F45, F48
Substance use disorder	303, 304	303, 304, 305	F10 – F19
Bipolar disorder	296.10, 296.30, 296.88	296C/D/E/W	F31
Other developmental disorders	-	299A	F84.0, F84.1, F84.5, F84.8, F84.9
Autism spectrum disorder	-	315A, 315B, 315D, 315W	F80, F81, F83
Other developmental disorders			
Autism spectrum disorder	-	299A	F84.0, F84.1, F84.5, F84.8, F84.9
Developmental disorders of speech/language and learning disorders	-	315A, 315B, 315D, 315W	F80, F81, F83
Intellectual disability	310–315	317-319	F70-73, F78-79
Motor disorders	-	307D, 315E, 307C	F98.4, F82, F95

In Study III, the covariates were assessed via self-report in the STAGE interview/questionnaire. The following variables were considered: 1) socioeconomic status, defined as educational attainment (categories: compulsory education, secondary level education, and higher education); 2) lifestyle factors: smoking (categories: never/just tried smoking, smoking occasionally, and regularly smoking) (Wennerstad et al., 2010), body mass index (BMI) based on self-reported weight and height, and categorized into four categories according to the WHO criteria: underweight (<18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25.0–29.9 kg/m2) and obese (≥30 kg/m2) (Tholin et al., 2009), and physical activity (categories: sedentary/low, moderate, high, and vigorous) (Helgadóttir et al., 2019), and 3) self-reported symptoms of psychiatric disorders: major depression, generalized anxiety disorder, and alcohol dependence, with a research diagnosis of the disorders established using the DSM-IV based criteria.

Study design and data analysis

Overview of study methods

Overview of study methods is provided in Table 4.

Table 4. Overview of applied study methods for Studies I-IV.

Study	Study design	Data source	Population	Measures	Statistical analysis
Study I	Systematic review and meta-analysis	Previously un/published studies	20,999,871 individuals, and 41,420 with ADHD from 20 relevant studies, 32 datasets	Prevalence estimates of ADHD: a) research diagnosis via validated scales, b) clinical diagnosis, and c) treatment of ADHD	Random-effects model: pooled prevalence estimates with 95% confidence intervals (CI). The Cochran Q test and I^2 index: heterogeneity of results.
Study II	Population-based cohort study	Swedish national registers	3,591,689 individuals born between 1932-1963, and 9,532 with ADHD	Exposure: ADHD diagnosis/medication prescription. Outcome: dementia and mild cognitive impairment	Cox proportional hazards model with hazard ratios (HR) were estimated with 95% CIs.
Study III	Co-twin control design using a population-based cohort study	STAGE and Swedish national registers	42,582 twins born in Sweden between 1959 and 1985	Exposure: self-reported ADHD symptoms. Outcomes: cardiometabolic disorders.	Cox proportional hazards model with hazard ratios (HR) were estimated with 95% CIs.
Study IV	Prediction mode using a population-based cohort study	Swedish national registers	24,186 adults residing in Sweden, born between 1932-1990, who started ADHD pharmacological treatment.	Predictors/risk factors: traditional CVD and novel risk factors. Outcome: cardiovascular diseases.	Cox proportional hazards model; bootstrapping; C index/AUC; Brier score; Net Reclassification Index and Integrated Discrimination Improvement index.

Systematic review and meta-analysis

Systematic reviews aim to identify all available empirical evidence (i.e., published and unpublished scientific papers) in accordance with prespecified eligibility criteria to answer a research question of interest (Higgins et al., 2019). To do so, systematic methods are implemented to minimize bias and provide reliable findings (Higgins et al., 2019). When possible, systematic reviews are accompanied by meta-analyses. Meta-analysis is a quantitative study design used to systematically summarize results from previous scientific evidence (i.e., relevant scientific papers) by providing an overall/combined effect size/prevalence with more precision and reliability in comparison with individual study results (Borenstein, Hedges, Higgins, & Rothstein, 2021; Haidich, 2010). Additionally, meta-analyses investigate and quantify heterogeneity across included studies, as well as publication bias of these studies. Two models can be used in meta-analysis: the fixed effect model, which assumes that the true effect is shared across studies, and the random effect model, which allows the true effect to vary across studies (Borenstein et al., 2021). Before conducting systematic reviews and meta-analyses, it is recommended to register a protocol of the systematic review in *PROSPERO, the International prospective register of systematic reviews* (Moher, Liberati, Tetzlaff, Altman, & Group*, 2009). Additionally, to ensure a good standard of conducting and reporting systematic reviews and meta-analyses, authors should follow the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement* (Moher et al., 2009).

In Study I, a systematic review and meta-analysis were conducted to synthesize available evidence on the prevalence of ADHD in adults aged 50 and older, considering different assessment methods. We applied the random-effects model to synthesize results from relevant studies. The random-effects model allows the true population prevalence to vary between included studies since we expected high heterogeneity across studies. The inverse variance method was used to obtain the pooled prevalence estimates, with the variance in the random model including both within- and between-study variance (Borenstein et al., 2021). To assess the heterogeneity of the results, we used the Cochran Q test, I^2 index (values of the I^2 index higher than 75 % are considered

high), and confidence intervals (Higgins, Thompson, Deeks, & Altman, 2003). To test whether prevalence estimates differed across different assessment methods (i.e., research diagnosis via validated scale, clinical diagnosis, or treatment for ADHD), we performed a subgroup analysis, with the mixed model method. This method applies the random-effects model to combine studies within subgroups, and the fixed-effects model to combine subgroups. Publication bias was not assessed in this study since the reported prevalence estimates should not affect the decision of whether a study would be published.

Population-based cohort study

In Studies II, III, and IV, we used data from record linkages from several Swedish population-based healthcare and population registers. Nationwide register data in Sweden allow the creation of cohorts with large sample sizes, long follow-ups, and, often, complete coverage of the population, as well as investigating rare exposures and outcomes (Maret-Ouda, Tao, Wahlin, & Lagergren, 2017).

Cohort study design refers to observational studies used in epidemiology where a cohort, a predefined set of individuals, is followed over a period of time (Song & Chung, 2010). The study population is defined based on their exposure status (i.e., unexposed versus exposed group) and followed over time until an outcome occurs, thus, the exposure comes before the outcome. This type of study has the advantage of investigating rare exposures, such as ADHD, and multiple outcomes at the same time. Disadvantages are the need for a large sample size and a potentially long follow-up (Song & Chung, 2010).

In Study II, we used a retrospective cohort study design. Individuals with ADHD and those without were identified and followed until they either developed dementia or MCI, moved out of Sweden, died, or the end of the follow-up period (December 31st, 2013). The term "retrospective" is used since the exposed and unexposed group are retrospectively identified and followed until the end of follow-up, i.e., both the exposure and outcome had already occurred in the past. In contrast, prospective cohort studies would demand a present identification of study groups based on their exposure status which would be followed prospectively until a time point in the future. In Study III, a cohort of

twins born in Sweden between 1959 and 1985 who completed the ADHD self-report scale within the STAGE interview/questionnaire were followed until they developed a cardiovascular or metabolic disorder, died, or the end of follow-up (December 31st, 2018). In Study IV, a cohort of individuals born between 1932 and 1990, initiating pharmacological treatment for ADHD was followed until they either developed a cardiovascular disease, died, moved out of Sweden, or the end of the follow-up (December 31st, 2013).

For statistical analysis, in Studies II, III, and IV, we used Cox proportional hazards model to test associations between exposures (Study II: ADHD clinical diagnosis/dispensed medication prescription, Study III: ADHD symptoms) or predictors/risk factors of cardiovascular disorders (Study IV); and outcomes (Study II: dementia and mild cognitive impairment, Study III: cardiometabolic disorders, Study IV: cardiovascular disease). The underlying timescale was the attained age in Study II and III, and in Study IV, it was the number of days since ADHD treatment initiation. Associations were presented as hazard ratios with 95% confidence intervals (CIs). The Cox proportional hazard model is a regression analysis method which allows modeling survival times as a function of a covariate set (Bagiella, 2008). Hazard ratio (HR) is an effect measure estimated via Cox proportional hazard regression models (Hernán, 2010). HR is defined as the hazard in the exposed group divided by the hazard in the unexposed group and can be interpreted as the incidence rate ratio (Hernán, 2010). Cox models can also include potential confounders as covariates.

Co-twin control study

Twin studies, a type of epidemiological study, are applied to unravel genetics from environmental influences (Sahu & Prasuna, 2016). They rely on the condition of twins living in the same families, thus sharing the same environment in addition to sharing genetics. More precisely, monozygotic twins share 100% of their segregating genes and 100% of their shared environment, while dizygotic twins share about 50% of their segregating genes and 100% of their shared environment (Sahu & Prasuna, 2016). A co-twin control study design uses the differences within twin pairs to investigate the associations between an

exposure/risk factor and an outcome of interest and it is informative to investigate the associations by zygosity separately within monozygotic and dizygotic twins (Goldberg & Fischer, 2005). In Study III, we used a co-twin control study design to control for unmeasured confounding (i.e., shared environmental and genetic factors) in the potential associations between ADHD symptoms and cardiometabolic disorders, using data from the STAGE questionnaire within the Swedish Twin Registry (STR). We used a stratified Cox proportional hazards model within twin pairs, with each twin pair entered as a separate stratum. We provided separate estimates for monozygotic and dizygotic twin groups. In this way, we investigated the correlation between the difference in ADHD symptoms and the difference in the outcome (i.e., cardiovascular or metabolic disorder present or not) within the same twin pair (Astenvald, Frick, Neufeld, Bölte, & Isaksson, 2022). Associations within dizygotic twins can be driven by both non-shared environment and genetics, while associations within monozygotic twins can be driven only by non-shared environment, as this is the only factor which makes them dissimilar from each other. Consequently, the presence of genetic effects can be assessed by comparing the estimates from monozygotic and dizygotic twin-pair by using a Wald-type $\chi 2$ test statistic (Neufeld et al., 2021). Statistically significant associations which are only present within dizygotic twin pairs suggest that the associations may be due to genetic factors influencing both the exposure and outcome variable. Additionally, statistically significant associations present within monozygotic twin pairs would indicate that the associations between the exposure and the outcome are driven by a non-shared environment.

Prediction modeling

Prediction models are developed with the aim of assisting healthcare providers in their clinical decision-making by estimating the risk that a disorder/condition is present (diagnostic model) or that a certain disorder or event will be developed in the future (prognostic model) (Collins, Reitsma, Altman, & Moons, 2015). There are two general methodologies commonly used: i) regression analysis, with a priori selected candidate predictors based on expert opinion and available literature, which can be easily applied in clinical practice, and ii) machine

learning, which does not require predefined hypotheses, and it is less likely to overlook unexpected predictors or potential interactions (Waljee, Higgins, & Singal, 2014). Conducting prediction research entails three main steps: 1) developing a predictive model, 2) independent validation of its performance, and 3) prospectively studying its clinical implications. Prediction models provide objective estimates of future outcomes to identify individuals at high-risk of developing a certain disorder. This can be further used to develop early interventions and to maximize cost-effectiveness of interventions and treatments (Waljee et al., 2014). To do so, prediction models should be properly developed, validated and their performance should be assessed with comprehensive assessment tools (Collins et al., 2015). To ensure clear and unbiased reporting of studies on developing, validating or updating prediction models (either diagnostic or prognostic), the *Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Initiative* has been developed (Collins et al., 2015). Statistical analysis in prediction modeling is conducted within model development, assessment of its performance, and model validation. Development of a prediction model entails the process of candidate predictors selection, which is either done via machine learning or regression models (Waljee et al., 2014).

In Study IV, we developed a 2-year risk prediction model of cardiovascular diseases (CVD) of adults initiating pharmacological treatment for ADHD, and we investigated whether the predictive accuracy of a model including traditional cardiovascular risk factors could be improved by adding novel CVD risk factors associated with ADHD, by using data from Swedish national healthcare registers. We used multivariable Cox proportional hazard regression to assess the associations between candidate predictors and cardiovascular diseases. Next, we used a limited backward stepwise procedure to decide whether to keep novel predictors in the model based on their p values (Fazel, Wolf, Larsson, Mallett, & Fanshawe, 2019). This was done by sequentially rejecting novel risk factors with the highest p-value until none of the risk factors had a p-value greater than 0.1. Traditional risk factors were held fixed in the model.

Model performance can be assessed by investigating its discrimination, defined as the ability of the model to correctly distinguish individuals with and without an outcome, and model calibration. In Study IV, model discrimination was assessed with Harrell's c-index and the receiver operating characteristic (ROC) curve with the area under the curve (AUC) (Heagerty & Zheng, 2005). The c-index/AUC can vary between 0.5 and 1, with 1 being perfect discrimination. Model calibration was assessed with the calibration plot and the integrated Brier score, a measure of the average discrepancies between observed outcome status and estimated predictive values (Brier, 1950). Values of the Brier score vary between 0 and 1, with values closer to 0 indicating better calibration. We also calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for prespecified high-risk thresholds of predicted probability.

Model validation is conducted to correct for model overfitting, and it entails internal and external validation (Steyerberg & Harrell, 2016). Internal validation is commonly done by the split sample method (i.e., splitting the sample into a training or derivation set and validation set), cross-validation (e.g., leave-one-out cross-validation) or bootstrapping (i.e., by drawing samples with replacement from the original data set) (Steyerberg et al., 2001). Bootstrapping is considered to be the preferred approach (Steyerberg & Harrell, 2016). In Study IV, we performed bootstrapping by creating 200 bootstrap samples drawn from the total sample with replacement (Harrell, Lee, & Mark, 1996). With external validation, a model should be independently validated using a different data set or a different setting (Steyerberg & Harrell, 2016). However, in Study IV, we only performed internal validation of the model, thus it is necessary to conduct external validation of the model and assessment of its clinical impact in the future.

Finally, to assess the incremental value of novel predictors, we used the following measures: the Net Reclassification Index (NRI), which summarises the reclassification of participants when new predictors are added based on predefined high-risk thresholds, and the category-free NRI; and the Integrated Discrimination Improvement (IDI) index, which covers all possible thresholds of predicted probability (Kerr, McClelland, Brown, & Lumley, 2011; Michael J Pencina, D'Agostino

Sr, D'Agostino Jr, & Vasan, 2008; Steyerberg et al., 2012). Positive values of these measures indicate an improvement in the performance of the model.

Results

Prevalence of ADHD in older adults (Study I)

We conducted a systematic review of the literature and a meta-analysis of prevalence estimates of ADHD in adults aged 50 and above, by considering different assessment methods: research diagnosis of ADHD via validated scales, clinical diagnosis, and pharmacological/non-pharmacological treatment for ADHD. The following electronic databases were used for the systematic literature search: Pubmed/MEDLINE, PsycINFO, Web of Science, and EMBASE, using search terms in relation to "Attention-Deficit/Hyperactivity Disorder", and "Aging", from the inception until June 6, 2019. We conducted an updated search on June 22-26, 2020.

Systematic search and description of the included studies

We screened a total of 9,784 references and assessed for eligibility 132 full-text papers (Figure 1). We included 20 studies with 32 data sets in the meta-analysis, with a total sample size of 20,999,871 participants (41,420 individuals presenting with ADHD research diagnosis, clinical diagnosis, or treatment). Nine studies used a research diagnosis of ADHD with 14 data sets; seven studies used a clinical diagnosis of ADHD, with nine data sets; and four studies provided the prevalence of treatment for ADHD, with nine data sets. The included studies represented the following geographic regions: Europe, North America, Asia, and Australia.

Meta-analysis and pooled prevalence estimates

The pooled prevalence was: 2.18 % (95 % CI=1.51, 3.16) for ADHD research diagnosis based on validated scales, 0.23 % for clinical diagnosis (95% CI=0.12, 0.43), and 0.09% for ADHD treatment (95% CI=0.06, 0.15) (Table 5). Heterogeneity (Cochran Q test) was significant with the I^2 values higher than 75 % (Higgins et al., 2003) across all analyses.

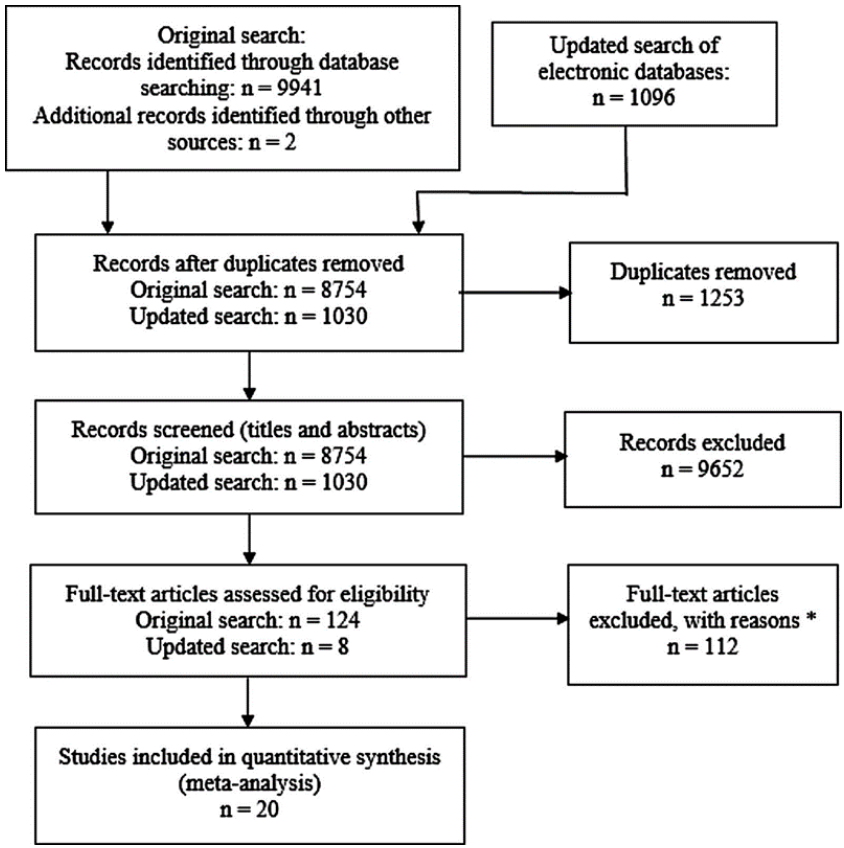

Figure 1. Flow-chart of the meta-analysis selection process.
Note: *Reasons for exclusion of full-text articles are provided in the online Supplementary Appendix of the article, doi: 10.1136/ebmental-2022-300492.

We found a significant difference in the pooled prevalence estimates between the studies based on three assessment methods, with $Q(2) = 108.74$, $p < 0.0001$. Direct subgroup comparisons revealed statistically significant differences between the prevalence based on research diagnosis of ADHD compared to clinically diagnosed ADHD ($Q(1) = 35.52$, $P < 0.0001$), research diagnosis compared to treated ADHD (Q

(1)=99.40, $p < 0.0001$), and the prevalence of clinically diagnosed as opposed to treated ADHD ($Q(1) = 4.80$, $p < 0.0001$).

We also conducted several sensitivity analyses to further address potential sources of heterogeneity: (i) geographical region, by limiting the analysis to geographical regions other than North America, (ii) lower age cut-off, by limiting the analysis to only those studies with the age cut off-set at 50 years, (iii) source of data, by limiting the analysis to only those studies using electronic health registries for clinically diagnosed ADHD, and (iv) by limiting the analysis to only those studies with confirmed childhood onset of symptoms for research diagnosis of ADHD (Table 5). These analyses yielded pooled prevalence estimates that only slightly varied from the main estimates, but with overlapping confidence intervals, and somewhat lower but still significant, heterogeneity.

Table 5. Summary of results of the meta-analysis of prevalence estimates of ADHD in older adults based on different assessment methods.

Type of analysis	N of data sets	Pooled prevalence (%)	95% CI	Heterogeneity Q	I
Research diagnosis – all	14	**2.18**	**1.51, 3.16**	273.05*	95.24
1. Limited to the symptoms present both in childhood and adulthood	7	1.75	1.01, 3.03	93.77*	93.60
2. Limited to geographical regions other than North America	10	2.66	1.78, 3.97	121.78*	92.61
3. Limited to age cut-off ⩾50	9	1.49	0.96, 2.30	72.36*	88.94
Clinical diagnosis – all	9	**0.23**	**0.12, 0.43**	14643.63*	99.94
1. Limited to registries	7	0.14	0.07, 0.29	13769.97*	99.96
2. Limited to geographical regions other than North America	4	0.11	0.04, 0.32	12752.78*	99.98
3. Limited to age cut-off ⩾50	7	0.19	0.11, 0.32	3834.47*	99.84
Treatment – all	9	**0.09**	**0.06, 0.15**	8399.43*	99.90
1. Limited to geographical regions other than North America	7	0.06	0.04, 0.10	3280.56*	99.82
2. Limited to age cut off ⩾50	2	0.02	0.00, 1.88	108.10*	99.07

Note: *p value<0.0001.

ADHD as a risk factor for dementia and mild cognitive impairment (Study II)

By linking data from several Swedish population-based registries, we investigated whether ADHD is associated with the risk of developing dementia and mild cognitive impairment (MCI). We further explored whether the potential associations of ADHD with dementia and MCI were affected by educational attainment, comorbid metabolic disorders (i.e., hypertension, type 2 diabetes, and obesity), sleep disorders, head injuries, psychiatric disorders (i.e., depression, anxiety, substance use disorder and bipolar disorder), and sex, and whether a potentially increased risk is shared with other developmental disorders.

Description of study population

Our total cohort comprised 3,591,689 individuals born between 1932 and 1963 who were alive and resided in Sweden in 2001. Individuals who emigrated from Sweden and died before 2001, before the age of 50, and/or those who immigrated to Sweden after 2001 and/or after the age of 50 were excluded from the cohort. The year 2001 was set in the exclusion criteria since diagnosis of ADHD has been mostly available from the outpatient care medical files in the National Patient Register (NPR) since 2001. The follow-up started from the date participants turned 50 years old, and the end of follow-up was the date of dementia/MCI diagnosis/emigration from Sweden/death/December 31st, 2018 (last available date to the researchers in the registries), whichever came first.

There were 9,532 (0.3%) individuals with ADHD diagnosis and/or with ADHD dispensed medication prescription, with 5,168 (54.2%) among them being male and with the median age of ADHD diagnosis/medication prescription being 52 years old (IQR 48-57). By the end of the follow-up, 55,194 (1.5%) individuals were diagnosed with dementia, and 23,507 (0.6%) were diagnosed with MCI. The median age of diagnosis for dementia and MCI was significantly lower in individuals with ADHD in comparison to those without ADHD (Wilcoxon Two-Sample Test: for dementia, $Z = -9.02$, $p < 0.0001$; for MCI, $Z = -11.55$, $p < 0.0001$).

The risk of dementia and MCI in individuals with ADHD

We found significant associations of ADHD with both dementia (HR = 2.92, 95% CI = 2.40, 3.57) and MCI (HR = 6.21, 95% CI = 5.25, 7.35), with adjustments for sex and birth year (Table 6). Additional adjustments for covariates showed that educational attainment, metabolic disorders, sleep disorders, head injuries, and other developmental disorders had a minimal impact on the associations of ADHD with dementia/MCI. On the other hand, the adjustment for psychiatric disorders significantly attenuated the observed associations (HR = 1.62, 95% CI = 1.32, 1.98, for the association of ADHD with dementia, and HR = 2.54, 95% CI = 2.14, 3.01, for the association with MCI (Table 6). The associations of ADHD with dementia were significantly stronger in men compared to women (ADHD by sex interaction coefficient 0.58, 95% CI = 0.38, 0.88, p = 0.01), but the risk of MCI was the same for both sexes (ADHD by sex interaction coefficient of 0.97, 95% CI = 0.69, 1.35, p = 0.84).

We conducted several sensitivity analyses to inspect our results depending on the definition of ADHD. We found that when ADHD identification was based on (a) clinical diagnosis only (i.e., excluding those individuals who only had a medication prescription without a confirmed diagnosis), (b) individuals with at least two confirmed diagnoses of ADHD, and (c) only those with a primary diagnosis of ADHD, the results showed, overall, similar patterns of the associations as the main analysis.

Table 6. Associations of ADHD with dementia and mild cognitive impairment (MCI) as hazard ratios (HR) with 95% confidence intervals (CI) adjusted for sex and birth, collapsed across sex, with additional adjustments for covariates, and stratified by sex.

	HR (95% CI)	Educational attainment	Metabolic disorders	Sleep disorders	Head injury	Psychiatric disorders	Other developmental disorders
Dementia	2.92 (2.40, 3.57)	2.90 (2.37, 3.54)	2.81 (2.30, 3.43)	2.73 (2.23, 3.33)	2.73 (2.23, 3.33)	1.62 (1.32, 1.98)	2.46 (2.01, 3.00)
Male	3.70 (2.89, 4.74)	3.65 (2.85, 4.68)	3.51 (2.74, 4.49)	3.50 (2.73, 4.48)	3.48 (2.72, 4.46)	1.92 (1.49, 2.46)	3.11 (2.42, 3.98)
Female	2.11 (1.51, 2.96)	2.10 (1.50, 2.94)	2.06 (1.47, 2.88)	1.94 (1.38, 2.71)	1.95 (1.40, 2.74)	1.24 (0.88, 1.73)	1.78 (1.27, 2.50)
MCI	6.21 (5.25, 7.35)	5.77 (4.87, 6.82)	5.81 (4.91, 6.87)	4.81 (4.06, 5.69)	5.58 (4.72, 6.60)	2.54 (2.14, 3.01)	5.47 (4.62, 6.48)
Male	6.58 (5.24, 8.27)	6.06 (4.82, 7.61)	6.07 (4.84, 7.63)	5.34 (4.25, 6.71)	5.86 (4.66, 7.36)	2.68 (2.12, 3.38)	5.89 (4.68, 7.42)
Female	5.86 (4.57, 7.52)	5.48 (4.28, 7.03)	5.55 (4.33, 7.12)	4.27 (3.33, 5.48)	5.34 (4.16, 6.84)	2.41 (1.87, 3.10)	5.09 (3.96, 6.55)

Note: Analyses stratified by sex were not additionally adjusted for sex.

ADHD symptoms and subsequent cardiometabolic disorders in adults (Study III)

We investigated the associations of ADHD symptoms severity in young- and mid-adulthood assessed in the STAGE interview/questionnaire with subsequent cardiometabolic disorders in later life based on Swedish health register data. Specifically, we investigated the following questions: i) whether ADHD symptoms in adulthood are associated with cardiometabolic outcomes in later stages of life, ii) whether ADHD symptoms are associated with cardiometabolic disorders after accounting for educational attainment, lifestyle factors and comorbid psychiatric disorders, and iii) after accounting for familial confounding (shared genetic and environmental factors).

Description of study population

The population consisted of 18,003 individuals, with 7,218 males (40.09%). The mean age of the participants at the time of the STAGE interview was 33.75 years (SD = 7.64, range = 19-47), and at the end of the follow-up, the mean age was 46.66 years (SD = 7.63, range = 33-59). We found that the scores on the ADHD scale were significantly positively skewed ($p<0.01$), and they significantly correlated with age (Pearson r coefficient = -0.08, $p<.0001$) but not with sex (t-test = 0.61, $p = 0.54$). Zygosity was established in 17,635 twins, with 6,915 monozygotic and 10,720 dizygotic twins, and 12,548 twin pairs (5455 twin pairs were complete). By the end of the follow-up, 2,530 (14.05% of the study population) individuals were diagnosed with or had a dispensed medication prescription for any CVD, and 1,481 (8.23%) were diagnosed with/received dispensed medication prescription for any metabolic disorder.

Association of ADHD symptoms with cardiometabolic disorders

We found that an increase of one unit in the severity of ADHD symptoms (score range 0-36) was associated with a 3% increase in the rate of CVDs (HR = 1.03, 95% CI 1.02-1.04) and metabolic disorders (HR = 1.03, 95% CI 1.02-1.04), after adjusting for birth year and sex (Table 7). After adjusting for covariates (i.e., education attainment, lifestyle

factors, and comorbid psychiatric disorders), the strength of the associations slightly attenuated but remained significant (HR = 1.01, 95% CI = 1.00, 1.02 for the association of ADHD symptoms with CVDs, and HR = 1.02, 95% CI = 1.01, 1.03 for the association with metabolic disorders). Our results also showed that the pattern of associations remained similar across individual categories of CVDs and metabolic disorders.

The role of familial factors for associations of ADHD symptoms with CVDs and metabolic disorders

When we adjusted the analysis for familial factors shared by dizygotic twins, the associations of ADHD symptoms with both CVDs (HR = 1.05, 95% CI = 1.02, 1.07) and with metabolic disorders remained statistically significant (HR = 1.04, 95% CI=1.01, 1.07) (Table 7). On the other hand, when we adjusted the analysis for familial factors shared by monozygotic twins, the associations were no longer statistically significant (HR = 1.00, 95% CI = 0.97, 1.03, for the association of ADHD with CVDs, and for the association with metabolic disorders, HR = 1.04, 95% CI = 0.99, 1.09). Additionally, we found that the estimates within monozygotic twins were statistically weaker than within dizygotic twins for CVDs (p = 0.02) but not for metabolic disorders (Table 7).

We found a similar pattern of associations across our sensitivity analyses. Overall, the associations of ADHD with cardiometabolic disorders were independent of: (i) the ADHD scale, by investigating the associations with the inattention and hyperactivity/impulsivity subscales, (ii) the definition of ADHD: clinical diagnosis, or research diagnosis of ADHD using the norm-based criteria (Capusan et al., 2015); (iii) the sex of the participants, and (iv) when the analysis was limited to the same-sex dizygotic twin pairs only.

Table 7. Associations between scores on ADHD scale and cardiovascular (CVD) and metabolic disorders, presented as hazard ratios (HR) with 95% confidence intervals (CI).

	CVD HR (95% CI)		Metabolic disorders HR (95% CI)	
Adjustment for birth year and sex:				
	1.03 (1.02, 1.04)*		1.03 (1.02, 1.04)*	
Additional adjustment for educational attainment, lifestyle, and psychiatric disorders:				
	1.01 (1.00, 1.02)*		1.02 (1.01, 1.03)*	
Additional adjustment for familial factors shared between twins in:				
Monozygotic twin pairs	1.00 (0.97, 1.03)	Monozygotic vs dizygotic twins: p=0.02*	1.04 (0.99, 1.09)	Monozygotic vs dizygotic twins: p=0.99
Dizygotic twin pairs	1.05 (1.02, 1.07)*		1.04 (1.01, 1.07)*	

Note: *Statistically significant associations

Prediction model of cardiovascular diseases in adults initiating ADHD pharmacological treatment (Study IV)

Using a data linkage from several Swedish population-based registers, we developed a 2-year prediction model for cardiovascular diseases (CVDs), optimized for adults initiating pharmacological treatment for ADHD. This model considered relevant novel risk factors, such as comorbid psychiatric disorders (i.e., anxiety, depression, bipolar disorder, schizophrenia, sleep disorders, substance use disorder), socio-economic factors (educational attainment and country of origin), and the use of other psychotropic medication. It has been shown that these variables are associated with both ADHD and cardiovascular risk, and they were considered as CVDs predictors in addition to traditional risk factors (i.e., blood pressure, obesity, smoking, diabetes mellitus, etc.).

Description of study population

We included 24,186 individuals born between 1932 and 1990, who started pharmacological treatment for ADHD in Sweden (Zetterqvist,

Asherson, Halldner, Långström, & Larsson, 2013b) between January 1st, 2008, and December 31st, 2011, aged 18 years or older, and without a previous diagnosis of CVD. The following medication prescriptions were considered: stimulant medications - amphetamine (ATC code N06BA01), dexamphetamine (ATC code N06BA02) and methylphenidate (ATC code N06BA04), and non-stimulant medication atomoxetine (ATC code N06BA09). Prescriptions returned to pharmacies by patients after dispensation and prescriptions for indications other than ADHD, such as narcolepsy, pain, handicap, multiple sclerosis, idiopathic hypersomnia, and catalepsy, were previously removed from the data set using natural language processing models for free-text prescriptions from the Prescribed Drug Register (PDR) (Zhang, Lagerberg, et al., 2021). We allowed a wash-out period (i.e., a period free of medication prescriptions for ADHD) of two years for a previous dispensation of medication for ADHD. To obtain a follow-up period of two years, the inclusion period ended on December 31st, 2011, since we had access to data registered until December 31st, 2013. All participants were followed from the date of their first ADHD medication dispensation until the date of their CVD diagnosis/medication dispensation, emigration from Sweden, death, or by the end of two years, whichever occurred first. During the follow-up period, 413 individuals received a CVD (1.7%) diagnosis or medication prescription, with 244 of them being male (59.2%).

Prediction model and novel risk factors

The prediction model included eight traditional risk factors: age at the treatment start, sex, hypertension, diabetes mellitus, obesity, hyperlipidaemia, tobacco use disorder, and family history of CVD before age 60; and four out of sixteen candidate predictors/novel risk factors: substance use disorder other than alcohol and tobacco, mood stabilisers, antipsychotics, and substance use disorder medication (Table 8). Among the traditional risk factors, we found that the strongest association with CVD had a diagnosis or medication prescription of diabetes mellitus (either type 1 or 2) (HR = 1.95, 95% CI = 1.34, 2.85, $p<0.001$). Among novel risk factors, the strongest association with CVDs was found with substance use disorders (other than alcohol and tobacco) (HR = 1.55, 95% CI = 1.25, 1.92, $p<0.001$).

Table 8. Associations of CVDs with predictors included in the model presented as hazard ratios (HR) with 95% confidence intervals (CI).

	Predictor	HR, 95% CI
	Traditional risk factors	
1	Age at treatment start	1.06 (1.05, 1.06)***
2	Sex	0.80 (0.66, 0.98)*
3	Hypertension	1.66 (1.31, 2.10) ***
4	Type 1 and type 2 diabetes mellitus	1.95 (1.34, 2.85) ***
5	Obesity	1.20 (0.78, 1.82)
6	Hyperlipidaemia	0.96 (0.64, 1.44)
7	Tobacco use disorder	1.84 (1.05, 3.21)*
8	Family history of CVD	1.28 (1.02, 1.61)*
	Novel risk factors	
9	Substances use disorder (other than tobacco and alcohol)	1.55 (1.25, 1.92)***
10	Mood stabilisers	1.28 (1.01, 1.66)*
11	Antipsychotics	1.32 (1.06, 1.65)*
12	Substance use disorder medication	1.25 (0.97, 1.61)·

Note: Significance codes: 0.001 '***'; 0.05 '*'; 0.1 '.'; Individuals with 0 days follow-up time were deleted from the analysis, N=1

Performance measures of the model and incremental value of novel risk factors

The model which included both traditional and novel CVD risk factors showed an acceptable overall discrimination (C-index corrected for overfitting = 0.72, 95% CI = 0.70, 0.74) and calibration (integrated Brier score corrected for overfitting = 0.008, calibration plot is presented in Figure 2). On the other hand, we showed that model discrimination was slightly lower in the model with traditional risk factors only, with the C index/AUC = 0.70, while measures of calibration remained similar, integrated Brier score = 0.008. The Integrated Discrimination Improvement (IDI) index, 0.003 (95% CI = 0.001, 0.007), p<0.001, and the category-free or continuous Net Reclassification Index (NRI), 0.16 (95% CI = 0.11, 0.22), p<0.001, were statistically significant, both of which indicated a significant improvement after adding novel risk

factors to the model. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the model with traditional risk factors only, and the model including both traditional and novel CVD risk factors for prespecified high-risk thresholds of 10% (Lloyd-Jones, 2010; Polonsky et al., 2010), and 20% (Grundy et al., 2004) of predicted probability (Table 9). The NRI did not show a significant improvement for the prespecified high-risk thresholds by adding the novel risk factors to the model with traditional risk factors only (Table 9).

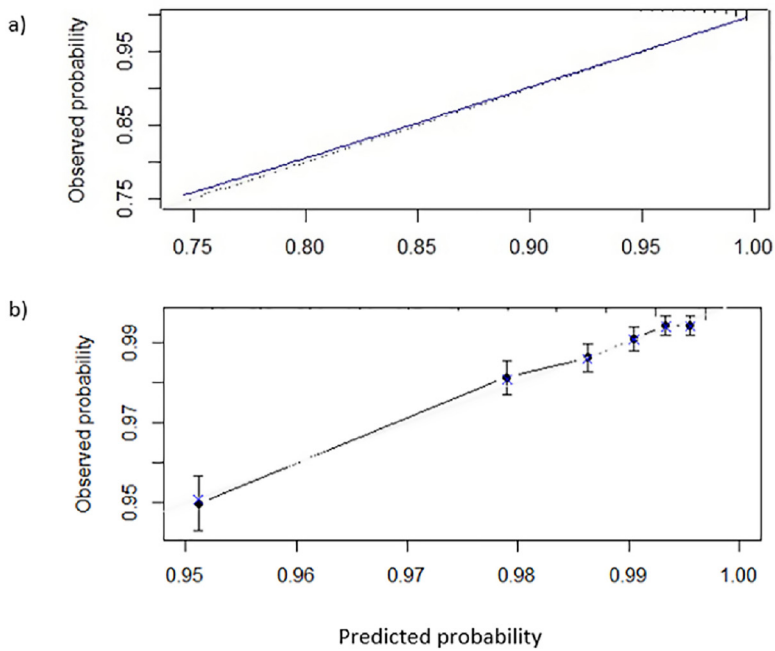

Figure 2. Calibration plots comparing predicted and observed probability of a 2-year cardiovascular disease-free survival/status (98.3% of the cohort) with grey line representing ideal calibration (A) each dot in black represents the observed proportion and each dot in blue represents the predicted proportion corrected for optimism. (B) Individuals are grouped according to percentiles of predicted probabilities of a disease-free survival, the vertical bars are 95% Cis (optimism corrected).

Table 9. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and net reclassification index (NRI) for two high-risk thresholds (20% and 10%), for a model containing traditional risk factors only (Model 1), and a model containing both traditional and novel risk factors (Model 2)

Threshold	Model	Sensitivity	Specificity	PPV	NPV	NRI, 95% CI
20%	1	0.48	0.81	0.07	0.98	0.01 (-0.02, 0.02)
	2	0.52	0.81	0.08	0.98	
10%	1	0.34	0.91	0.11	0.98	0.002 (-0.023, 0.025)
	2	0.34	0.91	0.10	0.98	

Summary of findings

Study I: The pooled prevalence estimates of ADHD in adults aged 50 years and older differed significantly across assessment methods, with 2.18% (95% CI=1.51, 3.16) based on research diagnosis via validated scales, 0.23 % (0.12, 0.43) using a clinical diagnosis of ADHD, and 0.09 % (0.06, 0.15) based on ADHD treatment rates.

Study II: Adults with ADHD have an increased risk of dementia and mild cognitive impairment (MCI), with a hazard ratio (HR) of 2.92 (95% CI 2.40, 3.57) for dementia, and 6.21 (5.25, 7.35) for MCI (analyses are adjusted for birth year and sex). However, after adjusting the analysis for comorbid psychiatric disorders, the strength of the associations substantially attenuated, with HR = 1.62 (95% CI 1.32, 1.98) for dementia and HR = 2.54 (95% CI 2.14, 3.01) for MCI.

Study III: A one-unit increase in the level of ADHD symptoms in young- and mid-adulthood is associated with a 3% increase in the rate of CVDs (HR = 1.03, 95% CI 1.02, 1.04) and metabolic disorders (HR = 1.03, 95% CI 1.02, 1.04) in later life (analyses are adjusted for birth year and sex). The associations remained statistically significant, although attenuated, after further adjustments for educational attainment, lifestyle factors, and psychiatric comorbidity. The associations also remained statistically significant after adjusting for familial factors shared by dizygotic twin pairs but became nonsignificant after adjusting for factors shared by monozygotic twin pairs, which suggests genetic confounding.

Study IV: We developed a 2-year risk prediction model of cardiovascular disease (CVD) in adults initiating pharmacological treatment for ADHD, which included eight traditional and four novel CVD risk factors. The model showed acceptable discrimination (C index = 0.72, 95% CI 0.70, 0.74) and calibration (Brier score = 0.008), and the Integrated Discrimination Improvement index showed a significant improvement after adding novel risk factors (0.003 (95% CI 0.001, 0.007), $p<0.001$), when continuous risk scores were used.

Discussion

The present PhD project has aimed to address a significant knowledge gap in research on ADHD in older adults and associated adverse health outcomes by using a systematic review of literature and meta-analysis, as well as data from large-scale, population-based registers from Sweden. Our findings, overall, indicate that ADHD continues to affect a substantial number of individuals until older age (Study I). Further, we demonstrate that ADHD is associated with an increased risk of age-related disorders, such as dementia/mild cognitive impairment (Study II) and cardiometabolic disorders (Study III). Thus, there is a need for providing a timely diagnosis of ADHD in adults and older adults, as well as adequate treatment for ADHD and comorbid disorders. Furthermore, although the underlying mechanisms of the association of ADHD and age-related disorders are complex, our findings suggest that modifiable risk factors, such as psychiatric comorbidities of ADHD and lifestyle factors, should be targeted in corresponding strategies for preventing age-related disorders and/or ameliorating their deleterious impact on individual's well-being. Additionally, our findings indicate that substance misuse and use of other psychotropic medications should be considered in identifying individuals with ADHD at high risk of cardiovascular diseases, in addition to traditional cardiovascular risk factors (Study IV).

Interpretation of the main findings

Prevalence of ADHD in older adults

In Study I, we used a systematic review of literature and meta-analysis to investigate the prevalence of ADHD in adults aged 50 and older, using different assessment methods. We found a significantly higher pooled prevalence estimate for older adults with a research diagnosis of ADHD (2.18%, 95% CI = 1.51, 3.16) than for those with a clinical diagnosis of ADHD (0.23%, 95% CI = 0.12, 043) or treatment prescriptions for ADHD (0.09%, 95% CI = 0.06, 0.15). In line with previous research (Polanczyk et al., 2007; Simon et al., 2009; Thomas et al., 2015; Willcutt, 2012), our results indicate high heterogeneity of reported prevalence estimates, even though we provided pooled prevalence

estimates for different assessment methods separately, and it remained high even after addressing other potential sources of heterogeneity in the sensitivity analyses.

We found that a considerable number of older adults experience elevated levels of ADHD symptoms based on studies using research diagnoses of ADHD. It has been suggested that clinicians may fail to recognize symptoms of ADHD in some older adults or that current diagnostic criteria may be age-inappropriate in this age group, as the clinical presentation changes with age (Brod et al., 2012; Lensing et al., 2015). This could consequently leave a notable number of older individuals who experience distressing ADHD symptoms without a diagnosis and proper healthcare (Goodman et al., 2016). On the other hand, studies based on a research diagnosis may overestimate the prevalence of ADHD in older adults. This is because, in most of these studies, only symptoms present in adulthood were assessed without considering childhood symptoms, while a confirmation of childhood-onset of ADHD symptoms is required by the ICD/DSM criteria. Symptoms of other psychiatric disorders (i.e., anxiety, depression, etc.) (Quinn & Madhoo, 2014) and neurodegenerative disorders (i.e., mild cognitive impairment or dementia) (Callahan et al., 2017) sometimes resemble symptoms of ADHD and consequently, individuals with these disorders may be misclassified as having ADHD.

Moreover, our findings indicate that the prevalence of individuals treated for ADHD is less than half of the prevalence of those who are clinically diagnosed with ADHD, with most studies considering pharmacological treatment only. Studies on the prevalence of pharmacological treatment among older individuals diagnosed with ADHD are largely lacking, and the available results are mixed, with the prevalence of treatment in ADHD patients varying from 28 to 88% (Polyzoi, Ahnemark, Medin, & Ginsberg, 2018). Although older adults may experience similar benefits from medications as other age groups, healthcare providers may lack awareness of these benefits and adequate knowledge on proper medication dosage in this population (Goodman et al., 2016; Lensing et al., 2015). Furthermore, additional clinical precautions are in place when it comes to pharmacological treatment of ADHD in older adults due to high comorbidity with other psychiatric

and somatic conditions, as well as due to potential interactions with other medications (Brod et al., 2012; Goodman et al., 2016; Lensing et al., 2015). Thus, the findings of this study highlight the need for increased awareness of ADHD in older adults, as well as the need for a timely clinical diagnosis and adequate treatment of these individuals.

ADHD as a risk factor for dementia and mild cognitive impairment

In Study II, using Swedish population-based registers, we investigated whether ADHD was associated with dementia and mild cognitive impairment (MCI). We found that ADHD was significantly associated with an increased risk of developing both dementia and MCI. Our findings provide further support for previous research which identified a significant association between antecedent ADHD and dementia (Fluegge & Fluegge, 2018; Golimstok et al., 2011; Ivanchak et al., 2011; Tzeng et al., 2019). Furthermore, our results partially support the hypothesis that cumulative, health compromising factors along the lifespan may affect the associations of ADHD with dementia and MCI. More specifically, we found that psychiatric disorders (i.e., anxiety, depression, substance use disorder, and bipolar disorder) substantially attenuated the associations. These psychiatric disorders are highly comorbid with ADHD (Fayyad et al., 2017) and also present significant risk factors for dementia (Norton et al., 2014; Zilkens, Bruce, Duke, Spilsbury, & Semmens, 2014). Additionally, some earlier studies have suggested that depressive symptoms probably mediate the effects of ADHD on cognition in older age (Das, Cherbuin, Easteal, & Anstey, 2014; Semeijn et al., 2015).

On the other hand, metabolic disorders (i.e., obesity, type 2 diabetes, and hypertension) only slightly affected the associations, in contrast to one previous study (Fluegge & Fluegge, 2018), which has found that metabolic dysregulation mediated the link between ADHD and dementia. Metabolic disorders may be underdiagnosed in individuals with ADHD in our cohort, which might have attenuated the effect of these disorders on the associations of ADHD with dementia and MCI. It has been shown that people with ADHD have low rates of seeking medical help (Fayyad et al., 2017), which could lead to missed diagnosis and misclassification of those having the disorders as not exposed.

Additionally, individuals with ADHD were significantly younger than those without ADHD at the end of the follow-up, and consequently had lower crude prevalence of metabolic disorders, since the prevalence of these disorders increases with age (Kuk & Ardern, 2010). Similarly, educational attainment, sleep disorders, head injury, and other developmental disorders only minimally affected the associations of ADHD with dementia and MCI.

Finally, we found that the association between ADHD and dementia was stronger in men, in contrast to one previous study, which has identified a stronger association in women (Tzeng et al., 2019). Additionally, we found lower rates of dementia in women than men with ADHD. Potential explanations of these findings could be either that dementia is underdiagnosed in women with ADHD, or that ADHD symptoms were not recognized in some women with dementia as ADHD is still likely underdiagnosed in women (Quinn & Madhoo, 2014).

The findings of this study indicate that adults with ADHD, particularly those with psychiatric comorbidities, may be targeted in corresponding prevention programs for dementia.

ADHD symptoms and subsequent cardiometabolic disorders in adults

In Study III, we aimed to investigate the association between ADHD symptoms in young and mid-adulthood and subsequent cardiometabolic disorders in later life, as well as the underlying mechanisms of the potential associations, using a longitudinal, twin study. Findings from this study suggest that the severity of ADHD symptoms is associated with an increased risk for both cardiovascular (CVDs) and metabolic disorders (i.e., cardiometabolic disorders) later in life. This result confirmed and extended the findings of several recent studies which identified significant associations of ADHD with cardiometabolic disorders (Q. Chen et al., 2018; Du Rietz et al., 2021; Li et al., 2022; Xu et al., 2022) by demonstrating the same associations even at the level of ADHD symptoms in a non-clinical population. The strength of the associations, although attenuated, remained significant after adjusting for educational attainment, lifestyle factors, and comorbid psychiatric

disorders (i.e., major depression, generalized anxiety disorder, and substance use disorder). This indicates that the effect of ADHD symptoms on cardiometabolic outcomes may be partially explained through adverse factors across the lifespan associated with ADHD (Fayyad et al., 2017), ranging from adverse socioeconomic status, lifestyle, and psychiatric health outcomes (Garcia-Argibay et al., 2022; Li et al., 2022; Xu et al., 2022).

Furthermore, we demonstrated that the associations of ADHD symptoms with cardiometabolic disorders were confounded by familial factors, in line with previous research (Du Rietz et al., 2021). In the case of the association of ADHD with CVDs, these familial factors seemed to be driven by shared genetic factors, corroborated by a recent genome-wide study which has reported significant genetic correlations between ADHD and coronary heart disease (Demontis et al., 2023). On the other hand, we did not find equally strong evidence for genetic confounding in the associations between ADHD symptoms and metabolic disorders. In contrast to our findings, a recent family-based study (Du Rietz et al., 2021) has indicated a significant sharing of underlying genetic factors between clinically diagnosed ADHD and metabolic/endocrine disorders as a group of disorders, although this was mainly driven by obesity. At the level of individual disorders, strong evidence has been found for shared genetic factors of clinically diagnosed ADHD and obesity (Demontis et al., 2023; Du Rietz et al., 2021) and type 2 diabetes (Demontis et al., 2023; Demontis et al., 2019). However, due to statistical power issues, we could not investigate the associations between ADHD symptoms and individual categories of cardiometabolic disorders. Furthermore, our results suggest more direct effects of hyperactivity/impulsivity symptoms (than inattentive symptoms) on metabolic disorders after controlling for shared genetic factors shared between monozygotic twins. This indicates that symptoms of hyperactivity/impulsivity may lead to health-compromising behaviors (e.g., unhealthy eating behaviors), which, in turn, could result in obesity and/or other metabolic disorders in later life (Cortese, Bernardina, & Mouren, 2007). Nevertheless, metabolic disorders alone are relevant risk factors for CVDs (Khan et al., 2020; Seidell & Halberstadt, 2015) and may play a role in mediating the link between ADHD symptoms and CDVs. These findings suggest that modifiable risk factors (i.e., eating

behaviors, physical activity, and psychiatric comorbidities of ADHD) for cardiometabolic disorders could be targeted in corresponding prevention programs in adults with ADHD.

Prediction model of cardiovascular diseases in adults initiating ADHD pharmacological treatment

In Study IV, we aimed to improve the accuracy of traditional cardiovascular disease (CVD) risk factors in predicting high-risk individuals with ADHD by considering novel risk factors relevant to this population. We developed a 2-year risk prediction model of CVD in a population consisting of 24,186 individuals initiating pharmacological treatment for ADHD, aged 18 or older, and residing in Sweden. Our findings demonstrate that by including novel cardiovascular predictors, i.e., variables relevant to the population with ADHD, the predictive accuracy of the model improves compared to the model containing traditional risk factors only (i.e., age at treatment start, sex, hypertension, diabetes mellitus, obesity, hyperlipidaemia, tobacco use disorder, and family history of CVDs). The model that included both traditional and novel risk factors provided a C-index/AUC of 0.72, which is considered acceptable in the literature on CVD risk prediction (Lloyd-Jones, 2010). The performance of the new model was consistent with the performance of standard CVD prediction models, for instance, the Framingham risk score, ASSIGN, QRISK, etc., applied in different populations across both sexes (Siontis et al., 2012). On the other hand, the model containing only traditional risk factors yielded a C-index/AUC of 0.70.

The incremental value of novel predictors was assessed using several measures. There were no significant improvements when we used the Net Reclassification Index (NFI) based on two predefined thresholds of predicted probability of 10% (Lloyd-Jones, 2010) and 20% (Polonsky et al., 2010). Conversely, category-free, or continuous measures of improvement, which are considered less dependent on the prevalence of the outcome (Pencina, D'Agostino, & Steyerberg, 2011), showed a significant improvement in model performance after adding the novel risk factors. The low positive predictive value and low sensitivity yielded by our model, taken together with the improvement of the

performance after adding novel risk factors only when we used category-free measures, indicate that the current model may potentially provide better prediction when applied with continuous probability scores. Further, previously established high-risk thresholds may need to be adjusted in younger and middle-aged populations when followed for shorter periods of time. Also, inputs from clinical specialists need to be acknowledged to establish more appropriate thresholds.

Our study validated the importance of traditional cardiovascular risk factors as well as the relevance of their regular monitoring (i.e., regular monitoring of blood pressure, heart rate, weight, etc.) and preventative efforts in individuals at risk upon initiating ADHD treatment. Among 16 considered novel predictors, the final model included the following four predictors: substance use disorder other than alcohol and tobacco, mood stabilisers, antipsychotics, and substance use disorder medication. ADHD is accompanied by high psychiatric comorbidity and, consequently, by the use of other psychotropic medications (Zhang, Reif, et al., 2021). These variables have been previously associated with cardiovascular risks (e.g., coronary artery diseases, cardiac arrhythmia, myocardial infarction, stroke, sudden cardiac death, and myocarditis) (Alinejad, Kazemi, Zamani, Hoffman, & Mehrpour, 2015; Correll, Detraux, De Lepeleire, & De Hert, 2015; K. L. Huang et al., 2017; Nakhaee, Amirabadizadeh, Qorbani, Lamarine, & Mehrpour, 2020). Additionally, it has been shown that treatment of psychiatric disorders with two or more medications (i.e., psychiatric polypharmacy) may lead to poor medication adherence and a greater risk of side effects (Sarkar, 2017). Thus, the novel risk factors should be considered in clinical practice on top of the traditional risk factors and related recommendations and treatment guidelines (Kooij et al., 2019). Further, individuals who are initiating ADHD pharmacological treatment may need to be additionally followed for potential substance use disorder and the use of other psychotropic medications.

Finally, the intention of this study was not to implement the present model in its current form in clinical practice. Studies of external validation of the model in different populations and the use of different data sources, as well as studies assessing its clinical impact, are warranted for future clinical implementation.

Methodological considerations

Age of included study populations

Due to a substantial knowledge gap in the literature regarding ADHD and its adverse health outcomes in individuals aged 50 and older, we primarily focused on this age group when we investigated the prevalence of ADHD (Study I) and the associations with dementia and mild cognitive impairment (MCI) (Study II). When we investigated the associations of ADHD with cardiometabolic disorders (Study III) and developed a two-year risk prediction model of cardiovascular diseases in adults initiating pharmacological treatment for ADHD (Study IV), we primarily included young and middle-aged adults. This might have affected our findings since individuals with ADHD who live until a more advanced older age (i.e., aged 65 and older) may differ from the ones who died earlier in life in terms of ADHD severity, with the latter group having more severe forms of ADHD (Dalsgaard et al., 2015). Nonetheless, it may be useful to investigate the risk of age-related disorders in individuals with ADHD who have not reached a more advanced older age yet, as ADHD-associated functional impairments and multimorbidity may lead to an increased risk of premature death (Dalsgaard et al., 2015) and earlier onset of age-related disorders. Indeed, we demonstrated this in Study II, with the group with ADHD having an earlier age of onset of dementia and MCI (median age 61.5 years for dementia, and 59 for MCI) compared to those without ADHD (median age 72 years for dementia, and 69 for MCI).

Furthermore, due to a relatively young study population in Study II, we might have captured the associations of ADHD with early onset dementia (i.e., before age 65), which is likely more affected by genetic factors than later onset dementia (Awada, 2015). Similarly, as the incidence rates of cardiometabolic disorders peak at ages 60-65 and above (Kuk & Ardern, 2010; Yazdanyar & Newman, 2009), in Study III, we captured only a fraction of individuals who might have potentially developed these disorders in the future. Future studies following individuals until a more advanced age are necessary to further explore the associations of ADHD with age-related disorders and the underlying mechanisms.

Additionally, although the prediction model of CVDs developed in Study IV includes age as one of the predictors, it may not generalize to older individuals since the median age at treatment start was only 33 years. A prediction model which would include a higher proportion of older individuals or tailored specifically to older individuals initiating pharmacological treatment for ADHD as a high-risk group (Sandra Kooij et al., 2016) may provide better predictive accuracy in this age group and additional clinical value.

Misclassification bias

The current thesis relied mostly on data from Swedish electronic health records. This type of data source provides many advantages, such as large, population-based samples and the possibility of exploring rare exposures and outcomes (Maret-Ouda et al., 2017). At the same time, there are several important limitations, one of them being potential misclassification bias, which is a type of systematic error when an individual is classified into a different category than the one this individual truly belongs to (Pham, Cummings, Lindeman, Drummond, & Williamson, 2019). In Study II, we defined individuals with ADHD as those having an ICD-based (ICD-9/10) diagnosis or dispensed medication prescription for ADHD, as it has been previously shown that these definitions are valid indicators of ADHD (Larsson, Rydén, et al., 2013). However, diagnoses based on ICD-9/10 classification systems and pharmacological treatment for ADHD may cover people with the most severe clinical presentations (Larsson, Rydén, et al., 2013). Furthermore, the information on outpatient diagnoses in the NPR has been available only since 2001, and the information on prescribed drugs from the PDR has been available since 2005. These reasons, taken together, might have caused incomplete coverage of all exposed individuals and false negatives, i.e., people falsely categorized as not being exposed. Conversely, in some instances, medications for ADHD are prescribed for indications other than ADHD, such as narcolepsy, idiopathic hypersomnia, catalepsy, multiple sclerosis, and pain (Zhang, Lagerberg, et al., 2021). Since we did not have access to the information regarding indications for medication prescriptions, some persons may have been falsely classified as having ADHD (i.e., false positives). Furthermore, due to the similar clinical presentations of ADHD, mild cognitive

impairment (MCI), and prodromal dementia in older age (e.g., sleeping issues, symptoms of anxiety and depression, etc.) (Pollak, 2012), it is possible that some people with ADHD were falsely diagnosed with MCI, and vice versa. Although this issue was partially addressed in Study II by conducting a sensitivity analysis with at least two established diagnoses of ADHD, future studies are needed to validate the classification criteria of ADHD and MCI in Swedish registers.

Next, some of the predictors in Study IV, such as tobacco use disorder and obesity, may only cover people with the most severe presentations of these disorders since the information in the NPR is based on specialist care only. Thus, self-reported information on these variables may provide better coverage of all affected persons in future studies.

Self-report of ADHD symptoms in adulthood

In Study I, we investigated the prevalence of ADHD in adults aged 50 and older using different assessment methods, with one of them being a research diagnosis based on validated scales and with almost half of the included studies using screening tools of currently present symptoms of ADHD (e.g., the Adult ADHD self-report scale screener version 1.1 (ASRS)) (Kessler et al., 2005). Similarly, in Study III, we used ADHD symptoms severity score based on a self-report of nine inattention and nine hyperactivity/impulsivity symptoms in accordance with DSM-IV diagnostic criteria for ADHD (Larsson, Chang, D'Onofrio, & Lichtenstein, 2014). These scales provide descriptions of ADHD symptoms adjusted to adults, and they have been previously validated in adults (Larsson, Chang, D'Onofrio, & Lichtenstein, 2014; Kessler et al., 2005). However, there are several important methodological limitations that need to be considered when screening tools are used in establishing a research diagnosis of ADHD or assessing the symptom severity. Firstly, the applied scales are based on the screening of currently present symptoms only, without confirmation of symptom childhood-onset and of accompanying functional impairments, which the DSM and ICD require as diagnostic criteria for ADHD. By applying screening tools for ADHD, we may identify individuals affected by ADHD symptoms who might have been otherwise undetected by a clinical diagnosis or by using more strict criteria (i.e., the confirmation of

childhood onset of symptoms and functional impairments). However, without fulfilling the required diagnostic criteria, ADHD-like symptoms due to other conditions with a similar clinical presentation may be misclassified as ADHD (Kooij et al., 2019; Pollak, 2012). Consequently, a research diagnosis of ADHD based on screening tools only may overestimate the prevalence of ADHD (Study I), or the symptoms described as ADHD symptoms might have been experienced due to other conditions (Study III). We tried to mitigate this issue by conducting a sensitivity analysis in Study III, where we investigated the associations of clinically diagnosed ADHD with cardiometabolic disorders. This analysis yielded results consistent with the main findings based on the ADHD symptoms severity, but of a larger effect size, potentially due to covering individuals with more severe ADHD.

To provide a more comprehensive picture of adult ADHD and the potential associations with adverse health outcomes, community-based studies may consider using ADHD screening tools as a first assessment step accompanied by a diagnostic interview. For instance, a study from the Netherlands has conducted such a two-step procedure and reported that 4.2% of adults aged 60 years and older have symptomatic ADHD based on a screening tool, while 2.8% have syndromatic ADHD, with the full DSM-IV-TR diagnostic criteria being met (Michielsen et al., 2012). However, exclusively relying on self-reported ADHD symptoms in adults may also provide an insufficient assessment. This is because it has been found that a self-report of ADHD symptoms in adults may underestimate the prevalence of ADHD compared to a parent-report due to recall bias (Barkley, Fischer, Smallish, & Fletcher, 2002; Simon et al., 2009). Thus, future studies may also need to consider corroborating self-report scales of ADHD symptoms with reports from a relative (e.g., parent, sibling, or spouse).

Timeline of the exposure, mediators, and outcomes

In Studies II and III, it was hypothesized that ADHD may increase the risk of adverse socioeconomic and health outcomes across the lifespan, which in turn increases the risk of developing age-related disorders. Thus, several covariates in these studies were assumed to have the role

of mediators in the associations, with the mediators occurring after the exposure but before the outcome (VanderWeele, 2016).

In Study II, the exposure variable was a diagnosis of/dispensed medication prescription for ADHD given at any time point. The following covariate sets were addressed as potential mediators: educational attainment before age 50, metabolic disorders (hypertension, type 2 diabetes, obesity), sleep disorders (organic and nonorganic), head injuries, and psychiatric disorders (depression, anxiety, substance use disorder, and bipolar disorder). Here we included a diagnosis of these disorders at any time point, but before the outcome occurrence. The outcomes, a diagnosis of dementia or mild cognitive impairment, had to be acquired after the age of 50, when the follow-up of the participants started.

In Study III, the severity of ADHD symptoms was the exposure, with ADHD symptoms being assessed in the STAGE interview/questionnaire in 2005-2006. The following covariates were considered as potential mediators: educational attainment, lifestyle factors (smoking, body mass index, and physical activity), and psychiatric disorders (major depression, generalized anxiety disorder, and alcohol dependence), and they were assessed at the same time point as ADHD symptoms. The outcome, a diagnosis of/dispensed medication prescription for a cardiovascular or metabolic disorder, was acquired after the STAGE assessment.

The hypotheses on the covariates acting as mediators relied on several assumptions: (i) ADHD has childhood onset in accordance with ICD and DSM criteria, (ii) ADHD is typically a temporally primary psychiatric disorder in relation to psychiatric comorbidities (Fayyad et al., 2017; Sobanski, 2006), and (iii) other considered disorders (e.g., type 2 diabetes, hypertension, obesity) typically have adult-onset (Kuk & Ardern, 2010). Nevertheless, to properly investigate whether these covariates truly have the role of the mediator, future longitudinal studies are needed to investigate the timeline between the onset of ADHD and the onset of potential mediators and outcomes.

Generalizability

Another potential issue with using data from electronic health records from one country, in this case from Sweden, is that the findings of the current studies may not generalize to other countries. This may be due to specific societal and economic conditions in Sweden as well as specific characteristics of the Swedish healthcare system and diagnostic and treatment guidelines for different conditions. Future studies from other counties, as well as studies using different types of study samples (e.g., community samples) and data sources (e.g., self-reported), are needed to validate our findings.

Ethical considerations

Study I, the systematic review and meta-analysis were not based on any collection or analysis of original data. Instead, data reported in the pertinent studies from publicly accessible documents were used, in this case, reports of prevalence estimates of ADHD. Although conducting systematic reviews and meta-analyses does not require obtaining ethical approval, certain ethical issues may arise, as in the case when included studies failed to obtain their own ethical approvals (Vergnes, Marchal-Sixou, Nabet, Maret, & Hamel, 2010). However, by systematically searching for and assessing all available evidence without restrictions regarding language or country of publication, year of publication, type of document, full-text published articles, or conference proceedings, we aimed to provide the most comprehensive and unbiased study findings (Suri, 2020).

Studies II, III, and IV were based on record linkage data acquired from several Swedish population-based registers. These record linkages and research projects have been reviewed and approved by the Regional Ethical Board in Stockholm. Ethical applications and decisions reference numbers by the study are the following: Study II and IV, DNR: 2013/862-31/5, and Study III, DNR: 2010/322-31/2. Statistics Sweden and the Swedish National Board of Health and Welfare are responsible for merging the data with generated identification codes for each participant, keeping the code list, and removing any personal information that could potentially lead to the revealing of personal identity. This code-list is not destroyed but it is kept by the responsible agency on a

protected server, and it is not available to the researchers, which makes the data pseudo-anonymized. Registry-based studies use data that are routinely collected by healthcare providers and do not involve direct contact with study participants, thus, generally, they do not require informed consent from participants according to current Swedish regulations (Ludvigsson et al., 2015). However, Study III utilized data from the Swedish Twin Registry (STR) and the Study of Twin Adults: Genes and Environment (STAGE), which required informed consent from the participants for the participation in the STAGE questionnaire/interview conducted in 2005-2006, and the subsequent record linkage.

The studies included in the present doctoral dissertation only report group means at the national level, hence the risk of identifying individual persons is considered minimal. As health-related data are considered sensitive, particular caution must be taken in order to persevere data confidentiality and personal integrity of participants: the data are not to be distributed to-, and the access to datasets is not to be given to- any unauthorized parties, and the data will only be used for the stated research goals. General Data Protection Regulations (GDPR) and appropriate Swedish legislations were followed in all data handling, analyses, and reporting. Additionally, the benefits from the knowledge in relation to adverse health outcomes in adults and older adults with ADHD acquired in the current studies, which would provide useful insights for public health agencies and the public in general, should outweigh any potential risks regarding ethical considerations.

General conclusions and clinical implications

The findings of the current thesis suggest that there is a substantial number of older adults with elevated levels of ADHD symptoms, many of whom do not receive formal diagnoses. Furthermore, we found that ADHD is associated with an increased risk of age-related disorders, namely, dementia/MCI and cardiometabolic disorders. We further aimed to improve the predictive accuracy of traditional risk factors of cardiovascular diseases in adults who are initiating pharmacological treatment for ADHD by additionally considering relevant novel risk factors.

Overall, our findings emphasize the need for healthcare providers and researchers to increase the awareness of ADHD in older adults and to provide them with more adequate clinical diagnoses and treatment. Timely diagnosis could be potentially achieved as per current clinical recommendations provided by the Updated European Consensus Statement on diagnosis and treatment of adult ADHD (Kooij et al., 2019), which suggest screening for ADHD in adults with a history of inattentiveness, hyperactivity/impulsivity, emotion dysregulation, other mental health disorders, behavioral problems, criminality, and in adults with family members diagnosed with ADHD. Furthermore, it is important to note that even individuals with ADHD symptom severity below contemporary clinical thresholds may experience significant distress and adverse health outcomes. Thus, such individuals should not be overlooked by clinicians. Future studies are needed to validate current diagnostic criteria for ADHD in older adults. Furthermore, due to an increased risk of age-related disorders in adults with ADHD, there is a need for more clinical awareness through a rigorous assessment of physical health in these individuals.

Moreover, our results indicate that the association of ADHD symptoms with cardiometabolic disorders is partly explained by an underlying genetic component. However, the association of ADHD with dementia and MCI, as well as cardiometabolic conditions, also appears to be partially explained by modifiable risk factors, such as comorbid psychiatric disorders or lifestyle factors. Thus, future prevention programs should target such modifiable risk factors in young or middle-aged adults with

ADHD, for instance, their eating behaviors, sleep hygiene, physical activity, smoking, or substance misuse, to prevent or ameliorate the effects of age-related disorders. Additionally, comprehensive treatment strategies for individuals with adult ADHD should encompass relevant psychiatric comorbidities. Furthermore, when initiating pharmacological treatment for ADHD, clinicians should consider the novel cardiovascular risk factors, such as the use of other psychotropic medication and substance abuse, in addition to the current clinical guidelines, to provide a more precise prediction of adults with ADHD who are at higher risk of developing cardiovascular disease.

Future perspectives

Investigation of more nuanced associations

Although our study findings are based on data from large, population-based study populations, there are several important considerations which limited our analyses. ADHD, as a relatively new clinical concept, is rarely diagnosed and treated in middle-aged and older adults. Epidemiological studies from the UK, US, Taiwan, and across Nordic countries have shown a trend of increasing incidence and prevalence in the last two decades of adults aged 50 and older who received diagnosis and treatment for ADHD, indicating an increased awareness of ADHD in adults and older adults (Castle, Aubert, Verbrugge, Khalid, & Epstein, 2007; C. L.-C. Huang, Chu, Cheng, & Weng, 2014; Karlstad et al., 2016; McCarthy et al., 2012). However, these prevalence estimates remain very low in comparison with the community-based estimates of the prevalence of ADHD in older adults (Das et al., 2014; Park et al., 2011; Kooij et al., 2005).

To counteract this issue to some extent, we covered somewhat younger study populations, and thus, the incidence of age-related disorders was low. Therefore, we did not have enough statistical power to investigate the associations of ADHD with individual subtypes of dementia (Study II) or with separate disease categories of cardiovascular and metabolic disorders (Study III). Future studies should investigate associations between ADHD and different subtypes of dementia (e.g., Alzheimer's disease (AD), vascular dementia, frontotemporal dementia, dementia with Lewy bodies) separately. For instance, there is no or very limited evidence for the associations of antecedent ADHD with AD within individuals (Fluegge & Fluegge, 2018; Golimstok et al., 2011; Ivanchak et al., 2011; Tzeng et al., 2019), but some recent multi-generation studies have indicated a shared familial risk between ADHD and AD (Zhang, Du Rietz, et al., 2022). Furthermore, neurobiological/genetic explanations to the observed associations were beyond the scope of Study II. Future research is needed to further investigate the underlying mechanisms of the associations between ADHD and dementia and whether they may differ for distinct dementia subtypes. Subtypes of dementia may be differentially associated with ADHD due to distinct

etiological pathways, and in some cases, ADHD might only share similarities in clinical presentation with dementia but have unrelated underlying mechanisms (Callahan et al., 2017).

Furthermore, in terms of cardiometabolic issues, family-based studies have reported strong evidence of shared genetic factors of ADHD and obesity but not for type 2 diabetes and cardiovascular disorders (Du Rietz et al., 2021), while genome-wide association studies have found significant genetic correlations of ADHD with obesity, type 2 diabetes, and coronary heart disease (Demontis et al., 2023; Demontis et al., 2019). Similar investigations should be done by considering ADHD symptoms severity in addition to clinically diagnosed ADHD to capture more individuals affected by ADHD and subclinical ADHD and to provide more precise input for healthcare providers and corresponding prevention and treatment considerations. Additionally, future molecular genetic studies are needed to pinpoint the specific biological mechanisms that explain the shared genetic components between ADHD and severe health outcomes. This information could provide useful insights for uncovering prevention and medication treatment strategies for aging patients with ADHD.

Persistence of ADHD until older age and the importance of longitudinal approaches

The current thesis investigated whether the persistence of ADHD until older age may adversely impact a person's health later in life. However, very few studies have assessed symptoms of ADHD within the same population at different stages of life. Several longitudinal studies have prospectively investigated the persistence of symptoms but mostly only until adolescence or early adulthood (<25 years of age) (Barkley et al., 2002; Biederman, Petty, Evans, Small, & Faraone, 2010; Hart, Lahey, Loeber, Applegate, & Frick, 1995; Biederman, Eric Mick, & Faraone, 2000), with one study following individuals until 38 years old (Moffitt et al., 2015). The results of these studies have indicated that persistent ADHD is associated with higher levels of comorbidity and functional impairment (Biederman et al., 2010). Further, the number and severity of ADHD symptoms decline with age leading to many individuals no longer meeting the criteria for an ADHD diagnosis but still

experiencing functional impairments (Biederman et al., 2000; Moffitt et al., 2015). Similarly, it has been suggested that although older individuals may experience less severe ADHD symptoms, the impairing effects of ADHD may remain (Brod et al., 2012; Biederman et al., 2000; Torgersen et al., 2016). This impairing effect may come from ADHD symptoms experienced earlier in life (e.g., lower educational attainment resulting in limited work opportunities and lower socio-economic status in later life) or due to related comorbid issues.

Until now, most community-based studies have addressed the persistence of ADHD across the lifespan by retrospectively assessing childhood symptoms in older individuals, in addition to currently present symptoms of ADHD (Bernardi et al., 2012; de Zwaan et al., 2012; Guldberg-Kjär, Sehlin, & Johansson, 2013; Michielsen et al., 2012). Nevertheless, the risk of recall bias and misclassification remains a substantial methodological issue in this approach. A potential solution would be to prospectively follow individuals from early until later life with the assessment of ADHD symptoms and associated functional impairments and health outcomes at different time points. One of the relevant challenges that needs to be considered comes from the changes of diagnostic criteria for ADHD over time, such were the relevant changes from the DSM-IV to DSM-5 and from the ICD-10 to ICD-11 (Caye et al., 2016). Nevertheless, future longitudinal studies are crucial to properly investigate the persistence of ADHD across life, as well as the associated risk of adverse functional and health outcomes.

Acknowledgements

I would like to express my deepest gratitude to **Henrik Larsson**, my principal supervisor, who accepted me as his PhD student and has guided me through my PhD journey and all its challenges with so much ease and kindness, flexibility, support, and trust in me. I have learned so much as a researcher from you, and I was truly fortunate to have you as a supervisor.

Big thanks to **Ebba du Rietz**, who became my assistant supervisor a little bit later in my PhD studies but has contributed to my work tremendously by sharing her knowledge with me and providing me with support and feedback whenever I needed it.

Henrik Andershed, my former assistant supervisor, thank you for providing valuable feedback on my work, and your guidance of our Newbreed psychosocial thematic group.

Thanks to the **Newbreed Successful ageing cohort,** and **Anette, Miles, and Eleonor** for welcoming us from all over the world and providing us with support and nice gatherings throughout these years as doctoral students at ÖRU. Also, during my doctoral education, I have been part of the **TIMESPAN** research project, where I have had the opportunity to learn a lot from the experts in the field.

Next, I would like to thank the **USÖ-Larsson group, Carmen, Lin, Anneli, Rebecca, Sofi, Anna-Karin, Rickard, Nilo and Shichun**, for many interesting discussions, valuable feedback, and a supportive and positive environment. Also, thanks to **Miguel** for all his help with the data analysis and his quick responses to my many questions.

Thanks to **Samuele Cortese** for welcoming Carmen and me, and for the nice working environment during our secondment at Southampton University in 2019. Also, thanks to **Le Zhang**, for welcoming me during my visit to MEB, Karolinska Institutet, in the beginning of 2020, and for sharing her knowledge with me. It has given me such a good start with the data analysis for the rest of my PhD studies.

Many thanks to all my **co-authors, Samuele Cortese, Zheng Chang, Lin Li, Le Zhang, Carmen Solares, Miguel Garcia-Argibay, Stephen**

V. Faraone, Seena Fazel, Tomas Jernberg, Johan Jendle, Qi Chen, Isabell Brikell, and Ralf Kuja-Halkola, who have provided valuable inputs and have helped me to grow my knowledge and skills as a researcher.

I would also like to thank the **colleagues at USÖ, and Snieguole**, my officemate, for their company and all the interesting lunch and fika conversations.

Next, I would like to thank the **research administrators** at the School of Medical Sciences, ÖRU. **Susanne Josefsson**, thank you so much for your assistance and patience though all the administrative hurdles.

Big thanks to my wonderful friends in Sweden: **Christiana, Carmen, Sarita, Nadya, Andreea, and Hany**, thank you for being my friends when I needed it the most, and friends from home, Serbia: **Ivana, Branka, Pedja, Bojana, Jelena K., Jelena S., Dragana, and Deki**, you have always been by my side! And, my dear **mom, dad, brother, niece Kalina, and nephews Jovan and Stefan**, thank you for your endless support, unconditional love, for making me the person I am today, and for always welcoming me back home with open arms.

And finally, thank you **Drissa and Sava**, for your love and the family we have created during these trying times.

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