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DEVELOPMENTAL TRAJECTORIES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER INTO ADULTHOOD AND AGING: MULTIMORBIDITY AND POLYPHARMACY

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Developmental Trajectories of Attention-Deficit/Hyperactivity Disorder into Adulthood and Aging: Multimorbidity and Polypharmacy

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To my beloved family

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by developmentally inappropriate levels of inattentiveness, hyperactivity, and impulsivity. Previous studies have shown that symptoms of ADHD often persist into adulthood. In addition, substantial psychiatric comorbidities as well as adverse somatic outcomes could emerge across the lifespan. However, health outcomes of ADHD in adulthood and old age, and the long-term consequences of ADHD medications remain understudied.

In study I, we described the patterns of co-medication and polypharmacy with ADHD medications among adults. Among all major classes of somatic medications, respiratory system medications, alimentary tract and metabolism system medications, and cardiovascular system medications have the highest odds of being dispensed when comparing individuals using ADHD medication to controls.

In study II, we examined whether ADHD is linked with Alzheimer's disease (AD) and other dementias within families. We found ADHD was associated with AD and any dementia across generations, for example, parents of individuals with ADHD were associated with a 55% increased risk of AD compared to parents of individuals without ADHD. The associations attenuated with decreasing genetic relatedness. The increased risk associated with ADHD was higher for early-onset AD than that for late-onset AD.

In study III, we performed a systematic review and meta-analysis to examine the association between ADHD medications and a broad range of cardiovascular diseases (CVDs). Nineteen studies with 4 million participants were included. The results show there was no statistically significant association between ADHD medication use and CVDs in general, but the pooled risk ratio does not exclude a modest risk increase, especially for the risk of cardiac arrest and tachyarrhythmias. The risk of CVDs among females and those with pre-existing CVDs, and the long-term risk associated with ADHD medication use require further evaluation.

In study IV, we assessed the association between the long-term use of ADHD medication and the risk of CVDs using a nested case-control design. We found longer duration of ADHD medication use was associated with an increased risk of CVDs compared with non-use. A one-year increase use of ADHD medication was associated with a 7% of increased risk of CVDs. A higher cumulative dose of ADHD medications was also associated with an increased risk of CVDs.

LIST OF SCIENTIFIC PAPERS

I   Zhang L, Reif A, Du Rietz E, Lagerberg T, Butwicka A, D'Onofrio BM, Johnell K, Pedersen NL, Larsson H, Chang Z. Comedication and polypharmacy with ADHD medications in adults: a Swedish nationwide study. *Journal of Attention Disorders*. 2021;25(11):1519-28.

II   Zhang L, Du Rietz E, Kuja-Halkola R, Dobrosavljevic M, Johnell K, Pedersen NL, Larsson H, Chang Z. Attention-deficit/hyperactivity disorder and Alzheimer's disease and any dementia: A multi-generation cohort study in Sweden. *Alzheimer's & Dementia*. 2022;18(6):1155-63.

III Zhang L, Yao H, Li L, Du Rietz E, Andell P, Garcia-Argibay M, Cortese S, D'Onofrio BM, Larsson H, Chang Z. Risk of cardiovascular diseases associated with medications used in attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *JAMA Network Open*. 2022;5(11):e2243597.

IV Zhang L, Li L, Pontus A, D'Onofrio BM, Johnell K, Larsson H, Chang Z. ADHD medications and long-term risk of cardiovascular diseases: a nationwide nested case-control study in Sweden. *(Manuscript)*

RELATED SCIENTIFIC PAPERS

(Not included in the thesis)

I   Zhang L*, Lagerberg T*, Chen Q, Ghirardi L, D'Onofrio BM, Larsson H, Viktorin A, Chang Z. Prediction of treatment dosage and duration from free-text prescriptions: an application to ADHD medications in the Swedish prescribed drug register. *Evidence-Based Mental Health*. 2021;24(4):146-52.

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

III Dobrosavljevic M, Fazel S, Du Rietz E, Li L, Zhang L, Chang Z, Jernberg T, Faraone SV, Jendle J, Chen Q, Brikell I, Larsson, H. Risk prediction model for cardiovascular diseases in adults initiating pharmacological treatment for attention-deficit/hyperactivity disorder. *Evidence-Based Mental Health*. 2022;25(4):185-90.

* Equal contribution

CONTENTS

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADHD	Attention-deficit/hyperactivity disorder
ATC	Anatomical therapeutic chemical
CDR	Cause of Death Register
CI	Confidence interval
CNVs	Copy number variants
CVD	Cardiovascular disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
GRACE	Good Research for Comparative Effectiveness
GWAS	Genome-wide association study
HR	Hazard ratio
ICD	International Classification of Diseases
IQR	Interquartile range
IRR	Incidence rate ratio
LISA	Longitudinal Integrated Database for Health Insurance and Labor Market
MGR	Multi-generation Register
NPR	National Patient Register
OR	Odds ratio
PDR	Prescribed Drug Register
PRISMA	Preferred Reporting Items for Systematic reviews and Meta Analyses
RCT	Randomized controlled trial
RR	Relative risk
TPR	Total Population Register

1 INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by developmentally inappropriate levels of inattentiveness, hyperactivity, and impulsivity.[1] Previous research has suggested that some symptoms of ADHD decline as individuals age, but still as many as two-thirds of individuals diagnosed with ADHD in their childhood are affected by the disorder at an impairing level in their adulthood. In addition, prior studies found symptoms of ADHD present in a considerable number of older adults.[2]

Substantial psychiatric comorbidities have been suggested among children and adolescents with ADHD in prior studies, such as depression, conduct disorder, and autism spectrum disorders.[3] Some recent studies have found that non-psychiatric comorbidities are common among individuals with ADHD, such as obesity,[4, 5] diabetes mellitus,[5] as well as disorders of chronic inflammation (e.g. asthma[6] and allergic rhinitis[7]). However, there remains a substantial amount of conflicting results surrounding these potential associations, especially among adults and late adulthood. Evidence on neurological and somatic comorbidity among adults, such as for Alzheimer's disease (AD) and other dementias and cardiovascular diseases (CVDs), which are the leading disease burden in Sweden,[8, 9] are limited.

Randomized controlled trials (RCTs) have suggested the effectiveness of ADHD medications for alleviating core symptoms, both stimulants and non-stimulants.[10] With the increasing awareness about ADHD and the knowledge about pharmacological treatment of the disorder, the use of ADHD medications has increased in the past decades, especially among adults.[11]

Due to the persistence of ADHD symptoms and the high rates of psychiatric and somatic comorbidities, simultaneous use of multiple medications, i.e. co-medication and polypharmacy, are possible. However, no prior studies have described the co-medication and polypharmacy pattern. In addition, several studies have raised concerns about the safety of ADHD medications. Non-serious events including sleep problems,[12] abdominal pain,[13] and decreased appetite[14] are well-established, but concerns regarding serious adverse effects, in particular cardiovascular safety, have been largely debated.[15]

Therefore, this thesis, including four studies, described the co-medication and polypharmacy pattern with ADHD medications in adults (study I), studied the link between ADHD and Alzheimer's disease and other dementias within families (study II), and evaluated the cardiovascular safety of ADHD medication use (study III and IV).

2 LITERATURE REVIEW

2.1 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

The signs and symptoms of ADHD have been reported for more than two centuries, starting in European countries.[16] The first description of attention deficit symptoms was found in a chapter of a medical textbook published in 1775, written by Melchior Adam Weikard, a prominent German physician.[17] In 1902, the description of the disorder was first written in a scientific journal by George Still, a British pediatrician.[3] In 1932, the term "hyperkinetic disorder" was coined by German researchers Franz Kramer and Hans Pollnow,[18] and it was later adopted by the World Health Organization in the *International Classification of Disease* (10th ed.; ICD-10) manuals.[19] The term ADHD was used in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.-revised; DSM-III-R) in 1987,[20] and continued to be used in the DSM-IV,[21] the new DSM-V,[1] and the new ICD-11 manuals.[22]

2.1.1 Diagnosis

Diagnosis of ADHD could not be made through a single test, rather it requires a multi-step process.[3] The diagnostic procedure often includes interviews with the patient, interviews with other significant people such as relatives and teachers, physical examination, and cognitive testing.[23] The disorder can only be diagnosed by a licensed healthcare professional including psychologists, pediatricians and specialists in child or adult psychiatry. In Sweden, DSM-5 is the most commonly used criteria for the diagnosis of ADHD.[23-25] The diagnosis requires, according to DSM-5, a persistence of developmentally inappropriate levels of inattentive and/or hyperactive-impulsive symptoms for ≥ 6 months; symptoms occurring in ≥ 2 settings and interfering with functioning; several symptoms and impairments first occurred before age 12 years; the symptoms are not better explained by other disorders. A detailed description of the diagnostic criteria is listed in Table 2.1.

The 2013 update to the DSM manual, i.e. DSM-V, has important alterations in the diagnosis of ADHD in adolescents and adults, compared to its previous versions.[26] The onset age of symptoms and impairments of ADHD required for a diagnosis was changed from 7 years to 12 years, and the minimum number of symptoms required was reduced from six to five for older adolescents and adults.[1] Examples were given regarding how relevant symptoms may manifest in adolescents and adults if any difference as in children.[27-29] With these changes, the diagnosis of ADHD in older adolescents and adults was made more applicable.[26]

Table 2.1 The DSM-V diagnostic criteria for ADHD

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention**: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions**.** For older adolescents and adults (age 17 and older), at least five symptoms are required.

   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).

   b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).

   c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).

   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily side tracked).

   e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).

   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).

   g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).

   h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).

   i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

2. **Hyperactivity and impulsivity**: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

   a. Often fidgets with or taps hands or feet or squirms in seat.

   b. Often leaves seat in situations when remaining seated is expected (e.g., leave his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).

   c. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)

   d. Often unable to play or engage in leisure activities quietly.

   e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).

   f. Often talks excessively.

   g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).

   h. Often has difficulty waiting his or her turn (e.g., while waiting in line).

   i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

2.1.2 Prevalence across the lifespan

ADHD is one of the most commonly diagnosed neurodevelopmental disorders, which affects around 5-7% of children,[30, 31] 3% of adults,[29, 32, 33] 1-2% of older adults.[2] It is well-established that clinically diagnosed ADHD declines with age, while the symptoms, especially the inattention presentation, often persist beyond adolescence.[34] Follow-up studies have shown that by the end of 25 years of age, there were still 15% of individuals with ADHD met the full diagnostics criteria of ADHD, and another 50% of individuals continued to experience ADHD symptoms with functional impairments.[34] This means that as many as two-thirds of children with ADHD are still affected by the disorder at an impairing level in their adulthood.[34, 35] However, until the last two decades, ADHD was not commonly recognized in adults.[36] The reason for this is likely to be the long historical perception of ADHD as a childhood disorder, as well as the lack of coordination between child/adolescent psychiatry and adult psychiatry.[37-39] Only a few studies have examined the prevalence of ADHD in older adults, and a recent meta-analysis of available studies showed that symptoms of ADHD were presented in a substantial number of older adults, i.e. an estimate of 1.5% in individuals age 50 or older.[2]

Besides age, there are important variabilities in prevalence across gender and countries. In children and adolescents, males are more likely to be diagnosed with ADHD than females, with a ratio ranging from 2:1 to 10:1.[40, 41] The sex discrepancy is largely diminished to a more balanced ratio in adults.[41, 42]

Although substantial variability in prevalence was reported across countries, research has found that the variability could be attributable to methodological differences in diagnostic criteria, source of information, the requirement of impairment for diagnosis, and geographic origin of the studies.[31, 43]

2.1.3 Etiology

ADHD has a strong genetic origin. Twin and family studies suggested a heritability of around 74%.[44-46] Recent studies have evaluated the heritability of ADHD in the adult population and found the estimates were similar to that among children and adolescents.[44, 47] These findings delivered a message that the heritability of clinically diagnosed ADHD was also substantial in adults.[47] These studies also implied a minimal role of shared environmental risk factors (e.g. familial social-economic status) in the etiology of ADHD, whereas the non-shared environment plays a non-negligible role.[47, 48]

Genome-wide association studies (GWAS) have implicated the polygenic component in ADHD heritability, with an estimation of single nucleotide polymorphism-based heritability at 0.22.[49] Around 30% of heritability could be attributable to common genetic variants.[45] Apart from common variants, rare chromosomal deletions and duplications, i.e. copy number variants (CNVs) were found to be associated with ADHD.[50] These CNVs were also found to occur in individuals with autism and schizophrenia.[50]

Previous studies have suggested various environmental risk factors to be linked to ADHD, including prenatal and perinatal factors (e.g. maternal smoking during pregnancy, maternal gestational diabetes mellitus, obstetric complications, low birth weight and preterm birth),[51, 52] exposure to environmental toxins (e.g. polychlorinated biphenyls, lead and mercury),[53, 54] and psychosocial adversity (e.g. severe early maternal deprivation, marital discord),[42, 55] but not all risk factors necessarily have causal effects on ADHD. Family studies have shown that the observed association between several risk factors and ADHD was due to familial confounding rather than a causal nature, for example, the association between maternal smoking during pregnancy and ADHD was due to familial confounding.[56, 57] On the other hand, some risk factors (e.g. low birth weight) were found to be causal for ADHD.[58-61]

2.2 CONSEQUENCES OF ADHD

Overall, ADHD has been found to be related to multiple adverse outcomes, including functional impairments, and adverse behavioral and health outcomes.[62-64] It is well-established that ADHD is associated with functional impairments (e.g. school dysfunction, poor social skills, and family conflicts) and multiple psychiatric disorders (e.g. oppositional defiant disorder, mood and anxiety disorders),[64, 65] but less attention has been focused on somatic health outcomes, in particular among adults with ADHD. It should be noted that despite the associations with several impairments and health outcomes, patients with ADHD should not be concerned they will experience all or most of the adverse outcomes.

2.2.1 Consequences across the lifespan

In general, if not managed or treated, individuals with ADHD are more likely to have functional impairments than non-ADHD in many aspects, for example, deficits in working memory,[66] reaction time variability or response inhibition,[67] problems of time management and organization.[68]

As discussed earlier, symptoms of ADHD start in childhood and decline with age. Still, two-thirds of children with ADHD are affected by the disorder in adulthood.[34, 35] The presentation of ADHD can be different throughout a person's lifetime. Children and adolescents with ADHD are more likely to have poor academic performance,[69] conflicts in sibling relationships,[70] and behavioral problems.[71] Adults with ADHD are more likely to have emotional dysregulation,[72] be unemployed or have lower income compared to those without the condition.[73] Older adults with ADHD have been suggested to be associated with decreased quality of life.[74]

2.2.2 Psychiatric comorbidity

The clinical manifestations of ADHD are extremely heterogeneous, and complicated by prevalent comorbid psychiatric disorders. Evidence suggests a large proportion of children with ADHD also exhibits co-existing psychiatric disorders,[75, 76] including conduct disorder, oppositional defiant disorder, learning disorders, tic disorders, autism spectrum disorder, schizophrenia, and anxiety disorders.[76, 77] These findings are consistent with data on

psychiatric comorbidity in adolescents and adults with ADHD, where 65-89% of adult patients were found to suffer from one or more co-existing psychiatric disorders,[64] such as substance use disorder, antisocial personality disorder, and mood disorders.[64, 78] Individuals with ADHD and comorbid psychiatric disorders were shown to have more heterogeneous clinical presentations, more distinct responses to treatment and worse health outcomes than those with ADHD alone.[79]

Genetic contributions common to ADHD and other psychiatric disorders have been shown to substantially account for the high prevalence of their co-existence.[63, 80] Analysis of GWAS summary statistics suggested significant correlations of common variant genetic risk for ADHD, major depressive disorder, bipolar disorder, and schizophrenia.[63] Additionally, multiple twin and sibling studies have suggested a general genetic factor responsible for the phenotypic overlapping.[81-83] One study estimated that the general genetic factor accounted for up to 45% of the variance across dimensions of child and adolescent psychopathology.[83]

2.2.3 Somatic comorbidity

While extensive research efforts have been made on psychiatric comorbidity in individuals with ADHD, less attention has been paid to somatic diseases associated with ADHD, particularly in adults.[84] Somatic comorbidity in some other psychiatric disorders, such as schizophrenia and bipolar disorders,[85] was well documented, where a higher proportion of poor physical health and reduced life expectancy among the affected individuals compared to the general population was reported.[86, 87]

With the growing recognition of ADHD in adults, comorbid somatic health conditions have attracted increasing attention, but still, research in older adults is scarce.[88] Available literature on this topic showed strong evidence for association with physical injuries (e.g. traumatic brain injury),[89, 90] epilepsy,[91] obesity,[4, 92-94] asthma[6] and sleep disorders,[95, 96] while rather tentative evidence for association with celiac disease[97] and migraine.[88, 98] Other somatic outcomes, particularly those that onset late in life, are less explored. The relationships of ADHD with Alzheimer's disease (AD) and other dementia and cardiovascular diseases (CVDs), which are the leading disease burden in Sweden,[8, 9] are relevant to this thesis and are described in details below.

2.2.3.1 Alzheimer's disease and other dementias

Dementia is a syndrome that involves progressive impairments to memory, thinking, behavior and the ability to perform everyday activities.[99] The most common form of dementia is AD, which contributes to 60-70% of cases.[99] A systematic review and meta-analysis estimated the age-standardized prevalence of dementia ranging from 5% to 7% in those aged 60 or above.[100] With the life expectancy of individuals prolonging, dementia represents an increasing public health concern.[101]

Very few studies, with limited sample sizes, explored the potential association between the neurodevelopmental disorder ADHD and the neurodegenerative disease AD, and the results

were inconsistent.[5, 102, 103] An ecologic study using state-level hospitalization discharge data from the U.S. found that antecedent ADHD significantly predicted AD later in life.[5] On the other hand, a case-control study in Buenos Aires, Argentina suggested that prior ADHD was not associated with AD.[102] Also, no statistically significant increased risks were suggested in a retrospective study using Taiwan's Health Insurance Research Database.[103] So far, no large-scale longitudinal studies have explored the potential association, as such a study would require very long follow-up from diagnoses of ADHD, which was not commonly diagnosed until recent decades,[104] to diagnoses of AD in older age. It might be possible that ADHD is linked to AD through consequences of ADHD, e.g. depression, metabolic syndrome, smoking, and low educational attainment,[84, 105, 106] which are well-established risk factors for AD. These research gaps require further investigation on whether and to what extent is ADHD linked to AD.

2.2.3.2 Cardiovascular diseases

CVD is an umbrella term for a cluster of diseases that affects the heart or blood vessels, involving coronary heart disease, heart failure, cardiomyopathy, peripheral artery disease, stroke and other less common cardiovascular system diseases.[107] CVD has become the leading cause of illness and death worldwide since the twentieth century,[108] accounting for 31% of mortality worldwide.[107] Although CVD is one of the leading causes of death and disability in Sweden,[8, 9] the risk of developing CVD could largely be reduced by managing behavioural risk factors.

There have been a few studies that evaluated the relationship between ADHD and cardiovascular events.[93, 109-113] A recent Swedish population-based study found that adults with ADHD were more likely to develop a wide range of CVDs, especially cardiac arrest, stroke and peripheral vascular disease.[109] The mechanisms underlying the potential association between ADHD and CVD are complex. The observed association could be explained by 1) mediating effects of risk factors for CVD, including obesity,[94, 114] cigarette smoking,[115, 116] and psychosocial factors.[4, 84, 117, 118] For example, individuals with ADHD are at higher risk of obesity, which is a well-established risk factor for CVD.[94, 114] 2) the speculation about adverse effects of ADHD medications on the cardiovascular system,[119, 120] which is based on findings from RCT that ADHD medications may increase heart rate and blood pressure.[14] This is discussed in detail in Section 2.3.3.

2.3 TREATMENT OF ADHD

Treatment of ADHD includes non-pharmacologic (e.g. psychoeducation, cognitive behavioral therapy), pharmacologic treatment, or a combination of both.[15, 121, 122] The choice of pharmacologic treatment varies across countries.[122, 123] For children younger than six years of age, psychological therapy is the first-line treatment and usually, pharmacological treatments are not recommended.[15, 121, 122, 124] For school-aged children and adolescents, psychological therapy and/or pharmacologic treatment are usually used for the management.[122, 123] Treatment guideline for adults has been incorporated in several countries,

where some guidelines recommend pharmacologic as the first approach for adult ADHD,[125, 126] others suggest non-pharmacologic can be sufficient for mild and moderate cases.

Approved medications in Sweden for ADHD include stimulants (i.e. methylphenidate, amphetamine, dexamphetamine, lisdexamphetamine) and non-stimulants (i.e. atomoxetine, guanfacine).[122] Stimulants have generally been recognized as the first pharmacologic treatment option in Sweden.[127] According to recommendations from Swedish Medical Products Agency, methylphenidate is recommended as the first choice of ADHD medications for children, adolescents and adults with ADHD, and atomoxetine can be the first choice in selected cases, for example, individuals with substance use disorder, severe tics or severe sleep disturbance.[127]

2.3.1 ADHD medications

2.3.1.1 Prevalence of ADHD medication use

The prevalence of ADHD medication use has increased substantially in the last decades, more rapidly among adults than children and adolescents.[11, 128, 129] The prevalence of ADHD medication prescriptions among adults has increased more than 4 fold over the 5 years from 2008 to 2012 in the UK.[128] Similar trends have been observed in the U.S. and Nordic countries.[129-131] In the meanwhile, the prevalence of ADHD medication use was found to be lower than the estimated prevalence of ADHD diagnosis, especially in adults.[125] Moreover, a recent meta-analysis on adult ADHD found that a considerable number of older adults presented ADHD symptoms, but only less than half of older adults with clinically diagnosed ADHD have received treatment.[2]

The prevalence of ADHD medication use demonstrates geographic differences, as there exist variations in diagnosis and prescribing guidelines regarding ADHD care across countries.[15, 121, 122, 124] Previous studies found that ADHD medication use prevalence in 2014 ranged from 0.39% to 5.56% in children and adolescents and from 0.01% to 2.11% in adults across 13 countries and one special administrative region.[11]

2.3.1.2 Co-medication and polypharmacy

The high rate of psychiatric comorbidity of ADHD necessitates concurrent use of ADHD medications and other psychotropic medications.[15] A national study in the U.S. has shown an increasing trend in the co-prescription of ADHD medications and other psychotropic medications, in particular antipsychotics.[132] In addition to co-prescription of psychotropic medications, long treatment periods with simultaneous use of somatic medications are possible, as both ADHD and commonly co-existing comorbid somatic diseases (e.g. hypertension, type 2 diabetes, obesity and asthma) feature a chronic, long-lasting course. There are concerns about the risk of adverse drug events with the use of multiple medications, possibly as a result of non-adherence, cumulative toxicity, and/or drug-drug interactions.[133] Despite potential risks, there is limited literature addressing polypharmacy patterns and assessing adverse outcomes of polypharmacy with ADHD medications.

2.3.2 Effectiveness of ADHD medications

While there is extensive evidence that both stimulants and non-stimulants effectively alleviate core symptoms of ADHD in children, adolescents and adults.[134-136] A meta-analysis of RCTs on effectiveness and tolerability of ADHD medications suggested methylphenidate in children and adolescents and amphetamines in adults to be the preferred first-choice medications for the short-term treatment of ADHD.[10]

In contrast to extensive evidence on short-term effectiveness, only a few studies have examined the long-term effects of ADHD medications. Follow-up of a 14-month RCT, i.e. Multimodal Treatment study of ADHD (MTA), showed no significant differences between various treatment groups (medication management, behavior therapy, their combination, and usual community care) at 6 and 8 years of follow-up from treatment enrolment. The study also found that although the improvements in functioning were maintained after treatment, all treatment arms still functioned less well than the non-ADHD controls at 6 and 8 years of follow-up.[137] Another RCT showed that compared to discontinuing treatment, a significant benefit on ADHD symptoms was observed for those who continued treatment compared to those switched to placebo, after an average of 4.5 years of stimulant treatment.[138]

Apart from beneficial effects on core symptoms of ADHD, pharmacoepidemiologic studies using more sophisticated designs and "real-world" data have also suggested benefits on psychiatric and behavioral outcomes. These studies have found significant reductions in depression,[139] substance abuse,[140] transport accidents,[141] criminal convictions, violent reoffending,[142] and suicidal behaviors[143] during periods on ADHD medication compared to periods off treatment within individuals.

2.3.3 Safety of ADHD medications

Overall, ADHD medications have been found to have some non-serious adverse effects.[10, 14] Common adverse effects associated with ADHD medications include nausea, dry mouth, sleep disturbances, decreased appetite, abdominal pain, deficits in height, weight loss, and short-term increase in blood pressure or heart rate. In addition, atomoxetine has been suggested to be associated with erectile dysfunction in adult men.

There has been extensive research on the possible serious outcomes of ADHD medications. One of the most debated serious outcomes of ADHD medication use is CVD.[144-148] In 2006, the US Food and Drug Administration's (FDA) recommended a label warning about the CVD risk of ADHD medications based on spontaneous reports of sudden deaths, but after a safety review in 2001, the FDA indicated no statistically significant association among youths or adults.

Previous studies have suggested a significant increase in blood pressure associated with both stimulant and non-stimulant ADHD medications in children, adolescents and adults.[10] A meta-analysis of RCTs in adults found that stimulants were associated with an average increase of 5.7 beats/min in heart rate, and an average increase of 2.0 mm Hg in systolic

blood pressure.[119] However, these changes were observed in the short term and could be of no clinical significance,[149] and whether the increase is significant in the long term remains less clear. A follow-up study of MTA over 10 years showed that a 14-month intensive stimulant treatment started in childhood did not increase the risk of hypertension during the 10 years, but a modest increase in the heart rate was found at 8 years after randomization.[150] This study has not found any other serious cardiovascular outcomes, such as sudden cardiac death, ventricular arrhythmia, myocardial infarction, stroke or heart failure.[150]

Apart from RCT studies, several observational studies on serious cardiovascular outcomes have emerged in recent years with inconclusive findings.[144-148] A review paper incorporating five large population-based studies in the U.S. concluded no association between stimulants and serious cardiovascular events in children, but none of the constituted studies had an average follow-up longer than two years.[151] In contrast, a meta-analysis of ten observational studies found an increased risk for sudden death and/or arrhythmia with stimulant ADHD medications, but not for stroke, myocardial infarction or all-cause death.[152] Further subgroup analyses suggested that the association was only significant in children but not adults.[152] A recent study from Denmark, which is not included in the above-mentioned reviews or meta-analyses, has followed individuals with ADHD for a median of 9.5 years and found a significantly increased risk of cardiovascular events associated with the use of stimulants. A complex dose-response relationship was also reported.[148]

These conflicting results call for further study with rigorous design to evaluate the CVD safety of ADHD medication use. CVD safety among high-risk patients, e.g. those with preexisting CVDs, is of particular concern. In addition, the long-term risk of CVDs associated with ADHD medication use remains unclear. Further studies filling these knowledge gaps are warranted to inform evidence-based ADHD medication prescribing guidelines.

3 RESEARCH AIMS

The overarching objective of this thesis is to advance the understanding of ADHD into adulthood and aging and to evaluate safety of ADHD medication use. Specifically, the thesis aims:

1. To describe patterns of psychiatric and somatic co-medication and polypharmacy with ADHD medications in adults;
2. To examine to what extent is ADHD associated with Alzheimer's disease and other dementias across generations;
3. To synthesize available evidence on whether ADHD medications are associated with increased risk of cardiovascular diseases;
4. To assess the long-term risk of cardiovascular diseases associated with ADHD medications.

4 MATERIALS AND METHODS

4.1 DATA SOURCES

All original studies (study I, II and IV) in this thesis were conducted using data from linkage of several national healthcare and administrative registers in Sweden, held at the National Board of Health and Welfare (Swedish: Socialstyrelsen) and Statistics Sweden (Swedish: Statistiska centralbyrån). The systematic review and meta-analysis (study III) synthesized data collected from published original studies.

4.1.1 Swedish national registers

Linkage of multiple Swedish National Registers is possible through the unique personal identity number (PIN),[24] which is a ten-digit number consisting of six digits of the date of birth, a three-digit number and a check digit. Since 1947 and onwards, the PIN is assigned to every residents living in Sweden. The PIN is maintained by the National Tax Board.

National Patient Register

The National Patient Register (NPR)[153] is kept by the National Board of Health and Welfare, and contains data on inpatient diagnoses since 1973 and outpatient diagnoses since 2001, from both private and public caregivers. The register contains four groups of information, including patient data (e.g. gender, age, place of residence), geographical data (e.g. county council, hospital/clinic), administrative data (e.g. date of admission, date of discharge, length of stay) and medical data (e.g. main diagnosis, secondary diagnosis). The diagnosis is made based on the ICD in its seventh (ICD-7; before 1969), eighth (ICD-8; 1969-1986), ninth (ICD-9; 1987-1996), and tenth (ICD-10; since 1997) revisions.[153] Information from the NPR was used to identify ADHD cases (the study population in study II and IV), diagnosis of AD and other dementias (the outcome of interest in study II), cardiovascular events (the outcome of interest in study IV), and other comorbid diseases used as covariates in all register-based studies of this thesis.

Total Population Register

The Total Population Register (TPR) is maintained by Statistics Sweden and covers demographic information on all Swedish inhabitants since its establishment in 1968.[154] It contains information on demographics, births, deaths, and all migrations in or out of Sweden. The TPR was used to obtain basic demographic information, including date of birth, sex, birth country and date of migration in study I, II and IV.

Multi-Generation Register

The Multi-generation Register (MGR) contains information on the biological and adoptive relationships of all individuals living in Sweden since 1961 and born since 1932.[155] The MGR is maintained by Statistics Sweden and is part of the TPR. The MGR allows for the construction of family pedigrees by linking all residents to their parents. In this thesis, the

MGR was used to identify different types of family members in study II, including parents, grandparents, uncles and aunts of the studied index individuals.

Prescribed Drug Register

The Prescribed Drug Register (PDR)[156] is maintained by the National Board of Health and Welfare and it contains data on all prescribed medications dispensed at pharmacies in Sweden since July 2005. The PDR contains information about the identifier of the patient, patient demographics, the identity of the prescribed drug, quantity and dosage of the drug, date of dispensation and prescription, and the prescriber's profession and practice.[156] The identity of the prescribed drug is defined according to the Anatomical Therapeutic Chemical classification (ATC) system. Information from the PDR was used to identify ADHD medication dispensations (in study I, II and IV) and dispensations of co-mediation (study I).

Causes of Death Register

The Cause of Death Register (CDR)[157] contains information on all deaths since 1952 (complete coverage since 1961) and is maintained by the Centre for Epidemiology at the National Board of Health and Welfare. It contains information on the date of death and underlying and contributing causes of death coded according to the ICD. Information from the CDR was used to identify death from AD and other dementias in study II, and used as the end of follow-up due to censoring in study II and IV.

Longitudinal Integrated Database for Health Insurance and Labor Market

The Longitudinal Integrated Database for Health Insurance and Labor Market (LISA),[158] held by Statistics Sweden, integrates data from the labor market, educational and social sectors. LISA covers the adult Swedish population aged ≥ 16 since 1990.[158] Information from the LISA was used in study IV to obtain educational attainment.

4.1.2 Systematic literature search databases

We conducted a systematic review and meta-analysis to assess the association between ADHD and CVDs using published original studies in study III. Data are obtained from four medical bibliographic databases, namely Ovid MEDLINE, Embase, Web of Science, and PsycINFO. The search strategy was first developed for search in Ovid MEDLINE and later translated to other databases.

4.2 MAIN MEASURES

4.2.1 ADHD diagnosis

Individuals with ADHD were defined through inpatient or outpatient diagnosis of ADHD based on ICD codes (ICD-9: 314 and ICD-10: F90) from the NPR. In study II and IV, information on dispensations of ADHD medications recorded in the PDR was also used for the identification of ADHD cases. ADHD case status was treated as a lifetime diagnosis in both study II and IV.

4.2.2 ADHD medications

Approved medications for pharmacological treatment of ADHD in Sweden included methylphenidate [ATC: N06BA04], amphetamine [N06BA01], dexamphetamine [N06BA02] and atomoxetine [N06BA09]) during the study period. In study I, all individuals with at least one record of ADHD medication dispensation during 2013 were included. In study IV, the cumulative duration of ADHD medication use was examined between 2006 and 2013.

Duration of ADHD medication use was derived from a validated algorithm which predicts treatment duration from free-text in prescriptions.[159] The algorithm also calculated the amount of defined daily doses (DDDs) from each dispensed prescription, by multiplying the number of packages by the number of DDDs per package. The cumulative duration in years and cumulative sum of DDDs were calculated for each individual. In study IV, the cumulative duration of ADHD medication use was categorized into four categories (no-use, $0<$duration≤1, $1<$duration≤3, and >3 years), and the cumulative sum of DDDs was also categorized into four categories (0, 1-365, 366-1095, and >1096 DDDs).

4.2.3 Alzheimer's disease and other dementias

Two outcomes of interest were identified: AD and any dementia (including AD).[160, 161] Information on diagnoses of AD and other dementias was obtained from the NPR and death due to AD and other dementias were obtained from the CDR. We estimated the date of disease onset as three years before incident diagnosis or five years before death, which is consistent with previous literature.[162] Similar to ADHD case identification, we used information on dispensations of medications from the PDR as a proxy for AD case status.[162] In this case, the date of AD onset was defined as the date of the incident dispensations of medications for treating AD. Medications used for treating AD in Sweden during the study period include donepezil, rivastigmine, galantamine and memantine.

4.2.4 Cardiovascular diseases

In study IV, the nested case-control study identified all individuals with incident CVD events. Information on CVD diagnosis was obtained from the NPR. We considered CVD events of the following types: ischemic heart disease, cerebrovascular disease, venous thromboembolism, hypertensive diseases, heart failure, arrhythmias, cardiac arrest and peripheral vascular disease/arteriosclerosis, based on prior work.[109]

In study III, the outcome of original studies included in the systematic review and meta-analysis was ICD code-based diagnosis of any type of cardiovascular event. Both incident and prevalent CVD cases were considered.

4.3 OVERVIEW OF STUDY METHODS AND MATERIALS

An overview of the study design, study population, measures (exposures and outcomes) and statistical methods used in the constituent studies is described in Table 4.1.

Table 4.1 Overview of study methods

Study	Data source	Study design	Study population	Measures	Statistical methods
I	TPR, PDR, and NPR	Cross-sectional study	41,840 individuals who dispensed ADHD medications during 2013 and 41,840 population controls	Exposure: ADHD medications Outcome: Concurrent use of medications	Logistic regression
II	TPR, PDR, NPR, MGR, and CDR	Familial co-aggregation study	2,132,929 individuals born 1980 to 2001 and their 2,293,961 parents, 2,518,669 grandparents and 933,263 uncles/aunts	Exposure: ADHD Outcome: AD and other dementias	Cox proportional hazard regression
III	Ovid MEDLINE, Embase, Web of Science, and PsycINFO databases	Systematic review and meta-analysis	Previous published original studies	Exposure: ADHD medications Outcome: CVDs	Meta-analysis
IV	TPR, PDR, NPR, CDR and LISA	Nested case-control study	115,250 individuals who had an incident diagnosis of ADHD or ADHD medication dispensations (2,129 CVD cases and 10,549 controls)	Exposure: Long-term treatment with ADHD medications Outcome: CVDs	Conditional logistic regression

Abbreviations: AD, Alzheimer's disease; ADHD, attention-deficit/hyperactivity disorder; CDR, Cause of Death register; CVDs, cardiovascular diseases; LISA, Longitudinal Integrated Database for Health Insurance and Labor Market; MGR, Multi-generation Register; NPR, National Patient Register; PDR, Prescribed Drug Register; TPR, Total Population Register.

4.4 STUDY DESIGNS

4.4.1 Cross-sectional study

A cross-sectional study is a commonly used observational study design, in which all of the information such as outcomes and exposures are measured at the same point in time.[163] These studies are snapshots of the participants with exposure and outcome status and can usually be conducted inexpensively and fast. However, as exposure and outcome are measured simultaneously, it is difficult to inform causation from cross-sectional studies. Cross-sectional studies are often prone to recall bias and suffer from reverse causation.[164] It is therefore more commonly used for measuring the prevalence of disease and evaluating associations rather than assessing causal relationships.

4.4.2 Nested case-control study

A nested case-cohort study, which means a case-control study nested in a cohort, is an observational design that generates study cases and controls from a cohort by sampling.[165] The study population in a nested case-control study are generated by sampling the risk set.[166] The risk set corresponding to each event contains all individuals under study at the time of the event.[166] This is illustrated in Figure 4.1, the risk set corresponding to an event consists of all individuals whose observation lines cross the grey vertical bar. This sampling strategy ensures that controls are included by sampling the risk sets from the whole population rather than the non-diseased population.[166] The design overcomes some of the disadvantages of case-control studies such as recall bias, and it also reduces the cost and labor.[167] The results from nested case-cohort are equally valid to the corresponding full cohort analysis.
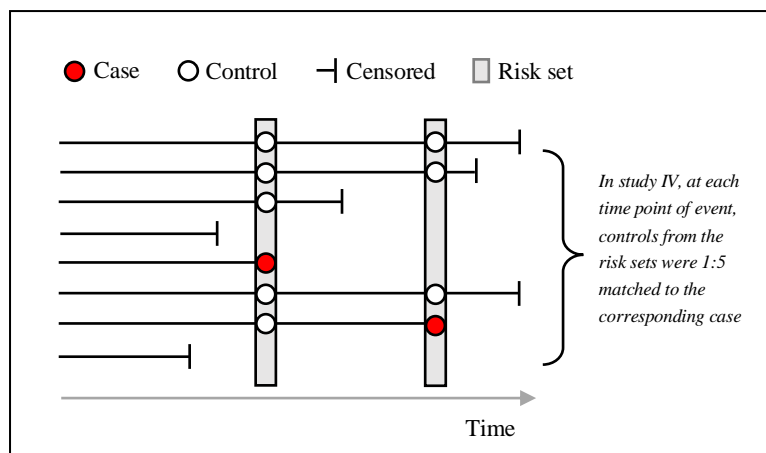

Figure 4.1 Illustration of risk set in a nested case-control design. At each event (red point), eligible controls are sampled from risk set (the observation lines cross the grey vertical bar).

In study IV, for each CVD case, we randomly selected up to five controls without CVDs for each case from the base cohort of individuals with ADHD. Controls were eligible if they were alive, living in Sweden, and free of CVDs at the time when their matched case received

a diagnosis of CVD. The matching criteria were age, sex and time since baseline. The index date for the controls was set to the date of CVD diagnosis of the matched case.

4.4.3 Familial coaggregation study

Familial coaggregation studies are an important approach in genetic epidemiology, which evaluates whether two traits or diseases co-aggregate in a family.[168] It is usually the first step for the identification of genetic determinants of a disease or trait, or for two traits or diseases.[168] The co-aggregation of two diseases in a family may be due to shared factors within a family including both genetic and environmental factors.

In this thesis, population-based familial coaggregation design is applied in study II, in which we examined to what extent ADHD and AD are linked across generations. A framework using directed acyclic graphs (DAG) for illustration of the familial co-aggregation between two conditions[169] has been proposed. The framework demonstrated how familial co-aggregation could be estimated and interpreted. Figure 4.2 shows a DAG of the hypothesized familial co-aggregation between ADHD and AD as an example (study II).
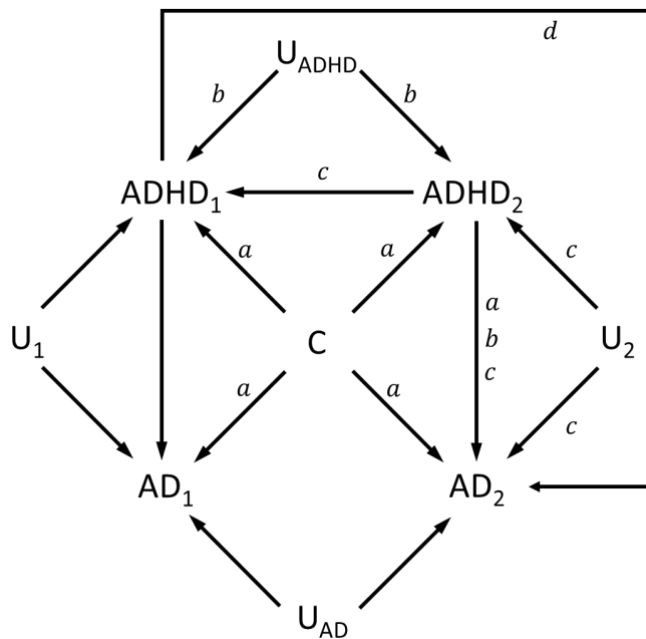

Figure 4.2 Illustration of the familial co-aggregation between ADHD and AD by a Directed Acyclic Graph.[169] AD, Alzheimer's disease; ADHD, attention-deficit/hyperactivity disorder. Subscript 1 denotes the index person and subscript 2 denotes the index person's relative. For example, $ADHD_1$ denotes ADHD status in the index person and AD_2 denotes AD status in the relative of the index person. C, U_{ADHD}, U_{AD}, U_1, and U_2 represent unmeasured factors. Specifically, C denotes familial risk factors common for ADHD and AD shared by both index person and his/her relative; U_{ADHD} represents common causes for ADHD alone, independent of C; U_{AD} represents common causes for AD alone, independent of C; U denotes individual specific risk factors for ADHD and AD. The path *a*, *b*, *c* and *d* represent four hypothesized mechanisms underlying the familial co-aggregation. Figure reproduced from the original publication under the open access license.

4.4.4 Systematic review and meta-analysis

Systematic review is a type of study design that synthesis all available evidence on a specific question.[170] With structured literature search and critically appraise, it is particularly useful in synthesizing research findings, sometimes conflicting results from primary research.[171] Following a systematic review, meta-analysis quantitively combines results across studies using statistical methods. As the overall sample size increases, the statistical power of the analysis improves.[171] To ensure the appropriateness of reporting a systematic review and meta-analysis, the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement is first developed in 2009.[172] It is updated in 2020 with changes in reporting guidance,[173] for example adding recommendations on reporting the certainty or confidence of the results.[174]

In study III, a systematic review and meta-analysis was conducted to evaluate the association between ADHD medication use and the risk of CVDs. We aimed to summarize all available evidence on the research questions and identify knowledge gaps, for example, the trade-off between benefits and risks of ADHD medications among high CVD risk groups, and whether there is sufficient information on assessing the long-term use of ADHD medications, and provide directions for future research.

4.5 STATISTICAL METHODS

4.5.1 Logistic regression

Regression models have been commonly used to describe the relationship between a response variable and one or more independent variables.[175] In medical research, the response variable is usually discrete, binary or has more categories. The logistic regression model is the most commonly used model for assessing the relationship between a binary response variable against one or more independent variables.[176] The log-odds is modelled as a function of the independent variables, in which odds is calculated as the ratio of the probability that the outcome of interest happens to the probability that the outcome of interest does not happen.[175] The measure of association is the odds ratio (OR). For a binary independent variable, the OR can be interpreted as the odds of the outcome occurring in the exposed group compared with the odds of the outcome occurring in the unexposed group. If the outcome of interest is rare among the study population, which means the "rare event assumption" holds,[177, 178] the OR approximates the risk ratio (RR).

4.5.2 Cox regression

Cox proportional hazards models are a type of survival analysis method which models the relationship between time-to-event and one or more dependent variables.[179] The underlying timescale such as attained age or time-on-study is defined to account for confounding.[180] For example, In study II, we used attained age as the underlying time scale, this means that we only compared the hazard rate of the outcome at the same age across individuals, and therefore the difference in baseline hazard across age (time) was fully accounted in the Cox

regression model. In the application of Cox proportional hazards models, the measure of association is the hazard ratio (HR). For a binary independent variable, HR can be interpreted as the ratio of the hazard rate in the exposed group to the hazard rate in the unexposed group. The Cox model is called a semi-parametric model, this is because the baseline hazard function is not estimated, meaning there are no underlying assumptions for the baseline hazard. However, one fundamental assumption of Cox should be noted - the hazards are assumed to be proportional over time. This means the relative hazard should remain constant over time with different independent variable levels. Nevertheless, a recent influential paper[181] suggested that even if the proportional hazards assumption is not met, the interpretation of the HR estimated from a Cox regression can still be seen as an average of HR over the study time.

4.5.3 Meta-analysis

Meta-analysis is a statistical method used to pool effect estimates from all eligible studies on a specific research topic and the pooled estimated is often presented using forest plots. There are two commonly used statistical models for pooling effect estimates, fixed-effect and random-effects models.[182] Fixed-effect models assume that there is only one true effect size, meaning no heterogeneity across all included studies. On the contrary, random-effects models allow for variation of the true effect across included studies as they assume a distribution of true effect size and the model estimated the mean of it.[182] Cochran's Q test is commonly used to test the significance of heterogeneity across studies, and the percentage of variability attributed to true heterogeneity, rather than chance, is estimated using the inconsistency index (I^2).[183] The between-study variability is represented as tau-squared (τ^2) and the restricted maximum likelihood method could be used to estimate it.[184] In study III, we used random-effect models to pool the estimates from all available observational studies assessing the association between ADHD medication use and CVDs.

5 RESULTS

5.1 CO-MEDICATION WITH ADHD MEDICATIONS (STUDY I)

In total, we included 41,840 adults aged 18-64 years who have dispensed ADHD medications in 2013 in Sweden. This included 20,629 young adults (18-29 years), 16,889 middle-aged adults (30-49 years) and 4,322 older adults (50-64 years). Among all individuals dispensed ADHD medications, methylphenidate was most commonly dispensed (82.9%-89.1% across age groups). The most common source of prescription was psychiatric care (87.9%-92.8% across age groups). Most individuals who dispensed ADHD medications experienced treatment periods ≥ 1 year. Similar prescription patterns were observed between women and men.

Co-medication and polypharmacy with ADHD medications

Individuals who dispensed ADHD medications had a higher degree of polypharmacy compared to population controls (Figure 5.1). Individuals who dispensed ADHD medications received on average 2.5 other medication classes at age 18, and the average number of medication classes increased to 5.0 at age 64. The corresponding numbers increased from 0.9 at age 18 to 2.7 at age 64 among controls (Figure 5.1 a). Among individuals receiving ADHD medications, the proportion of polypharmacy with five or more medication classes increased from 10.1% to 60.4% from age 18 to age 64 (Figure 5.1 b).
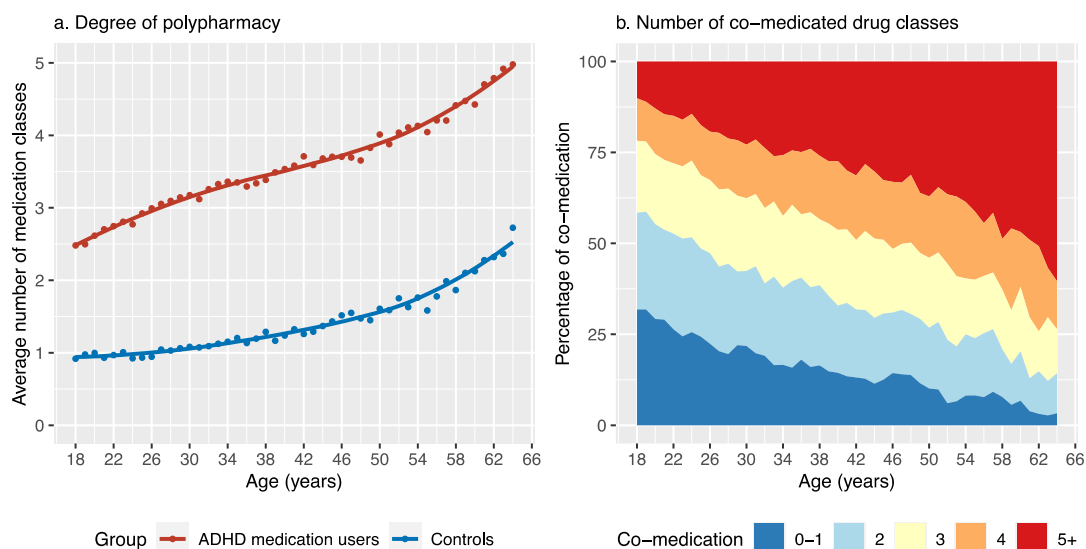

Figure 5.1 Co-medication and polypharmacy among individuals who dispensed ADHD medications across ages. Co-medication classes were ascertained based on first-level ATC codes. Figure (a) illustrated the degree of polypharmacy among ADHD medication users and controls. Figure (b) illustrated the number of co-medicated medication classes among individuals who dispensed ADHD medications. The Figure is reproduced from the original publication under the open access license.

Dispensations of somatic and other psychotropic medications

Co-medication	Age Group	ADHD medication users (N = 41,840)	Control group (N = 41,840)	Odds ratio (95% CI)
Somatic medications	Young adults	15,818 (76.7%)	10,134 (49.1%)	4.1 (4.0, 4.3)
	Middle-aged adults	14,631 (86.6%)	8,951 (53.0%)	6.2 (5.9, 6.6)
	Older adults	4,037 (93.4%)	2,865 (66.3%)	7.4 (6.5, 8.5)
Psychotropic medications	Young adults	13,812 (67.0%)	2,673 (13.0%)	15.5 (14.7, 16.3)
	Middle-aged adults	14,458 (85.6%)	3,846 (22.8%)	21.7 (20.5, 23.0)
	Older adults	3,859 (89.3%)	1,394 (32.3%)	18.6 (16.5, 20.9)

Table 5.1 Dispensations of any somatic and other psychotropic medications among individuals receiving ADHD medications. Young adults, 18-29 years; Middle-aged adults, 30-49 years; Older adults, 50-64 years. Table reproduced from the original publication under the open access license.

The proportion of individuals who were co-medicated with any somatic medications increased with age groups (Table 5.1). Compared to population controls, the proportions of dispensation with any somatic medication and any psychotropic medications were higher among individuals receiving ADHD medications.

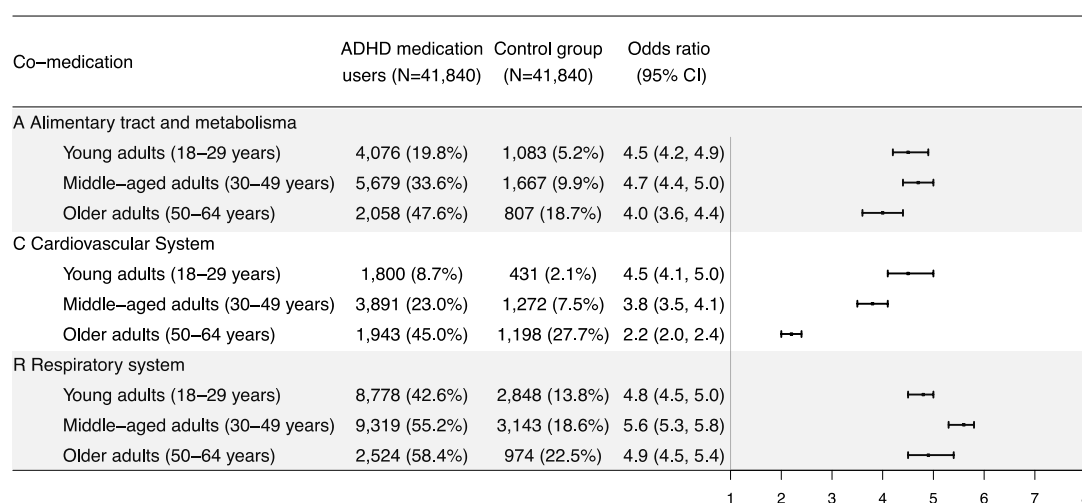| Co–medication	ADHD medication users (N=41,840)	Control group (N=41,840)	Odds ratio (95% CI)	
A Alimentary tract and metabolisma				
Young adults (18–29 years)	4,076 (19.8%)	1,083 (5.2%)	4.5 (4.2, 4.9)	
Middle–aged adults (30–49 years)	5,679 (33.6%)	1,667 (9.9%)	4.7 (4.4, 5.0)	
Older adults (50–64 years)	2,058 (47.6%)	807 (18.7%)	4.0 (3.6, 4.4)	
C Cardiovascular System				
Young adults (18–29 years)	1,800 (8.7%)	431 (2.1%)	4.5 (4.1, 5.0)	
Middle–aged adults (30–49 years)	3,891 (23.0%)	1,272 (7.5%)	3.8 (3.5, 4.1)	
Older adults (50–64 years)	1,943 (45.0%)	1,198 (27.7%)	2.2 (2.0, 2.4)	
R Respiratory system				
Young adults (18–29 years)	8,778 (42.6%)	2,848 (13.8%)	4.8 (4.5, 5.0)	
Middle–aged adults (30–49 years)	9,319 (55.2%)	3,143 (18.6%)	5.6 (5.3, 5.8)	
Older adults (50–64 years)	2,524 (58.4%)	974 (22.5%)	4.9 (4.5, 5.4)	

Figure 5.2 Dispensation of common somatic medications (selected ATC class) among individuals receiving ADHD medications, by age group. ATC, Anatomical Therapeutic Chemical. Figure reproduced from the original publication under the open access license.

Individuals receiving ADHD medications had higher odds of receiving a specific class of somatic medications, compared with controls, across age groups. The ORs for dispensing selected somatic medication ATC classes among individuals receiving ADHD medications are shown in Figure 5.2. When compared to controls, individuals with ADHD medication prescriptions had higher odds of being dispensed with respiratory system medications. The OR was 5.6 (95% CI, 5.3-5.8) among middle-aged adults. Alimentary tract and metabolic

system medications were also associated with high ORs of being dispensed, with ORs estimated at 4.7 (95% CI, 4.4-5.0) among middle-aged adults. Among all somatic medication classes, cardiovascular system medications had the third highest ORs of being dispensed, with an estimate of OR at 4.7 (95% CI, 4.4-5.0) among middle-aged adults.

5.2 ADHD AND AD ACROSS GENERATIONS (STUDY II)

Cross-generation cohort

A total of 2,132,929 individuals (index persons) born between 1980 and 2001 were identified and included in the analysis. The index persons were linked to their biological relatives and the eligible study cohorts included 2,293,961 parents, 2,518,669 grandparents and 933,263 uncles or aunts. Among the 2,132,929 index persons, 68,379 (3.21%) had a recorded diagnosis of ADHD. The median follow-up time was 8.0 years for parents, 25.0 years for grandparents and 8.5 years for uncles or aunts. By the end of the follow-up, a total of 3,042 (0.13%) parents were diagnosed with AD, and 171,732 (6.82%) grandparents were diagnosed with AD.

Association between ADHD and AD and any dementia

We found the risk of AD was higher among parents of index persons with ADHD compared to parents of index persons without ADHD (HR=1.55, 95% CI, 1.26-1.89; Figure 5.3). The associations attenuated when we examined the association among grandparents and uncles or aunts. The association with AD in grandparents was (HR=1.11, 95% CI, 1.08-1.13), and the association in uncles or aunts was not statistically significant (HR=1.15, 95% CI, 0.85-1.56). The results stratified by sex showed similar results. The HR for mothers of index persons with ADHD was 1.77 (95% CI, 1.23-2.54) and for fathers of index persons with ADHD was 1.46 (95% CI, 1.16-1.84). A similar pattern was also observed when examining any dementia as the outcome (Figure 5.3).

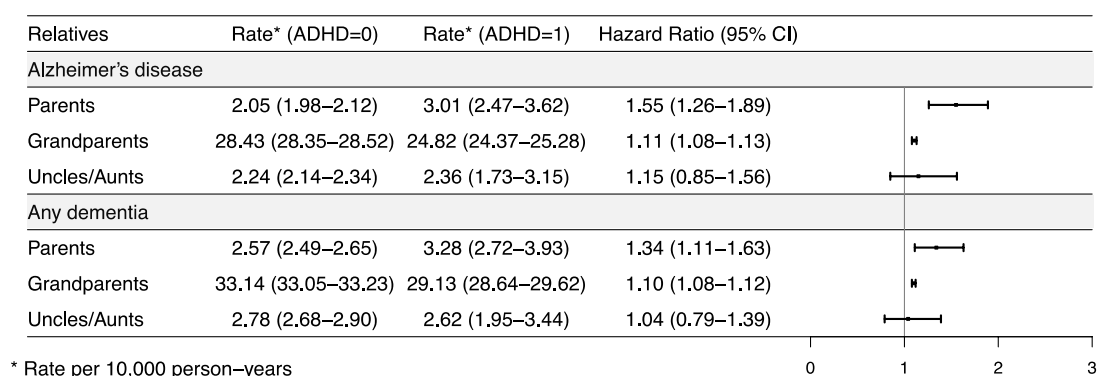| Relatives	Rate* (ADHD=0)	Rate* (ADHD=1)	Hazard Ratio (95% CI)	
Alzheimer's disease				
Parents	2.05 (1.98–2.12)	3.01 (2.47–3.62)	1.55 (1.26–1.89)	
Grandparents	28.43 (28.35–28.52)	24.82 (24.37–25.28)	1.11 (1.08–1.13)	
Uncles/Aunts	2.24 (2.14–2.34)	2.36 (1.73–3.15)	1.15 (0.85–1.56)	
Any dementia				
Parents	2.57 (2.49–2.65)	3.28 (2.72–3.93)	1.34 (1.11–1.63)	
Grandparents	33.14 (33.05–33.23)	29.13 (28.64–29.62)	1.10 (1.08–1.12)	
Uncles/Aunts	2.78 (2.68–2.90)	2.62 (1.95–3.44)	1.04 (0.79–1.39)	

* Rate per 10,000 person–years

Figure 5.3 Association between ADHD and Alzheimer's disease and any dementia in relative cohorts. ADHD, attention-deficit/hyperactivity disorder. Figure reproduced from the original publication under the open access license.

When considering the onset age of dementia, the risk of having early-onset AD was higher than for late-onset AD, comparing relatives of individuals with ADHD to relatives of individuals without ADHD (Figure 5.4). For example, among the parent cohort, the risk of early-onset AD (HR=1.69, 95% CI, 1.34-2.13) was higher than the risk of late-onset AD (HR=1.20, 95% CI, 0.82-1.77). Similar patterns were observed in the grandparents, uncles or aunts cohort, and for the risk with any dementia.
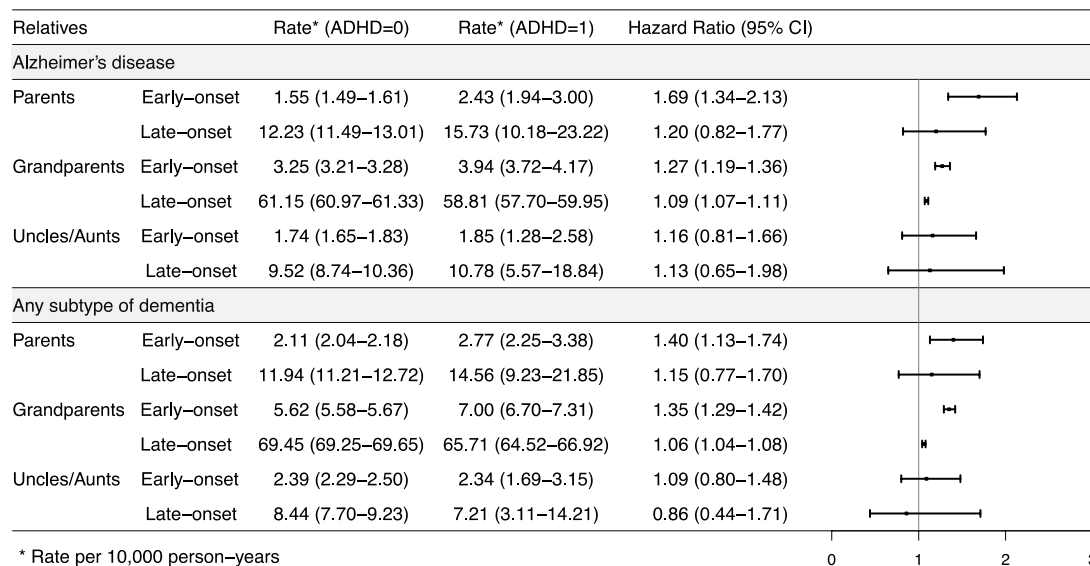
Relatives		Rate* (ADHD=0)	Rate* (ADHD=1)	Hazard Ratio (95% CI)
Alzheimer's disease				
Parents	Early–onset	1.55 (1.49–1.61)	2.43 (1.94–3.00)	1.69 (1.34–2.13)
	Late–onset	12.23 (11.49–13.01)	15.73 (10.18–23.22)	1.20 (0.82–1.77)
Grandparents	Early–onset	3.25 (3.21–3.28)	3.94 (3.72–4.17)	1.27 (1.19–1.36)
	Late–onset	61.15 (60.97–61.33)	58.81 (57.70–59.95)	1.09 (1.07–1.11)
Uncles/Aunts	Early–onset	1.74 (1.65–1.83)	1.85 (1.28–2.58)	1.16 (0.81–1.66)
	Late–onset	9.52 (8.74–10.36)	10.78 (5.57–18.84)	1.13 (0.65–1.98)
Any subtype of dementia				
Parents	Early–onset	2.11 (2.04–2.18)	2.77 (2.25–3.38)	1.40 (1.13–1.74)
	Late–onset	11.94 (11.21–12.72)	14.56 (9.23–21.85)	1.15 (0.77–1.70)
Grandparents	Early–onset	5.62 (5.58–5.67)	7.00 (6.70–7.31)	1.35 (1.29–1.42)
	Late–onset	69.45 (69.25–69.65)	65.71 (64.52–66.92)	1.06 (1.04–1.08)
Uncles/Aunts	Early–onset	2.39 (2.29–2.50)	2.34 (1.69–3.15)	1.09 (0.80–1.48)
	Late–onset	8.44 (7.70–9.23)	7.21 (3.11–14.21)	0.86 (0.44–1.71)

* Rate per 10,000 person–years

Figure 5.4 Association between ADHD and Alzheimer's disease and any dementia stratified by onset age of dementia. ADHD, attention-deficit/hyperactivity disorder. Figure reproduced from the original publication under the open access license.

5.3 META-ANALYSIS ON ADHD MEDICATIONS AND CVD RISK (STUDY III)

Study characteristics

Overall, the meta-analysis included nineteen original studies published during 2007-2021.[146, 185-202] A total of 3,931,532 participants from six countries or regions (United States, Canada, Denmark, Spain, South Korea and Hong Kong) were included. The study samples included participants of all ages and 60.9% were male. The median follow-up time of included studies was 1.5 years. Of the 19 included studies, 14 used cohort design, 3 were nested case-control studies and 2 used self-controlled case series design.

Association between ADHD medication use and CVD risk

A forest plot illustrating the risk estimates of each included study is shown in Figure 5.5. After pooling the estimates from the included original studies we found ADHD medication use was not statistically significantly associated with the risk of any CVD in general (RR=1.22; 95% CI, 0.88-1.68) as well as among children and adolescents (RR=1.18; 95% CI, 0.91-1.53), young and middle-aged adults (RR=1.04; 95% CI, 0.43-2.48) and older adults

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(RR=1.59; 95% CI, 0.62-4.05). We found high heterogeneity between studies (I^2=93.2%, Cochran's Q =292.7, P<0.01). When examining specific CVD outcomes, the highest point estimate of the risk was found for cardiac arrest and/or arrhythmias, however, the risk was not statistically significant (RR=1.60; 95% CI, 0.94-2.72). Among the included studies, the only two studies[185, 199] with relatively longer follow-up (> 2 years) showed statistically significant elevated risk (RR=2.34, 95% CI, 1.15-4.75 and RR=3.07, 95% CI, 1.09-8.64 respectively).
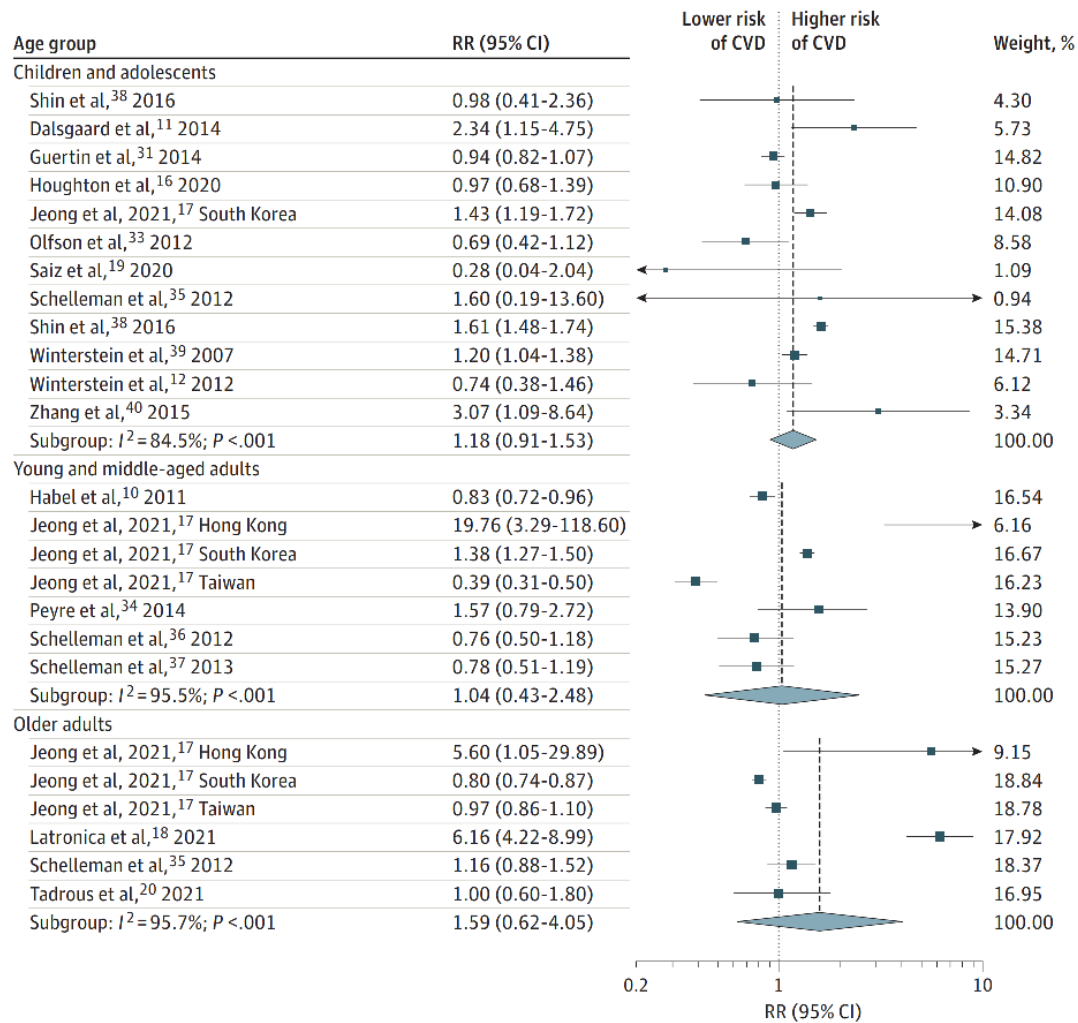
Figure 5.5 Risk of any cardiovascular event by age group associated with ADHD medications. CI, confidence interval; CVD, cardiovascular disease; RR, relative risk. The pooled estimate for all ages was RR=1.22 (95% CI, 0.88-1.68; not shown in the figure). This figure is reproduced from the original publication under the open access license.

5.4 ADHD MEDICATION USE AND LONG-TERM CVD RISK (STUDY IV)

Study participants

The study cohort comprised 115,250 individuals aged 6-64 years. The mean age of study participants at baseline was of 22.4 (SD 13.2) years. After applying exclusion criteria and

matching, the analysis included 2,129 CVD cases and 10,549 matched controls. CVD cases had a median age of 36.2 (IQR, 20.7-46.0) years at baseline. The most common types of CVDs were hypertensive diseases (40.3%) and arrhythmias (23.9%). Follow-up time ranged from 0.25 to 6.9 years. During a median of 2 years of follow-up, the incidence rate of CVDs was 7.02 per 1000 person-years. The CVD cases have higher rates of comorbidities and lower educational attainment compared to controls.

Association between ADHD medication use and long-term CVD outcome

A similar proportion of cases (81.9%) and controls (82.1%) had used ADHD medication during the entire follow-up. The associations between different length of ADHD medication use and the risk of CVDs are shown in Table 5.2. We found longer cumulative duration of ADHD medication use was associated with a modest increased risk of CVDs compared with non-use (adjusted ORs: 0<duration≤1 year, 0.97 [95% CI, 0.84-1.11]; 1<duration≤3 years, 1.12 [95% CI, 0.96-1.32]; and duration>3 years, 1.34 [95% CI, 1.07-1.68]). When using a regression model where the duration of ADHD medication use was measured as a continuous variable, a statistically significant linear dose-response pattern was suggested (the quadratic term was insignificant, p=0.29). One-year increase use of ADHD medication was associated with a 7% of increased risk of CVDs (OR=1.07, 95% CI, 1.02-1.13).

Exposure	Case (n=2129)	Control (n=10549)	Crude ORs (95% CI)[a]	Adjusted ORs (95% CI)[b]
Cumulative duration in years				
0	385 (18.1%)	1885 (17.9%)	1	1
0<duration ≤1	938 (44.1%)	4971 (47.1%)	0.92 (0.81-1.05)	0.97 (0.84-1.11)
1<duration ≤3	599 (28.1%)	2826 (26.8%)	1.09 (0.93-1.26)	1.12 (0.96-1.32)
>3	207 (9.7%)	867 (8.2%)	1.31 (1.05-1.62)	1.34 (1.07-1.68)
Age 6-24 years				
0	110 (16.2%)	557 (16.4%)	1	1
0<duration ≤1	306 (45.0%)	1623 (47.7%)	0.95 (0.75-1.21)	0.98 (0.76-1.27)
1<duration ≤3	198 (29.1%)	927 (27.3%)	1.14 (0.86-1.51)	1.17 (0.87-1.58)
>3	66 (9.7%)	293 (8.6%)	1.27 (0.85-1.88)	1.36 (0.91-2.06)
Age 25-64 years				
0	275 (19.0%)	1328 (18.6%)	1	1
0<duration ≤1	632 (43.6%)	3348 (46.8%)	0.91 (0.78-1.06)	0.97 (0.82-1.14)
1<duration ≤3	401 (27.7%)	1899 (26.6%)	1.06 (0.89-1.27)	1.11 (0.91-1.34)
>3	141 (9.7%)	574 (8.0%)	1.33 (1.02-1.72)	1.35 (1.03-1.77)

Table 5.2. Risk of CVD associated with cumulative duration of ADHD medication use. ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; CVD, cardiovascular disease. [a]Crude ORs were based on cases and controls matched on age, sex, and time since baseline. [b]Adjusted ORs were based on cases and controls matched on age, sex, and time since baseline and adjusted for country of birth, highest educational level, somatic comorbidities, including type 2 diabetes, obesity, dyslipidemia, sleep disorders, heavy smoking and psychiatric disorders, including anxiety, autism spectrum disorder, bipolar disorder, conduct disorder, depression, eating disorders, intellectual disability, personality disorders, schizophrenia, and substance use disorders.

Analyses on cumulative dispensed DDDs also showed an increased risk of CVDs associated with a higher cumulative amount of ADHD medications (adjusted ORs: 1-365 DDDs, 0.92 [95% CI, 0.80-1.07]; 366-1095 DDDs, 1.11 [95% CI, 0.94-1.30]; and ≥1096 DDDs, 1.22 [95% CI, 1.04-1.44]; Table 5.3). Similar pattern of estimates was observed when examining the association in children and youths and adults.

Exposure	Case (n=2129)	Control (n=10549)	Crude ORs (95% CI)[a]	Adjusted ORs (95% CI)[b]
Cumulative Dose, DDDs				
0	388 (18.2%)	1904 (18.0%)	1	1
1-365	730 (34.3%)	4101 (38.9%)	0.87 (0.76-1.00)	0.92 (0.80-1.07)
366-1095	477 (22.4%)	2265 (21.5%)	1.06 (0.91-1.24)	1.11 (0.94-1.30)
≥1096	534 (25.1%)	2279 (21.6%)	1.23 (1.05-1.44)	1.22 (1.04-1.44)
Age 6-24 years				
0	112 (16.5%)	565 (16.6%)	1	1
1-365	263 (38.7%)	1459 (42.9%)	0.91 (0.71-1.16)	0.95 (0.73-1.23)
366-1095	183 (26.9%)	810 (23.8%)	1.18 (0.90-1.55)	1.22 (0.91-1.62)
≥1096	122 (17.9%)	566 (16.6%)	1.16 (0.85-1.58)	1.17 (0.84-1.61)
Age 25-64 years				
0	276 (19.0%)	1339 (18.7%)	1	1
1-365	467 (32.2%)	2642 (37.0%)	0.86 (0.73-1.01)	0.92 (0.77-1.10)
366-1095	294 (20.3%)	1455 (20.4%)	1.00 (0.84-1.21)	1.05 (0.87-1.28)
≥1096	412 (28.4%)	1713 (24.0%)	1.25 (1.05-1.50)	1.25 (1.03-1.51)

Table 5.3. Risk of CVD associated with cumulative DDDs of any ADHD medication use. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; CVD, cardiovascular disease; DDDs, Defined Daily Doses. [a]Crude ORs were based on cases and controls matched on age, sex, and time since baseline. [b]Adjusted ORs were based on cases and controls matched on age, sex, and time since baseline and adjusted for country of birth, highest educational level, somatic comorbidities, including type 2 diabetes mellitus, obesity, dyslipidemia, sleep disorders, heavy smoking and psychiatric comorbidities, including anxiety disorders, autism spectrum disorder, bipolar disorder, conduct disorder, depressive disorder, eating disorders, intellectual disability, personality disorders, schizophrenia, and substance use disorders.

6 DISCUSSION

6.1 CO-MEDICATION WITH ADHD MEDICATIONS

In the national cohort of adults receiving ADHD medications in Sweden, we found that compared to the general population, co-medication with somatic medications was more common in individuals receiving ADHD medications, in particular with respiratory medications, alimentary tract and metabolic system medications, and cardiovascular system medications. A high degree of polypharmacy across ages was presented among individuals receiving ADHD medications.

The increased OR of co-medication with respiratory medications might be attributable to the comorbidity between ADHD and chronic conditions, such as allergic rhinitis,[7] eczemas,[203] asthma,[6] and smoking behavior.[204] It is also possible that antihistamines were prescribed for alleviating ADHD comorbidity and/or ADHD medication-related side effects, such as anxiety disorders, sleep disorders, nausea and vomiting. The most commonly dispensed alimentary tract and metabolic system medications were omeprazole, esomeprazole and proton pump inhibitors. These medications are generally indicated for treating gastroesophageal reflux disease and gastric/duodenal ulcers. The explanation underlying the co-prescription is not clear and requires further investigation.[205] The most commonly dispensed cardiovascular system medications were propranolol, enalapril and metoprolol, which are commonly indicated for hypertension and arrhythmias. This might be explained by an increased risk of CVD among individuals with ADHD,[93] but also might be explained by the possible risk of CVD associated with ADHD medication use through increasing heart rate or blood pressure.[119] Nevertheless, both explanations are inconclusive with limited evidence and conflicting findings, which require further investigation.

6.2 ADHD AND AD ACROSS GENERATIONS

In the nationwide multigenerational cohort study, we observed that the risk of developing AD and any dementia was higher among relatives of individuals with ADHD compared to relatives of individuals without ADHD. The observed association attenuated with decreasing level of shared genetic relatedness.

There are several mechanisms that might underlie the observed familial co-aggregation of ADHD and AD within families. One possible mechanism is that there may be familial risk factors shared by both ADHD and AD within families, such as genetic variants and environmental factors affecting both traits. Some genes, e.g. *SORCS2* and *SORCS3,* have been suggested to be related to both ADHD and AD, which might alter the processing of amyloid precursor protein and neuronal plasticity.[206, 207] It is also possible that some rare genetic variants contribute to both conditions.[208] In addition to shared genetic factors, familiar environmental risk factors, such as social economic status, may influence the development of both AD[209] and ADHD.[210] Another possible mechanism is that the co-aggregation in families was linked through within-individual association. This indicates that adverse health

consequences of ADHD, e.g. low educational attainment, obesity, and type 2 diabetes mellitus, have mediated the association between ADHD and AD. Other possible mechanisms underlying the familial co-aggregation could be related to a direct effect of ADHD in the relative on the ADHD status of the index person,[211] and a direct effect of ADHD in the index person on AD status of the relative.[212]

6.3 ADHD MEDICATION USE AND CVD RISK

In the systematic review and meta-analysis (study III), we did not find a statistically significant association between ADHD medication use and CVDs, although the pooled RR did not exclude a modest risk increase, especially for the specific CVD cardiac arrest and arrhythmias. In the nested case-control study (study IV), we found a modest risk of incident CVDs associated with ADHD medication use and the strength of the association increased with increasing duration of ADHD medication use. The increased long-term CVD risk associated with ADHD medication use was found for both the stimulant medication methylphenidate and the non-stimulant medication atomoxetine.

In the systematic review and meta-analysis, the Good Research for Comparative Effectiveness (GRACE) checklist was used for quality assessment of the included observational studies and there were methodology flaws in some studies, such as selection bias, immortal time bias and prevalent user bias. Two included studies had long-term follow-up, but one[185] only included children and the other[199] was not in general ADHD patients and both were subject to prevalent user bias.

In the nested case-control study, we found individuals with ADHD medication use were associated with an increased risk of developing CVDs in a dose-response manner. As mentioned above, few but two previous studies (median follow-up of 9.5 and 7.9 years respectively[185, 199]) have investigated the long-term risk of CVDs associated with ADHD medications.[213] These two studies found 2-fold and 3-fold increased risk of CVDs with ADHD mediation use respectively, yet both were subject to prevalent user bias. Results from the current study suggest that the CVD risk associated with ADHD medication use, i.e. 7% increased risk associated with a one-year increase use of ADHD medication, was lower than previously reported. The increased risk was also supported by estimates using cumulative DDD as measurement, acknowledging that the absolute risk is relatively low (the incidence rate was 7.02 per 1000 person-years in the base cohort). Since both the absolute risk and the risk ratio were relatively low, it should be noted that the moderate risk increase may be offset by the benefits of ADHD medications.[10, 214]

6.4 STRENGTHS AND LIMITATIONS

6.4.1 Strengths

The key strength throughout the studies is that it uses representative nationwide registers with prospectively collected data, ensuring that the results of this thesis are generalizable to the

entire Swedish population, including different patient groups and age groups. In addition, the rigorous design generated robust results, controlled for or reduced biases from measured confounders.

In study I, the nationwide representative data gave us unique insight into the pattern of somatic co-medication and polypharmacy among adults who dispensed ADHD medications from a complete population-based cohort. In study II, the nationwide representative register allowed us to conduct the first study exploring the familial association of ADHD with AD and any dementia. In addition, the use of multi-generational design in study II enabled us to follow relatives of index persons from their younger elderly to older elderly, thus providing insight into ADHD and cognitive decline in older age. In study IV, the nationwide representative database also allowed us to investigate the long-term ADHD medication use with a relatively long follow-up time. The longitudinal prescription data and the treatment period prediction algorithm allowed us to derive an accurate measure of total ADHD medication exposure accounting for the quantity and dose prescribed. In study III, we conducted a meta-analysis using rigorous searching and quality assessment strategy to synthesize all available data and provided insight for clinical guidance on ADHD prescribing.

6.4.2 Limitations

Throughout the studies in this thesis, we used dispensed prescriptions from the PDR when assessing ADHD medication use, but we cannot be sure if the dispensed ADHD medications were consumed. Therefore, the estimate involving ADHD medication use should be considered and interpreted as intention-to-treat, which may bias the effect estimation.[215]

Also, we did not have information on the underlying indications for dispensations of ADHD medications, which meant that we were unable to determine if any of the ADHD medications were dispensed for other problems, i.e. off-label use. ADHD medications are only licensed in Sweden for treating ADHD, but off-label use for alleviating fatigue, pain or sleep symptoms caused by narcolepsy or multiple sclerosis is rare but possible.[216]

In addition, all the studies of this thesis were observational, although we adjusted for multiple potential confounders but were not able to account for all of them such as unmeasured confounding, and for example, in study IV, we were not able to account for time-varying confounding. This means that we have only shown associations throughout the thesis but were not able to imply any causality.

Further, there is variability in terms of the prevalence of ADHD, dementia, and CVD and ADHD medication use across countries.[34, 217] The clinical practices on disease diagnosis and medication prescribing also vary between countries. Thus, generalizations to other contexts should be made with caution.

In study I, we included most of the main medication classes in the ATC classification system but not all. We did not have information on medications used for blood and blood-forming organs. Apart from that, some medications not used or licensed in Sweden were also not able

to be examined. Thus, the co-medication pattern with such medications may not be generalizable to other contexts.

In study II, although we used a multi-generation design, the parents and uncles/aunts were only able to be followed until their sixties. However, the onset of AD and other dementias usually peaks around 80 years.[218] We repeated the analysis among different birth cohorts, i.e. index persons born 1980-1989 and 1990-2001, and found similar results, which suggested that the difference in length of follow-up did not bias our estimates. We were also not able to examine the risk of specific dementia subtypes such as vascular dementia, frontotemporal dementia and lewy bodies dementia due to an insufficient number of cases. Future studies are needed to examine whether the associations are different for other subtypes. Further, there might be misclassification in the diagnosis of AD or any dementia. Although validation research has reported high specificity of the diagnoses in the NPR and CDR, the sensitivity was low (estimated at 63%).[160, 161] Such misclassifications of cases would bias the estimates towards the null. Nonetheless, prescriptions for AD were used for case identification, therefore such bias may be minimal.

In study III, we observed high and significant heterogeneity across included original studies. Therefore, the pooled RR may not summarize the estimates from all included studies appropriately, although high heterogeneity did not invalidate our results. This means that the pooled estimates should be interpreted with caution.[6] In addition, we were not able to compare the risk of any CVD with specific ADHD medications due to a lack of original studies focusing on that. Further, we used the validated GRACE checklist for assessing the quality of observational studies, but whether using a total score approach is valid for risk of bias assessment needs to be evaluated.

In study IV, the identification of patients with CVDs was based on recorded diagnoses. This means that there might be under-ascertainment of cardiovascular cases, so some controls may have had undiagnosed CVDs that did not yet require medical care, which would tend to underestimate associations with treatment if assumed increased risk of ADHD medications. In addition to that, we presented the types of cardiovascular disease among cases but were not able to examine the association by CVD subtypes due to the limited number of cases. Results of subgroup estimates by sex, age and ADHD medication type need to be replicated by studies with larger sample sizes and longer follow-up time.

6.5 ETHICAL CONSIDERATIONS

This thesis includes epidemiological research using data linkage of several national registers. Our research adheres to the ethical requirements of research on human participants according to Swedish law (autonomy, justice, beneficence and non-maleficence), and studies in this thesis were approved by the Stockholm Regional Ethics Committee with reference number 2013/862-31/5. This thesis aims to further the understanding of the developmental trajectories of attention-deficit/hyperactivity disorder into adulthood and aging, which would benefit both individuals with the disorder, their family members, and clinical practice of ADHD treatment.

The benefits of conducting such research, e.g. delivering important health-related information, outweigh the potential ethical consequences.

The main effort made to address ethical consequences in the current thesis was the way we handled sensitive personal data - not doing any harm to individuals' privacy. From a legitimate point of view, informed consent for register-based is generally waived in Sweden.[219] When performing register-based studies, we have been using pseudonymization datasets delivered by the data holders, i.e. Statistics Sweden and the Swedish National Board of Health and Welfare, with a serial number of individuals instead of personal identity number, which prevent information of individuals from being traced back to a living or dead person, and minimize the risk of violating the confidentiality of individuals. In addition, other efforts for protecting the privacy of individuals included that we only presented summary statistics at a group level. When a rare disease is presented in combination with other detailed information, sensitive information of the individual would be at risk of being exposed. We made sure that individuals are not identifiable in this thesis. Furthermore, the data used in this thesis is stored, analyzed and destroyed carefully under laws and regulations, i.e. Personal Data Act and the General Data Protection Regulation (GDPR). The good data management practice guaranteed disciplinary rectitude in the handling of personal data in this thesis.

7 CONCLUSIONS

ADHD is a common neurodevelopmental disorder that persists into adulthood and even old age. Substantial psychiatric comorbidities and somatic outcomes could emerge across the lifespan. This thesis anticipates advancing the knowledge on the health outcomes of ADHD in adulthood and old age and evaluating the safety of ADHD medication use. The findings from this thesis suggest that 1) co-medication with somatic medications was common among adults receiving ADHD medications; 2) ADHD was associated with Alzheimer's disease and any dementia within families; and 3) long-term use of ADHD medications was associated with a modest increased risk of cardiovascular diseases in both children and adults.

8 FUTURE PERSPECTIVES

8.1 ALTERNATIVE DESIGNS OF OBSERVATIONAL STUDY

The present thesis has used cross-sectional, nested case-control and cohort designs as well as systematic review and meta-analysis of observational studies, which have their strengths and limitations (section 6.4). In non-randomized studies, confounding may hinder the comparability between groups and thus lead to confounding bias.[220] A confounder is a variable that influences both the exposure and the outcome but is not an intermediate variable in the causal pathway. To account for confounding,[220] efforts including multivariate modelling, matching and stratification have been made in this thesis. For example, in study I, II and IV we used multivariate regression models to adjust for a list of covariates, and in study IV we matched cases to controls on key confounders. However, time-varying confounders were not accounted for, this is because adjusting for time-varying confounders would introduce collider stratification bias if the time-varying confounding is affected by past exposures.[221] In addition, these confounding control approaches, i.e. multivariate statistical modelling, matching and stratification, could only adjust for measured confounders which rely heavily on the measurement, while the unmeasured confounding could not be addressed. Alternative designs, e.g. applying within-individual comparisons,[141] using an instrumental variable,[220] emulating a target trial[222] and applying G-methods[221] are important to triangulate our findings.

8.2 MECHANISMS UNDERLYING ADHD WITH SOMATIC COMORBIDITIES

Several prior studies have suggested that ADHD might be linked to some somatic outcomes with limited discussion or exploration of the underlying mechanism. In this thesis, we found a familial association between ADHD and AD. Using a causal framework, we have discussed possible mechanisms underlying the association, which needs to be validated in further research. For example, one of the possible mechanisms stated that the co-aggregation could be explained by shared familial risk factors by the two conditions. Therefore, family studies aiming to identify family-wide environmental risk factors contributing to both conditions are warranted. In addition, further efforts are also needed to identify pleiotropic genetic variants shared by both conditions, for example conducting GWAS studies of ADHD and AD based on larger sample sizes, which could unravel shared genetic mechanisms through linkage disequilibrium score regression.[223] Another possible mechanism stated that ADHD might increase the risk of late-life AD through adverse health outcomes associated with ADHD such as depression, hypertension, type 2 diabetes, physical inactivity, smoking, and low educational attainment.[105] These conditions have been shown to be risk factors for AD. Revealing the mechanisms underlying the co-aggregation between ADHD and AD could answer whether early-life psychiatric prevention can help to prevent the development of neurodegenerative diseases.

8.3 DETECTION OF POTENTIAL ADVERSE EFFECTS OF POLYPHARMACY WITH ADHD MEDICATIONS

We found elevated rates of co-medication and polypharmacy with somatic and psychotropic medications in adults receiving ADHD medications. For example, 67% of young adults prescribed ADHD medications were treated with at least one other psychotropic medication compared to 13% among the control group in 2013. Safety concerns of the concurrent use of multiple medications with ADHD medications have been raised, regarding possible increased risks of adverse drug events due to cumulative toxicity, non-adherence, or drug-drug interactions.[133, 224] Despite this, there is limited literature addressing the risks or benefits of the use of ADHD medications in combination with other medications. Further research to investigate whether adding additional psychotropic or somatic medications during ADHD medication treatment would increase the risk of adverse events, for example, acute events requiring emergency visits, is needed. This research question could be explored using a data-driven screening approach, which could allow for screening a large number of drug-drug pairs simultaneously with adjustment for multiple testing.[225]

9 ACKNOWLEDGEMENTS

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