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ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ADVERSE HEALTH OUTCOMES: FROM ASSOCIATION TO PREVENTION

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Attention-Deficit/Hyperactivity Disorder and Adverse Health Outcomes: From Association to Prevention
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By

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且莫空山听雨去，有人花底祝长生。

——清 龚自珍

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurodevelopmental disorder, characterized by persistent inattention and/or hyperactivity-impulsivity that are inappropriate for one's developmental stage. Individuals with ADHD suffer from adverse outcomes including somatic and psychiatric comorbidities. ADHD is also associated with increased risk of factors that may impose higher mortality risks. However, evidence has been limited on the association between ADHD and somatic diseases such as asthma. Also, the association between ADHD and premature death, as well as the potential effects of ADHD medication treatment is largely unknown.

The overarching aim of this thesis is to investigate the associations between ADHD and specific adverse outcomes including asthma and premature death. Individual studies were conducted to clarify the magnitude and etiology of the associations, as well as potential effects from medication treatment that may prevent poor prognosis.

In Study I, we combined a meta-analysis of existing studies and a Swedish national population-based analysis to investigate the population-level association between asthma and ADHD. In the meta-analysis, we found a significant cross-sectional association between asthma and ADHD when considering both unadjusted and adjusted odds ratios. The sub-group and meta-regression analyses showed consistently robust results across study settings. Estimates of the association from the Swedish population analysis were similar with the pooled results from the meta-analysis, and the association remained statistically significant after adjustment of potential confounders in the population-based analysis.

In Study II, we investigated the familial liability to the comorbidity between asthma and ADHD. In the familial co-aggregation analysis, relatives of individuals with asthma had an increased risk of ADHD compared to relatives of individuals without asthma. The association was strongest in monozygotic twins and attenuated with decreasing degree of genetic relatedness. Results from the twin modelling analysis supported that a substantial part of the association between asthma and ADHD was explained by genetic factors. Estimates for contributions from shared and non-shared environment factors were not statistically significant.

In Study III, we investigated the all-cause and cause-specific mortality risks in ADHD and the role of psychiatric comorbidity. We found that ADHD was associated with significantly increased all-cause and cause-specific mortality risks, with suicide and unintentional injuries being the leading causes of death. Psychiatric comorbidity largely mediated the elevated mortality risks in ADHD, as the mortality risks increased substantially with the number of comorbid psychiatric disorders. Early-onset disorders such as conduct disorders contributed substantially to the association for natural deaths, while later-onset disorders such as substance use disorders may have mediated most of the risk for unnatural deaths in ADHD.

In Study IV, we investigated how ADHD medication initiation and continuation associated with mortality risks among individuals with ADHD. During follow-up to a maximum of 2 years, the mortality rates due to any cause and unnatural causes were significantly lower among those who initiated medication treatment compared to those who had not initiated medication. Among individuals who had been on ADHD medication for up to 6 months after diagnosis, continuation of medication treatment was significantly associated with substantially lower all-cause and unnatural cause-specific mortality risks including suicide and unintentional injuries compared to discontinuation.

In summary, results of Study I and II together support the significant association between asthma and ADHD. The comorbidity may largely be explained by shared etiology, with substantial influences from shared genetic factors. The findings also point out shared genetic factors as an important direction to understand the mechanisms of adverse conditions related to ADHD other than asthma. Study III and IV together reveal that ADHD is associated with significantly increased all-cause and cause-specific mortality risks, and ADHD medication treatment may help to reduce the risks. The findings point out medication treatment as a promising way to prevent extremely severe adverse outcomes among individuals with ADHD.

In conclusion, findings from this thesis work support that individuals with ADHD are at increased risk of adverse outcomes including somatic conditions such as asthma and severe adversities such as premature death. Shared genetic factors largely explained the association between asthma and ADHD, indicating the significance of detecting within-individual and family history of either disorder for preventing delayed diagnosis of the other condition. Moreover, psychiatric comorbidities and medication treatment play crucial roles in understanding the mechanisms of ADHD associated mortality risks and in preventing premature deaths among individuals with ADHD.

LIST OF SCIENTIFIC PAPERS

* Equal contribution.

I. Cortese S*, **Sun S***, Zhang J, Sharma E, Chang Z, Kuja-Halkola R, Almqvist C, Larsson H, Faraone SV. Association between attention deficit hyperactivity disorder and asthma: a systematic review and meta-analysis and a Swedish population-based study. *Lancet Psychiatry.* 2018, 5 (9), 717-726.

II. **Sun S**, Kuja-Halkola R, Chang Z, Cortese S, Almqvist C, Larsson H. Familial liability to asthma and ADHD: A Swedish national register-based study. *(Submitted)*

III. **Sun S**, Kuja-Halkola R, Faraone SV, D'Onofrio BM, Dalsgaard S, Chang Z, Larsson H. Association of psychiatric comorbidity with the risk of premature death among children and adults with attention-deficit/hyperactivity disorder. *JAMA Psychiatry.* 2019, 76 (11), 1141-1149.

IV. **Sun S**, Lichtenstein P, Kuja-Halkola R, D'Onofrio BM, PhD, Larsson H, Chang Z. Association between ADHD medication treatment and premature mortality in individuals with ADHD: A Swedish nationwide cohort study. *(Manuscript)*

CONTENTS

LIST OF ABBREVIATIONS

A	Additive genetic factors
ADHD	Attention-deficit/hyperactivity disorder
aHR	Adjusted hazard ratio
AIC	Akaike information criterion
ASD	Autism spectrum disorder
ATC	Anatomical therapeutic chemical
BMI	Body mass index
C	Shared environmental factors
CD	Conduct disorders
CDR	Cause of Death Register
CI	Confidence interval
D	Dominant genetic factors
DAG	Directed acyclic graph
DZ	Dizygotic (twins)
DSM	Diagnostic and Statistical Manual of Mental Disorders
E	Unique environmental factors
GDPR	The European General Data Protection Regulation
GWAS	Genome-wide association study
h^2	Heritability
HKD	Hyperkinetic disorder
HR	Hazard ratio
ICD	International Classification of Diseases and Related Health Problems
ID	Intellectual disorder
LISA	Longitudinal Database for Health Insurance and Labor Market Studies
MBR	Medical Birth Register
MGR	Multi-Generation Register
MZ	Monozygotic (twins)
NPR	National Patient Register

OR	Odds ratio
PDR	Prescribed Drug Register
PIN	Personal identification number
PUL	The Personal Data Act in Sweden
r	Correlation
rg	Genetic correlation
rPh	Phenotypic correlation
SNP	Single nucleotide polymorphism
STR	Swedish Twin Register
SUD	Substance use disorders
TPR	Total Population Register
WHO	World Health Organization

1 INTRODUCTION

1.1 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

1.1.1 Origin of ADHD

The first reference of the disorder can trace back to the year of 1775, when a Germany physician described a syndrome of "attention deficit".[1] It was until 1980 when reliable diagnostic criteria were available in the revised third edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R).[2] Since then, numerous clinical and research efforts have revealed that ADHD is a highly prevalent and persistent disorder.

1.1.2 Clinical diagnosis

Currently both DSM and the International Classification of Diseases (10th edition; ICD-10)[3] are used for clinical diagnosis of ADHD. Clinical diagnosis of ADHD requires assessment of the symptoms, considering the severity and lasting time (usually more than 6 months) of functioning impairment manifestations, as well as developmental age of the individual.[4]

Both DSM and ICD classifications evaluate whether the afflicted individuals present developmentally inappropriate and impairing levels of inattention, hyperactivity and impulsivity with childhood onset and impairments to school/social performance, and intellectual and occupational functioning.[5,6] When assessing ADHD symptoms, information from several informants is typically needed, and the patients themselves, parents, and school teachers have been shown to provide valuable information.[7] Clinicians also need to consider the age of the patient, and the age-of-onset of the symptoms are also important when deciding on whether a clinical diagnosis is appropriate, because the presentation of symptoms may change across age,[7,8] The DSM-IV classification system is less restrictive when identifying ADHD compared to the ICD-10 where the disorder is described as hyperkinetic disorder (HKD).[9] The DSM-IV also define three subtypes of ADHD based on symptoms, including primary inattentive, primary hyperactive-impulsive, or combined,[10] which are not available in ICD-10.

The fifth edition of DSM (DSM-5) published in 2013[7] introduced profound changes regarding diagnosis of ADHD. For example, instead of defining three subtypes, DSM-5 now uses the term "presentation", to acknowledge the heterogeneity of the behavioral manifestations of ADHD in different developmental stages.[11] Another significant change was to the age-of-onset criteria from 7 to 12 years old, which may affect the subsequent estimates of prevalence. Moreover, ADHD usually persists into adulthood, with substantially heterogeneous presentations across age.[8,12,13] Accordingly, DSM-5 decreased the threshold of symptoms for diagnosis in cases older than 17 years old, from six symptoms in DSM-IV to five in DSM-5. Diagnosis of ADHD in adults also requires evidence of symptoms and corresponding functioning impairments, as well as possible age of onset. Information source can be the patient through clinical interview, and close informants if possible.[14]

Recently, the ICD-11 was published with noticeable updates of terminology and diagnostic criteria for ADHD.[15] In short, ADHD is now included in the category of neurodevelopmental disorders, described with inattentive and hyperactive/impulsive presentations without defined age of onset and duration of symptoms. Such updates helped bring the DSM-5 and ICD-11 systems more consistent in defining symptoms and diagnostic criteria for ADHD,[16] which may facilitate the generalizability and communication of both clinical practice and relevant research on the disorder in different countries.[17]

Standardized scales are available to help collect information from the patients or informants. Although not accurate enough to estimate the onset age of ADHD, studies have reported that parent-rated questionnaires are valuable in early identification and treatment decision making among children.[18] Rating scales for adults such as Conners' Adult ADHD Diagnostic Interview[19] and the Adult Self-Report Scale [20] have also been shown reliable in structured diagnostic interviews for both the patients and informants.

1.1.3 Epidemiology

The prevalence of ADHD among children has been estimated to be around 5% worldwide.[21,22] Results from meta-analysis indicate substantial variation in the prevalence across studies, primarily due to different diagnostic criteria (DSM vs. ICD), information source (patient vs. informants), and requirement of functional impairments.[4,9] For example, North America uses DSM classification as the diagnosis tool, but European countries commonly use ICD system, which has relatively more restrictive criteria for ADHD diagnosis. In a recent meta-analysis, ADHD prevalence became stable across geographical regions and populations after adjusting for these factors.[23] Moreover, there has been no significant increase in ADHD prevalence during the past three decades, worldwide, regardless of concerns about the issue of over-diagnosis recently with improved awareness.[24]

ADHD affects around 2.5% of adults in the world.[25-27] Prevalence of ADHD among adults substantially depends on how ADHD persistence into adulthood is defined, following the childhood onset of the disorder.[8] Many of the children with a diagnosis of ADHD may not meet the full criteria of ADHD in their adulthood, in part due to a decline in symptoms across age.[12] However, almost two-thirds of ADHD cases with childhood diagnosis persistently suffer from relevant impairments in adulthood.[8,28] Due to the corresponding updates in DSM-5, more details are available to describe ADHD in adulthood, where the diagnosis criteria among adults became more inclusive.[7] Studies reported that such updates resulted in a slightly increased prevalence of ADHD among young adults, from 2.8% using DSM-IV to 3.5 % using DSM-5.[29] It is not known how the recently published ICD-11 would affect ADHD prevalence among adults, but no specific descriptions of ADHD symptoms or impairments in adulthood were provided.[30]

Studies have shown that the prevalence of ADHD differs substantially across sex, especially among children with boys accounting for almost two-thirds of the identified young ADHD cases.[21,31] Although the sex discrepancy largely attenuates in adulthood, it may be due to possible referral bias. Girls and adult women with ADHD are less prone to seek for

professional help and treatment compared to their male peers; diagnosed female ADHD cases usually present relatively more severe symptoms or pertaining impairments.[32,33] Socio-economic status within a population and ethnicity are among other factors that researchers suggested may affect the incidence or prevalence of ADHD, with arguments of health resource accessibility or cultural stigma.[34-37] However, inconsistent evidence exists and it is unclear if such factors affected incidence of ADHD or if ADHD itself leads to the risk of lower socio-economic status in the family.[38]

1.2 ETIOLOGY OF ADHD

ADHD is etiologically a multifactorial disorder influenced by both genetic and environmental risk factors.[9,39] Each of the risk factors may have limited effects, and accumulation of effects from many different factors build up to the general susceptibility, where both additive and interactive reactions between factors may exist.[4] The multifactorial causation of ADHD leads to heterogeneity of clinical manifestations and prognostic outcomes. Meanwhile, because no single factor has been determined to cause ADHD independently from other factors, diagnosis and prevention efforts targeting specific risk factors may end up with limited efficacy.

1.2.1 Genetic susceptibility

Familial aggregation is common regarding incidence of ADHD, with parents and siblings of ADHD probands presenting 5-10 times higher risk of developing the disorder compared to the general population.[40-42] Family and twin studies have reported heritability of ADHD as high as 70%-90%.[42-44] Single Nucleotide Polymorphism (SNP)-based heritability for ADHD symptoms range from 5% to 34%, indicating substantial influence from common genetic variants on ADHD symptom scores and possibility of polygenic correlation.[45]

Approximately 40% of the heritability of ADHD estimated from genome-wide association studies (GWAS) can be attributed to common genetic variants.[46] Additionally, rare genomic insertions and deletions, known as copy number variants (CNV), also affects ADHD.[47-49] Researchers suggested that potential candidate genes involved in the monoamine neurotransmitter systems are related to ADHD.[50] For example, the *SLC6A3* gene encoding dopamine transporters may also affect ADHD, based on potential pathophysiology of ADHD where stimulant drugs acting on these dopamine transporters alleviate ADHD symptoms. Several GWAS analyses supported that the group of genes regulating the dopamine, noradrenaline, serotonin, and neurite outgrowth systems associates with ADHD and symptoms of hyperactivity or impulsivity.[51-53] Recently, a GWAS meta-analysis covering 20 183 ADHD cases and 35 191 controls identified 12 independent loci with genome-wide significant association with ADHD for the first time.[54] Findings from this study furtherly indicated the significant influence of common genetic variants in the polygenic architecture of ADHD. Moreover, several of these 12 loci relates to genes influencing neurodevelopmental process.

1.2.2 Environmental factors

Perinatal exposures to adverse conditions may predispose the risk for ADHD. Complications suggested in previous studies included toxemia, poor maternal health during pregnancy, maternal age at birth, long duration of labor, fetal distress, and antepartum hemorrhage.[55-57] Maternal smoking and alcohol use, and exposures to other environmental toxins during pregnancy such as organophosphate pesticides, polychlorinated biphenyls, zinc and lead are also potential risk factors for ADHD.[58,59] Effects of each environmental factor are relatively small and usually accumulate to increase the overall risk.[9,58] In addition, psychosocial adversity has also been a major suspected factor regarding the risk of developing ADHD. Rutter's index of adversity incorporated six risk factors describing adverse family environment including severe marital discord, low social class, large family size, paternal criminality, maternal mental disorder, and foster placement.[60] Population-based studies revealed that the Rutter's index was positively correlated not only with ADHD, but also with ADHD associated psychopathology, impaired cognition, and psychosocial dysfunctions.[61,62]

1.3 TREATMENT OF ADHD

The European clinical guidelines for management of ADHD (hyperkinetic disorder) defined a hierarchal model, where psychological interventions, educational change, medication and dietary measurements are integrated.[63] Non-pharmacological treatments include mainly educating the parents or behavioral interventions toward both parents and ADHD patients.[64] Efficacy of behavioral approaches is relatively good, and combination therapy together with ADHD medication treatment may predict better prognosis.[65,66] Results from meta-analyses have reported that dietary approaches including supplement or exclusion of specific food can have potentially beneficial effects,[67] but the effects were limited to small subgroups of those with ADHD.

Pharmacological treatment including stimulant and non-stimulant medications are recommended for individuals diagnosed with ADHD in clinical guidelines for both children and adults.[68-74] The first regulatory approval of stimulant treatment among children with ADHD was issued in 1960s.[75] Since then, prescription of medications has been increasing globally and stimulants (mainly methylphenidate and amphetamine) have been the predominant choice for clinical treatment of ADHD.[76,77] Stimulants can improve neurotransmission of dopamine and norepinephrine,[78] which is involved in the pathophysiology of ADHD. Non-stimulants, mainly represented by atomoxetine (selective noradrenaline reuptake inhibitor), clonidine and guanfacine (long-acting α2-adrenergic agonists), are also effective alternatives.[79-81] Choice of medication depends on clinical severity and presentation of symptoms, as well as comorbid somatic and psychiatric conditions. Specific treatment intentions concerning different situations are also important, as medications with transient vs. relatively long-lasting effects are now available.[82]

1.4 ADVERSE OUTCOMES OF ADHD

1.4.1 Somatic comorbidity in ADHD: association and etiology

Classically defined nervous system disorders are now also thought to include alterations in other physiological systems.[83] This notion has prompted research into the possible associations between neuropsychiatric and somatic conditions. Relatively poorer health status with comorbid somatic conditions such as obesity and asthma were more common in ADHD cases compared to individuals without the disorder.[84] However, evidence on somatic comorbidities in ADHD is largely limited and potential mechanisms underlying most of the observed comorbidities remain unclear.

Obesity is one of the most investigated somatic conditions associated with ADHD. Meta-analyses of population-based studies reported around 30% elevated risk of obesity/overweight associated with ADHD, with the hypothesized mediating effects of abnormal eating habits or sedentary lifestyle.[85-87] A later study on Swedish national register data found that ADHD and obesity co-aggregate in families, and the comorbidity between the two conditions can be entirely attributed to shared genetic factors.[88] Combined results from the general population and the family data indicate that the association between ADHD and obesity may be etiologically attributed to the same genetic factors underlying both conditions. Moreover, the possible mediation effects from poor eating behavior was supported by a recent twin study identifying weak genetic overlaps of inattention with high-sugar food (genetic correlation 0.16; 95% CI, 0.07-0.25) and hyperactivity/impulsivity with unhealthy dietary pattern (genetic correlation 0.05; 95% CI, −0.05-0.14), respectively.[89] But the twin study was based on symptoms of ADHD measured from questionnaire survey and self-reported eating behavior. Further studies are needed to clarify the causality between clinically diagnosed ADHD and eating disorders, with consideration of obesity as the endpoint outcome.

Asthma is the most prevalent chronic respiratory disease, affecting around 3-5% children in low-income countries and as high as 20% in high-income countries.[90] An association between asthma and ADHD has been tested in clinical and population data, with the hypothesis originating from a possible link between ADHD and allergic or atopic diseases such as eczema.[91] Specifically, the two main hypotheses causally linking asthma and ADHD were that 1) children with asthma experiencing excessive stress from peer and parents lead to ADHD related alterations in the brain; and/or 2) that the hyper-secretion of pro-inflammatory cytokines from allergic reactions pass through the blood-brain barrier and affect the prefrontal cortex which is closely related to the pathophysiology of ADHD.[92-94] However, findings from previous studies were not conclusive for either the existence of the association or the potential mechanisms underlying such comorbidity. An early meta-analysis including five cross-sectional studies reported a significant association between ADHD and asthma, but the included five studies were with low quality and the authors only pooled unadjusted odds ratio (OR) of 1.80 (95% CI, 1.57-2.07).[95] Another meta-analysis of six longitudinal studies found that early asthma imposed over 30% increased risk of later ADHD onset, but there were overlapping samples across studies and representativeness of the samples were not clear.[96] More importantly, previous studies have not fully addressed if the reported association is due to potential confounders. Therefore, the hypothesis of a significant association between

asthma and ADHD awaits rigorous testing. Moreover, it remains to be investigated if the comorbidity of asthma and ADHD is explained by shared etiology or direct causality between the two disorders. Recently, a large genome-wide association meta-analysis[54] of ADHD reported a small genetic correlation with asthma, but the extent to which these findings replicate in family and twin data remains unclear. Once a robust association is established between asthma and ADHD, large-scale family co-aggregation studies incorporating quantitative genetic modelling analysis can be substantially informative for both causally understanding the association and clinically improving early detection of ADHD in asthmatic children or vice versa.

1.4.2 Psychiatric comorbidity in ADHD: association and etiology

Symptoms and impairments are heterogeneous among individuals with ADHD.[4,16] A small subgroup (around 13%-30%) of individuals with ADHD do not have any comorbid psychiatric disorders,[97] whereas the majority may suffer from multiple problems. Literature reviews and meta-analyses reported elevated risk of both internalizing and externalizing disorders in individuals with ADHD, and the link was usually observed to be bi-directional from observational data.[98-103] Specifically, conduct disorders (CDs) and oppositional defiant disorder (ODD) are among the most commonly identified comorbidities, as 45-65% of children with ADHD were also diagnosed with ODD and half of the children with such comorbidity may progress to CDs.[104,105] ADHD also associates with other neurodevelopmental disorders including autism spectrum disorders (ASD)[106-108] and intellectual disability (ID).[109] For example, different studies reported that 31-95% of children with ASD presented ADHD like symptoms including inattention and hyperactivity/impulsivity,[110] and about 20-50% of children with ADHD also met the diagnostic criteria for ASD.[111] ADHD in childhood predicts later substance use disorders (SUD), as meta-analyses of cohort studies reported that compared to their peers without ADHD, children with the disorder presented around doubled risks of developing misuse or dependence of substances including alcohol, nicotine and marijuana in adolescence or early adulthood.[112,113] Another meta-analysis revealed that about one in every four adolescents and adults with SUD met the DSM criteria for ADHD.[114] Studies found that approximately 20% (ranging from 10% to 35%) of children with anxiety also had ADHD; and 50% of children with ADHD suffered from anxiety.[115] Similar levels of co-occurrence were present for ADHD and mood/affective disorders, as well as bipolar disorders.[97] Risk of developing major depressive disorders was over five times higher among youth with ADHD than youth without.[116] Moreover, evidence supports associations between ADHD and eating disorders[117,118] and personality disorders,[119,120] although pooled associations from meta-analysis have been limited.

The underlying mechanisms of the comorbidity between ADHD and other psychiatric disorders are not totally established yet. Genetic factors may play a crucial role in understanding the psychiatric comorbidity of ADHD. Sibling and twin based studies identified a general genetic factor influencing the co-occurrence of neurodevelopmental disorders including ADHD and internalizing and externalizing problems.[121] The findings

indicate that common psychiatric disorders including ADHD may share the same genetic origins. Familial co-aggregation studies between ADHD and other psychiatric disorders including ASD, SUD, anxiety, depression, and personality disorders also support that shared familial liability mostly contributed from genetic factors may largely explain the comorbidity.[108,109,122-128] A meta-analysis summarized similar magnitudes of pooled genetic correlations between ADHD and externalizing problems (0.49 [95% CI, 0.37-0.61]), internalizing problems (0.50, [95% CI, 0.44-0.56]), and neurodevelopmental disorders (0.56, [9.% CI, 0.47-0.66]).[129] The recent GWAS reported 12 loci of genome-wide association with ADHD and provided insights into understanding the links between ADHD and other psychiatric disorders.[54] For example, among the identified genetic variants, the *FOXP2* located on chromosome 7 may influence the comorbidity between ADHD and intellectual disability (ID), and the *SORCS3* on chromosome 10 were previously reported to be associated with neurodevelopmental disorders and depression. Environmental factors may also explain part of the psychiatric comorbidities in ADHD. For instance, children with ADHD may develop depression several years after the onset of ADHD, as a result of excessive pressure from peers or parents.[116] A related hypothesis is that although ADHD and depression may share the same familial liabilities, the heterogeneity in symptom spectrums and severity across patients is mainly driven by non-shared environmental factors unique to the individual. Moreover, sex differences in the relative risks and patterns of psychiatric comorbidities were found in previous studies. An early study from Denmark found that girls with ADHD had higher risk of multiple psychiatric disorders in adulthood compared to boys with ADHD.[130] A recent study using the Danish national registers with a much larger sample found that females with ADHD presented higher risk of developing ASD, CD/ODD, ID, SUD, and personality disorders.

1.4.3 Preventing adverse outcomes in ADHD

Individuals with ADHD have poorer quality of life, and are at increased risk of multiple adversities including morbidity and mortality. Somatic and psychiatric comorbidities may be important contributors to the overall risk of adverse outcomes in ADHD, and can also provide significant clues of preventing specific adversities with better understanding of the etiology underlying the comorbidities. For instance, establishment and awareness of the link between asthma and ADHD could prompt asthma specialists to refer asthmatic children with ADHD-like symptoms to specialists for early diagnosis of ADHD and encourage psychiatrists to refer ADHD cases with early signs of asthma. Delayed diagnosis has been a big issue for both asthma and ADHD, and early diagnosis and management can substantially alleviate adverse outcomes.[16,131,132] Furthermore, direct causality between the two disorders can provide clear directions of preventing both conditions; shared causality, apart from emphasizing the importance of family history when considering clinical referral as mentioned above, can also improve the research into the links between ADHD pathophysiology and allergic conditions at large.

Individuals with ADHD are prone to higher risks of adverse outcomes including criminality,[133] accidents,[134,135] and suicidal behavior.[136-139] Potential additive or mediating

effects of psychiatric comorbidity are often among the most mentioned hypotheses for possible mechanisms. On the other hand, various psychiatric disorders such as SUD and depression were associated with increased risk of premature death, especially due to unnatural causes including suicide.[140-142] However, evidence has been limited how ADHD directly associates with premature death, and how various types of psychiatric comorbidities affect the association. For example, as ADHD onsets early in childhood, it may be reasonable to hypothesize that ADHD predisposes increased risk of developing depression in adolescence or adulthood, and then leads to higher susceptibility of committing suicide later in life. Potential mediation effects from psychiatric comorbidities are possible, so as for additive effects or interactions with having ADHD. A Danish register-based study found a two-fold increased risk of all-cause mortality in ADHD, with majority of deaths due to unnatural causes in the ADHD group.[143,144] The mortality rates were higher among individuals with co-occurring CD/ODD, and/or SUD, supporting the additive or mediating mechanisms of psychiatric comorbidity. However, the authors did not have the power to explore cause-specific mortality risks and missed exploration of the possible effects from different types of psychiatric comorbidities. Investigation of the overall mortality risks in ADHD and exploration of the potential effects from psychiatric comorbidities can substantially facilitate identification of high-risk groups in clinical practice, and prioritization of resources for preventing premature deaths. For instance, if specific types of psychiatric comorbidities impose the most contribution to the excessive mortality risks in ADHD, more efforts could be prioritized clinically in early identification and proper management of such comorbidities.

A recent meta-analysis[145] evaluating efficacy of medications concluded that methylphenidate in childhood and amphetamines in adulthood present good tolerability and treatment effects. A review study mentioned potential side effects from ADHD medication treatment, including sleep problems, decreased appetite, and suppressed growth of height in childhood.[4] More severe outcomes including adverse cardiovascular events and sudden death were mentioned, but existing evidence do not predominantly indicate causal relationships between the medication use and observed outcomes.[146-148] On the contrary, multiple studies reported the potentially beneficial effects of medication treatments on both ADHD symptoms and related problems.[149] Potential benefits from ADHD medication were reported on adversities such as suicide,[150,151] accidents,[134,135] and SUD.[152-154] However, it is largely uninvestigated how ADHD medication treatment affects the risk of premature death among individuals with ADHD. More specifically, it remains unknown if ADHD medication treatment initiation and continuation would affect the all-cause and cause-specific mortality risks. Further research into the potential effects from ADHD medication treatment on adverse outcomes such as cause-specific premature deaths can provide both clinical and public health implications in preventing premature deaths in ADHD.

2 AIMS

2.1 OVERARCHING AIM

To investigate the association between ADHD and adverse outcomes including asthma and premature death, with focus on investigating the mechanisms underlying the associations and potential treatment effects to prevent the adversities.

2.2 SPECIFIC AIMS

Study I: To summarize existing evidence on the population-level association between asthma and ADHD using meta-analysis and to validate the association in a Swedish population-based analysis.

Study II: To investigate patterns of familial co-aggregation of asthma and ADHD and also to quantify the relative contribution of genetic and environmental influences.

Study III: To investigate the all-cause and cause-specific mortality risks in ADHD and to explore the potential role of psychiatric comorbidities.

Study IV: To investigate how initiation and continuation of ADHD medication associate with all-cause and cause-specific mortality risks in individuals diagnosed with ADHD.

3 DATA SOURCES AND MEASURES

3.1 DATA SOURCES

We have linked several Swedish national registers using the unique personal identification numbers (PINs). Since 1947, every resident in Sweden was assigned with a unique ten-digit PIN which is used by Swedish governmental agencies for the purpose of administration and linkage through different national registers.[155] Data of this thesis was extracted mainly from the following nationwide registers.

Medical Birth Register (MBR), initiated from 1973, consists records of nearly all births in Sweden with information on perinatal status.[156]

National Patient Register (NPR), contains information of all inpatient discharges since 1987 and specialist outpatient care since 2001, with diagnoses coded according to the Swedish version of International Classification of Diseases 10th revision (ICD-10; from year 1997).[157]

The Prescribed Drug Register (PDR) has complete coverage of dispensed medications in Sweden since July 2005, coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[158] The PDR does not include information on medications used during hospitalization.

The Swedish Twin Registry (STR), established in 1950s, includes questionnaire survey information on almost 200 000 twins born in Sweden since 1886.[159]

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) since 1990 keeps census information including employment and highest completed education of all individuals aged 16 or older.[160]

The Cause of Death Register (CDR) initiated in 1952 provides information on dates and causes of all deaths in Sweden. Causes of death were coded by the ICD systems.[161]

The Multi-Generation Register (MGR) covering people born after 1932 in Sweden was used to identify parents to cohort members, and the Migration Register was linked to account for all emigrations from Sweden.[162]

3.2 MAIN MEASURES

3.2.1 ADHD

Two sources of information from the Swedish registers can be used for ADHD definition. Clinical diagnosis records of ADHD according to the ICD systems (ICD-9: 314; ICD-10: F90) from NPR are used to define ADHD in Study I and Study II when investigating the comorbidity between asthma and ADHD. In Study III, ADHD was identified by first diagnosis from NPR or the first prescription of ADHD medications (methylphenidate hydrochloride [ATC code N06BA04], amphetamine [ATC code N06BA01], dextroamphetamine sulfate [ATC code N06BA02], and atomoxetine hydrochloride [ATC

code N06BA09]) from PDR. In Study IV, we identified individuals with ADHD by the NPR diagnosis.

3.2.2 ADHD medication treatment

In Study IV, information on prescribed medication and dosage was extracted from PDR to define the treatment periods of ADHD medication. Treatment periods from each prescriptions were estimated from the prescriber's free-text prescription using a validated algorithm.[163] Natural language processing models were developed to extract information from each free-text prescription and to predict daily dosage and treatment duration, taking into account features including titration, stockpiling and non-perfect adherence.

3.2.3 Asthma

In Study I and II, asthma was defined as clinical diagnosis after three years old (ICD-9 code 493 or ICD-10 code J45–J46) from NPR or prescriptions of asthmatic medications (ATC codes R03AC, A03AK, R03BA, and R03DC) from PDR.[164]

3.2.4 Psychiatric comorbidity

In Study III and IV, we identified diagnosis of psychiatric comorbidities with ADHD from NPR. The ICD-10 codes for each psychiatric disorder is presented in Table 3.2.4. In Study III, we further categorized these psychiatric comorbidities into two groups according to the relative diagnosis age to ADHD in our data.

Psychiatric and behavior disorders	**ICD-10 codes**	**Category for analysis**
Autism spectrum disorders (ASD)	F84	Early-onset disorder
Intellectual disability (ID)	F7x	Early-onset disorder
Conduct disorders (CD/ODD)	F90.1, F91	Early-onset disorder
Eating disorders (ED)	F50.0-F50.3, F50.9	Later-onset disorder
Substance use disorders (SUD)	F10-F16, F18-F19	Later-onset disorder
Depressive disorders (Dep)	F32-F34	Later-onset disorder
Bipolar disorders (Bip)	F30-F31	Later-onset disorder
Anxiety disorders (Anx)	F40-F41	Later-onset disorder
Schizophrenia (SCZ)	F2x	Later-onset disorder
Personality disorder (PD)	F60-F62, F69	Later-onset disorder

Table 3.2.4 ICD-10 codes for diagnosis of psychiatric comorbidities.

3.2.5 Other psychotropic medication

Prescription records of psychotropic medications other than ADHD medications were identified from PDR, including antipsychotics [ATC code N05A]; anxiolytics, hypnotics, and sedatives [ATC code N05B or N05C]; antidepressants [ATC code N06A]; antiepileptic drugs

[ATC code N03A]; drugs used in addictive disorders [ATC code N07B]; and opioid pain medications [ATC code N02A]. The information was used as additional identification of psychiatric comorbidities in Study III, and baseline covariates in Study IV.

3.2.6 Premature death

Both all-cause and cause-specific premature deaths were used as outcomes in Study III and IV. Specific causes of death consisted of natural causes, including somatic diseases and medical conditions (ICD-10 codes A00-R99), and unnatural causes, including un- intentional injuries (ICD-10 codes V00-X59), suicide (ICD-10 codes X60-X84 and Y87.0), and other external causes (ICD-10 codes S00-T98 and X85-Y98, excluding Y87.0). In the analysis, premature deaths were measured by mortality rates per 10 000 person-years.

4 METHODS

4.1 CAUSAL INFERENCE FROM OBSERVATIONAL STUDIES

The scope of epidemiological research covers both describing features of a health-related issue and linking specific factors with the outcome of interest.[165] For the latter, a causal link can be hypothesized and tested via either interventional settings such as conducting randomized controlled trials (RCTs) where certain factors can be manipulated or observational settings such as conducting analysis on population-based datasets. In an RCT, eligible subjects are randomly assigned into different groups with or without the intervention of interest, and inferences can then be made by comparing outcome incidences across different groups. Subjects across different intervention groups are exchangeable regarding baseline features. Since the only difference across groups is the intervention factor, given proper sample size and adherence, RCTs can serve as the highest level of evidence for investigating whether the factor of interest can cause the outcome under research.[166] However, significant limitations of RCTs including potential ethical issues, high costs of practicality, unpredictable adherence, and exclusion of severe cases substantially impede the feasibility and generalizability of RCTs to answer many important research questions.[167,168]

Observational data may be obtained through a survey on a sample of the pre-defined population, or acquired through access to existing population data such as the national register linkage or insurance claim datasets. Although with the risk of potential biases and measurable/unmeasurable confounding, proper design and analysis plan can largely facilitate the understanding of causality, making observational study an important alternative approach to RCTs, with applications such as in identifying risk factors for a health condition or analyzing treatment effects on prognosis.[169,170]

4.1.1 Directed acyclic graph

Causality can be inferred from observation studies, but never from observed associations without proper design to avoid biases or adjustment of factors that may affect both the exposure and the outcome. Ideally, possible confounders should be identified based on available knowledge before conducting the study, so that both measured and unmeasured confounding can be dealt with to the largest extent from the beginning. Using existing evidence and knowledge, researchers could use directed acyclic graphs (DAGs) to illustrate the possible causal pathways from the exposure to the outcome, incorporating relevant covariates to the causal pathway.[171,172] These covariates may be categorized into potential confounders (common causes of the exposure and outcome), mediators (covariates lying on the causal pathway), and colliders (common results of the exposure and outcome), illustrated using directed arrows in the DAG(Figure 4.1.1). Consequently, unmeasured confounding can be addressed in the study design stage, such as accounting for genetic confounding by family-

based designs;[173] measured confounding can be dealt with by adjustment in statistical models.[174,175]

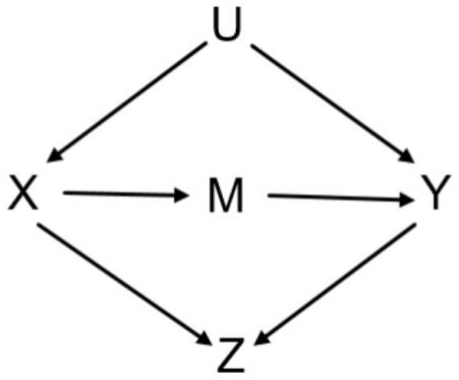

Figure 4.1.1 A DAG example. The figure illustrates a simplified causal diagram from exposure (X) to the outcome (Y), with a mediator (M) on the causal link, a confounder (U), and a collider (Z).

4.1.2 Genetically informative studies

4.1.2.1 Application of genetically informative designs

Genetically informative studies incorporate traditional epidemiological analysis in the settings of families or relatives, based on assumptions of known genetic and environmental relatedness across family pedigrees. Such designs, given proper sampling and reliable measurements, can provide more concrete evidence on understanding the causality underlying an observed association from traditional population-based research. Genetically informative studies can be conducted to answer various research questions, including estimating the broad-sense heritability, clarifying the shared causality for comorbidity between diseases, and quantifying the genetic and environmental influences on phenotypes. For example, monozygotic (MZ) twins are 100% genetically identical, while dizygotic (DZ) twins share 50% of segregating alleles; MZ and DZ twins both share the same familial environmental factors as they grow up in the same households. A stronger association between an exposure and outcome in MZ twins than in DZ twins may indicate genetic influences to the association.

Analyzing the aggregation (familial aggregation analysis) of a phenotype across family pedigrees using quantitative genetic modelling methods provides results in heritability, interpreted as how important the genetic background underlies the etiology of this phenotype. For example, twin modelling studies have estimated the heritability of ADHD being around 74%, indicating the significance of genetic predisposition on development of the disorder.[121] When extending the aggregation analysis into two phenotypes (familial co-aggregation analysis), researchers could estimate to which extent the familial liability consisting of genetic and shared environmental factors underlies an observed association between two phenotypes. Moreover, estimates of the non-shared environmental factors (environmental factors that are unique to the individual) can shed insights on direct causality between the two phenotypes. For instance, a familial co-aggregation study on ASD and ADHD revealed that

the commonly observed comorbidity between the two neurodevelopmental disorders may be explained by shared etiology, as ASD and ADHD co-aggregate in families.[176] Another common application is to view the familial relatedness as "familial confounding" when investigating if the observed population-level association between two phenotypes reflects direct causality or can actually be attributed to unmeasured confounding. For example, population-based studies reported a stable association between maternal pre-pregnancy body mass index (BMI) and offspring ADHD, raising concerns over the effects of maternal obesity on causing offspring ADHD. However, the association substantially attenuated to non-significant when running the analysis among siblings, indicating that the observed association on population level may actually be explained by unmeasured confounding.[177]

4.1.2.2 Comparative significance with genomics research

The tremendous development of research on genomic data in the past two decades have enabled researchers to understand the development of human traits onto the micro level. Genome-wide association studies (GWASs) made it possible to identify individual genetic loci underlying specific phenotypes. Consequently, summary statistics data from GWASs can also be used in integrated polygenic risk scores (representing the aggregate effects of individual genetic loci) in further understanding the etiology of phenotypes or provide insights into investigation of biological functions. The largest GWAS on ADHD[54] to date identified 12 genetic loci with genome-wide significance, and investigated genetic correlations between ADHD and 219 phenotypes using summary statistics, with results substantially improving the understanding of etiology underlying both ADHD and correlated phenotypes. Furthermore, genetic variants can also be used as instrumental variables in designs such as Mendelian randomization studies to make causal inferences on an observed association, with assumptions that the instrumental variable is independent from potential confounding and can thus avoid reverse causation.[178]

However, the profound advances and massive application of genomics research may not necessarily downplay the significance of population-based genetically informative studies. Fundamentally, findings from familial aggregation/co-aggregation analysis and quantitative genetic modelling analysis can provide insights and hypotheses for genomics research with estimates of relative influences from genetic and environmental factors on specific phenotypes. Also, observed familial aggregation of a disorder or co-aggregation of two disorders has important clinical implications by emphasizing the necessity of collecting information on within-individual and familial history of certain diseases. More importantly, the differences of the broad-sense heritability estimated from twin modelling analysis and the SNP-based heritability estimated from genomics data (the "missing" heritability problem of complex diseases[179]) have facilitated the understanding and discovery of other genetic factors not commonly captured by GWASs such as identification of the rare genetic variants for ADHD.[121] On the other hand, comparison between the broad-sense heritability and SNP-based heritability can also imply to what extent common genetic variants have influenced the genetic predispositions of a phenotype.

4.1.3 Pharmacoepidemiologic studies

By definition, pharmacoepidemiology investigates the use and effects of drugs in large numbers of people.[180] Pharmacoepidemiologic studies suffer less from the practical costs compared to RCTs and have the possibility to include patients with various disease severity. On the other hand, though, pharmacoepidemiologic studies investigating treatment effects may suffer from potential biases and confounding. Observational data can be used to estimate potential treatment effects on prognosis using pharmacoepidemiologic designs. However, given the limitations of observational data compared to RCTs, proper efforts in study deigns and analysis plans should be made to avoid obvious biases and confounding that affect the quality of study findings. To begin with, a new user design (individuals who are naïve to the medication at cohort entry), excluding prevalent users (individuals who have been on medication for a while at cohort entry), should be used.[181] Pharmaco-epidemiological studies including prevalent users at baseline may suffer from substantial biases. Since prevalent users are often "survivors" from early stage of medication use, including them may end up with underestimating the risk of events correlated to the initiation stage of treatment, especially for medications with time-varying effects. Within-individual analysis can be used for some outcomes, where the risk of outcome is compared between treated and untreated periods for the same individual to account for conditions constant for the same individual.[182] Another important effort in pharmaco-epidemiological studies is to emulate a target trial to achieve the exchangeability across the treated and untreated groups at baseline.[183] Propensity score methods are commonly used, where the propensity of getting or not getting the medication for all cohort members are calculated based on measured covariates.[184-188] The calculated propensity score can then be used for matching or model adjustment, as well as inverse probability of treatment weighting (IPTW).

4.2 STUDY DESIGNS

4.2.1 Cohort studies

Cohort study is one of the most fundamental study designs in epidemiology, initiated by identifying groups of participants according to their status of the exposure, then following them for a specific amount of time, and finally comparing the risks of having the outcome between the exposed and unexposed groups.[165] Clinical trials are special cases of cohort studies, where the exposure (intervention) variable is randomly assigned to groups of participants that are exchangeable regarding conditions other than the exposure.

Register-based studies are another group of special cohort study, where the data were usually not originally collected for a specific research project. Researchers start by identifying a cohort from a defined population (such as a birth cohort or a group of patients diagnosed within specific time windows), obtaining relevant information of cohort members via linkage through different registers. It is worthwhile to emphasize that the data should be analyzed as it is prospectively collected, namely the researchers should not manipulate the cohort or data based on conditions that are recorded later than the cohort entry or start of follow-up.

4.2.2 Systematic reviews and Meta-analysis

Systematic reviews summarize the existing evidence on a clearly defined research question, and usually offer both qualitative and quantitative assessments of previous findings on the research question. The quantitative assessment is usually conducted by a meta-analysis, resulting in pooled estimation of included studies. Meta-analysis was first defined by Gene V Glass in 1976 as "The statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings".[189] In medical science, meta-analysis, usually incorporated in a systematic review study, has been used as an important epidemiological design to systematically summarize and evaluate the quality and quantity of existing evidence on a specific topic.[190] All possible evidence from published literature are searched from databases such as PubMed or Medline. Unpublished results are also acquired by direct contact with researchers if needed. After quality control, eligible studies are then included in the systematic review for qualitative summary and the meta-analysis to obtain the pooled estimates. In evidence-based medicine, summary from meta-analysis ranks the top in the hierarchy of evidence, superior than individually conducted RCTs.[191,192] In the past few decades, publications of meta-analysis studies accumulated dramatically, and standard guidelines on reporting meta-analysis such as the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) has been developed and widely adopted by researchers.[193] Advances in methodology including the development and application of network meta-analysis made it possible to compare different exposures or treatment for the same topic from separate individual studies.[194]

4.2.3 Familial co-aggregation studies

Familial co-aggregation studies investigate to what extent two traits may cluster within families, usually used to explore if there is shared etiology (familial liability) to the observed association between the two traits. For example, if relatives of individuals with trait X have significantly higher risk of having trait Y, compared to relatives of individuals without trait X, it is possible that at least some of the co-occurrence of X and Y can be explained by familial liability. The familial liability can then be decomposed to genetic and environmental factors by using quantitative genetic modelling analysis. Different relatives such as within-generation relatives including twins, full- and half-siblings, as well as full- and half-cousins or inter-generational relatives such as parent-offspring pairs can be identified from the population. A structural approach using DAGs to illustrate and test the potential causal pathways between trait X and Y in a familial co-aggregation study was proposed by Hudson JI et al.[195] This approach have been used to test if there is familial liability causing both traits, as well as if the co-occurrence can be more possibly due to direct causality between X and Y or other unmeasured confounding.[176,196]

4.2.4 Twin studies

Monozygotic (MZ) twins are genetically identical, and dizygotic (DZ) twins share 50% of their segregating alleles; MZ and DZ twins are both assumed to share 100% of common environment influences. Based on the above assumptions, twin designs are used to compare

the resemblance of one or more traits across twin pairs, and then to estimate the relative genetic and environmental influences to a single trait or to the co-occurrence of two traits.[197] For example, based on the measurement of two traits in MZ and DZ twin pairs, one can calculate the intra-class (ICCs, correlations of the same trait across twins) and cross-twin-cross-trait (CTCT, correlations of trait one in sibling one and trait two in sibling two) correlations. Bivariate twin modelling can be used to further estimate the relative genetic, shared-, and non-shared environmental contributions to the familial liability and to estimate the genetic correlation between asthma and ADHD.

4.3 STATISTICAL METHODS

4.3.1 Logistic regression

Logistic regression models are commonly used in cross-sectional studies to estimate the potential effects of exposures on a dichotomized outcome, with consideration of other relevant covariates.[198] The regression coefficient estimated from the model represent the change of log-odds for the binary outcome by per unit change in the exposure level, while controlling all other covariate levels to be constant. Odds ratios (ORs) can then be calculated by taking the exponential of the regression coefficient. ORs are interpreted as comparing the odds of developing the outcome among those exposed vs. the odds of developing the outcome among those who are not exposed.

4.3.2 Cox proportional hazard regression

Cox proportional hazard regression models are generally used in survival analysis on time-to-event data. Hazard ratios (HRs) are estimated by comparing the hazard functions among groups of different exposure levels, assuming that the hazards in the exposed and unexposed groups remain proportional within the analysis time. However, it is rarely possible to fulfill the assumption of proportional hazards in real-world scenarios, which does not necessarily affect the application and interpretation of Cox regression models.[199] Cox models does not make assumptions on the baseline hazards, and would not estimate the effects of the time variable chosen as the underlying time scale (such as attained age).

4.3.3 Meta-analysis

The main results in a meta-analysis are usually pooled effect estimates from individual studies, in most cases presented in a forest plot including estimates of both individual studies and the pooled meta-analysis.[200] Studies that meet the qualification criteria are weighted based on the inverse of variances so that studies with smaller sample size or greater variances contribute less to the pooled estimates.[201] The choice of fixed-effect models or random-effect models is based on specific research questions and the quality of selected studies. While fixed-effect models assume homogeneity across the individual studies regarding the source population, sampling criteria and the effects of the exposure or intervention, random-effect models accept heterogeneity across studies and results. Random-effect models are more frequently used especially in meta-analysis of observational studies since it is rarely expected

that all conditions are the same across studies conducted in different settings or populations. In addition to the inverse of variance, heterogeneity among study results is also used for study weighting in random-effect models. Moreover, quality assessment of the included studies and the pooled meta-analysis can be achieved by testing the heterogeneity of studies (for example, indicated by the I^2 index or through meta-regression), conducting sensitivity or sub-group analysis of studies that are more homogeneous, and by testing the potential publication biases (for example, by conducting the Egger's test or generating the funnel plots).[202-204]

4.3.4 Structural equation modelling

Structural equation modelling (SEM) is a multivariate statistical method combining factor analysis and regression analysis to analyze the structural relationships between both measured variables and inferred latent constructs. The method is widely used in quantitative genetic modelling analysis such as twin modelling, where additive genetic factors (A), dominant genetic factors (D), shared environmental factors (C) and non-shared environmental factors (E) are treated as latent components contributing to the total variances of measured traits.[205,206] Given a trait X measured as a binary variable, the total variance can be decomposed by the latent components as in the following equation:

$$X_i = \mu + A_i + D_i + C_i + E_i$$

X_i indicates the measured value of the trait in individual i from the population, and μ is the population mean or constant. Assuming that A, D, C and E are independent with no covariance between each other, the variance of the trait then consists of the variances of A, D, C and E:

$$Var(X) = Var(A) + Var(D) + Var(C) + Var(E)$$

Therefore, the proportion of variance of each latent variable represents the influence of genetic or environmental factors on the trait. For example, the relative influence of additive genetic influence (narrow-sense heritability, or h^2) can be calculated by:

$$h^2 = \frac{Var(A)}{Var(X)}$$

In twin analysis, however, it is not possible to estimate C and D simultaneously because the information from twins is not sufficient to estimate all the A, D, C and E parameters in the same model. A convenient way is to estimate ADE model and ACE model separately, to investigate the potential effects from dominant genetic factors or shared environmental factors.[197]

5 SUMMARY OF INDIVIDUAL STUDIES

5.1 STUDY I: ASSOCIATION BETWEEN ASTHMA AND ADHD

5.1.1 Background

Several studies have assessed the possible association between asthma and ADHD, but evidence from published studies is inconclusive as no previous original studies or meta-analyses adequately addressed the potential effects from important confounders.[95,96,207,208] Therefore, the hypothesis of a direct link between asthma and ADHD needs to be rigorously investigated. To fill this knowledge gap, we first conducted a comprehensive systematic review and meta-analysis of the cross-sectional association between asthma and ADHD on published and unpublished data. We then validated the results from the meta-analysis in a Swedish population-based cohort study while addressing the role of confounding for this association.

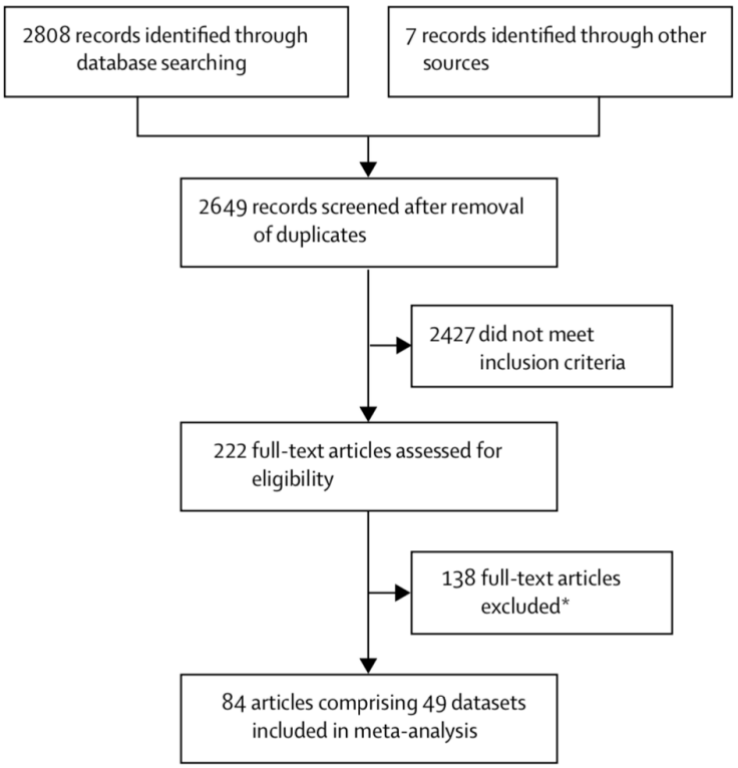

Figure 5.1.2.1 Flow diagram of identifying individual studies for meta-analysis.

* References of excluded studies, with reasons for exclusion, are reported in the appendix.

5.1.2 Methods

5.1.2.1 Systematic review and meta-analysis

We searched databases including PubMed, PsycINFO, Embase, Embase Classic, Ovid MEDLINE, and Web of Knowledge databases (Web of Science [Science Citation Index Expanded], Biological Abstracts, BIOSIS, and Food Science and Technology Abstracts) for

publications up to Oct 31, 2017, without any restrictions on language, date, or article type. Observational studies investigating the association between asthma and ADHD were included, but we excluded studies with less than ten participants per group. More details of search strategies and inclusion/exclusion criteria can be found in the publication of Study I.[209] The flow diagram of identifying individual studies is shown in Figure 5.1.2.1. Quality of studies were rated according to the Newcastle-Ottawa Scale.[210]

We used random-effect models considering that the population effect sizes may vary among studies. Different studies were weighted by the reciprocal of the variance of the effect size. The primary analysis pooled unadjusted ORs from cross-sectional studies (or data from longitudinal studies at baseline) with lifetime or current prevalence (as available) of ADHD and asthma (when data on both lifetime and current asthma or ADHD prevalence were available in the same study, data related to the lifetime prevalence were considered for the primary analysis). The secondary analysis pooled adjusted ORs from cross-sectional studies. We tested the heterogeneity across studies using the I^2 index, and Egger's test and funnel plots to estimate potential publication bias.

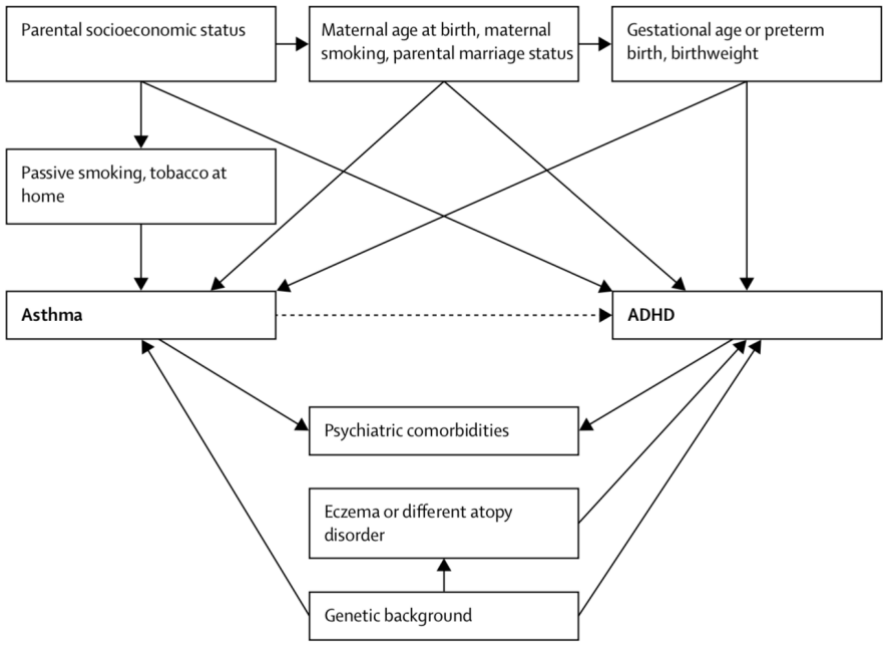

Figure 5.1.2.2 DAG for the association between asthma and ADHD.

Age and sex are not presented in the figure, but adjusted in the model.

5.1.2.2 Swedish population-based cohort study

We first created a list of all covariates used in the individual studies of our systematic review. We then used a DAG (Figure 5.1.2.2) to visually depict the association between asthma and ADHD, considering all covariates that were mentioned in the individual studies and could be identified through Swedish registers. The covariates were categorized as confounders (common causes of asthma and ADHD), mediators (covariates lying on the causal pathway from asthma to ADHD), and colliders (common results of asthma and ADHD). More details

on the rationale of covariates categorization can be found in the supplementary file in the publication of Study I.[209] To estimate the adjusted OR, we adjusted only for covariates that were classified as potential confounders in the directed acyclic graph because adjustment for mediators and colliders can introduce bias.[171]

5.1.3 Results

5.1.3.1 Meta-analysis

Studies included in the meta-analysis pooled together 210 363 individuals with ADHD and 3 115 168 without. The primary analysis indicated a significant association between asthma and ADHD (pooled unadjusted OR 1.66; 95% CI, 1.22–2.26), although with high heterogeneity (I^2=99.47), and possible publication bias indicated by Egger's test (p=0.049). The pooled adjusted OR was similar (OR 1.53; 95% CI, 1.41–1.65; Figure 5.1.3.1); although still with potentially high heterogeneity (I^2=50.76) and possible publication bias (p=0.026 in Egger's test).

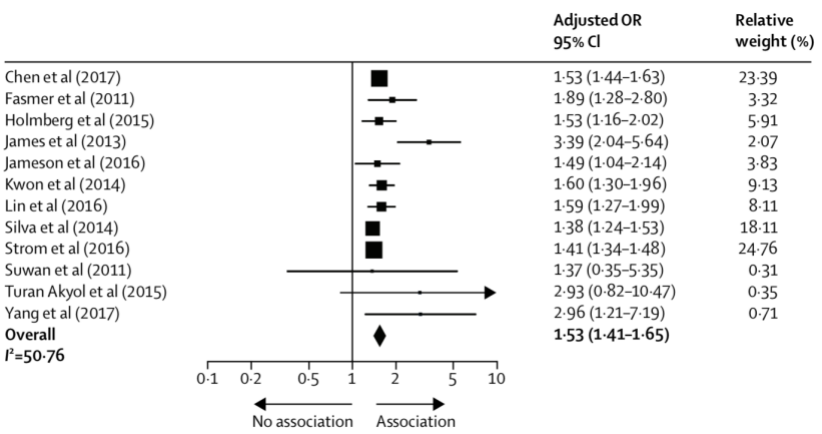

Figure 5.1.3.1 Forest plot of adjusted ORs.

This analysis only included cross-sectional studies with lifetime or current prevalence estimates of asthma (if both were available, lifetime estimates were used).

5.1.3.2 Swedish population-based study

We included 1 575 377 individuals in the Swedish population-based cohort study, of whom 259 253 (16.5%) had asthma and 57957 (3.7%) had ADHD. Asthma was significantly associated with ADHD (OR 1.60; 95% CI 1.57–1.63), and the association remained significant after adjusting for all potential confounders (OR, 1.45; 95% CI, 1.41–1.48).

5.2 STUDY II: FAMLIAL LIABILITY TO ASTHMA AND ADHD

5.2.1 Background

In a recent meta-analysis, we found a significant association between ADHD and asthma,[209] but underlying mechanism of the association is still unknown. Asthma and ADHD are both highly heritable disorders.[44,211] A large genome-wide association meta-analysis[54] of ADHD

reported a small genetic correlation with asthma, but the extent to which these findings replicate in family and twin data remains unclear. Findings from early clinically-based sibling studies[212,213] and twin studies[214,215] were inconclusive due to limited statistical power and incomplete clinical diagnosis information. To fill these gaps, we used the nationwide Swedish register data to investigate the shared familial liability to asthma and ADHD, and to conduct the first twin study using clinically diagnosed asthma and ADHD to estimate the relative contribution of genetic and environmental influences to the association.

5.2.2 Methods

The main cohort including 927 956 individuals born between 1992 and 2001 in Sweden was identified from MBR. We extracted all possible pairs of MZ and DZ twins, full-siblings, maternal and paternal half-siblings and full- and half-cousins for the familial co-aggregation analysis; unique MZ and DZ twin pairs were used for the twin modelling analysis.

5.2.2.1 Familial co-aggregation analysis

Using logistic regression models, we estimated the ORs of having ADHD in individuals (outcome person) whose relatives (exposure person) had asthma compared to individuals whose relatives did not have asthma. Existence of familial liability can be inferred by the different magnitude of associations in different degrees of siblings.[176,216] To test the alternative explanation of direct causality underlying the association instead of shared familial liability, we conducted sensitivity analyses adjusting asthma in the outcome person when ADHD was the outcome, and adjusting ADHD in the outcome person when asthma was the outcome.

5.2.2.2 Twin modelling analysis

We calculated the intra-class (ICCs, correlations of the same trait across twins) and cross-twin-cross-trait (CTCT, correlations of trait one in sibling one and trait two in sibling two) correlations. In the bivariate twin modelling, we first fitted a saturated model on means, variances and correlations, including sex and year of birth as covariates. Sub-models including ACE, ADE and AE models were then fitted to estimate the parameters for A, D, C and E.

5.2.3 Results

5.2.3.1 Familial co-aggregation analysis

The pattern of associations across twins, siblings and cousins indicated familial liability and genetic influences as the association being strongest in MZ twins (OR, 1.67; 95% CI, 0.99-2.84) and attenuating by genetic relatedness. Sensitivity analyses adjusting for the exposure

disorder in the outcome person further supported the underlying familial liability, although the association slightly attenuated from the main analysis.

5.2.3.2 Twin modelling

The ICCs for asthma and ADHD were higher among MZ twins than DZ twins. CTCT was also higher among MZ twins (0.13; 95% CI, 0.07-0.19) than DZ twins (0.08; 95% CI, 0.03-0.13). In twin modelling, ACE model was the best fiting model with the lowest AIC value. The phenotypic correlation between asthma and ADHD was 0.09 (0.05-0.14) and the genetic correlation was 0.12 (0.02-0.21). Univariate estimates and correlation coefficients are illustrated in Figure 5.2.3.2. Genetic factors explained most of the phenotypic correlation (0.88; 0.30-1.46). Estimates for shared and non-shared environmental factors were not statistically significant.

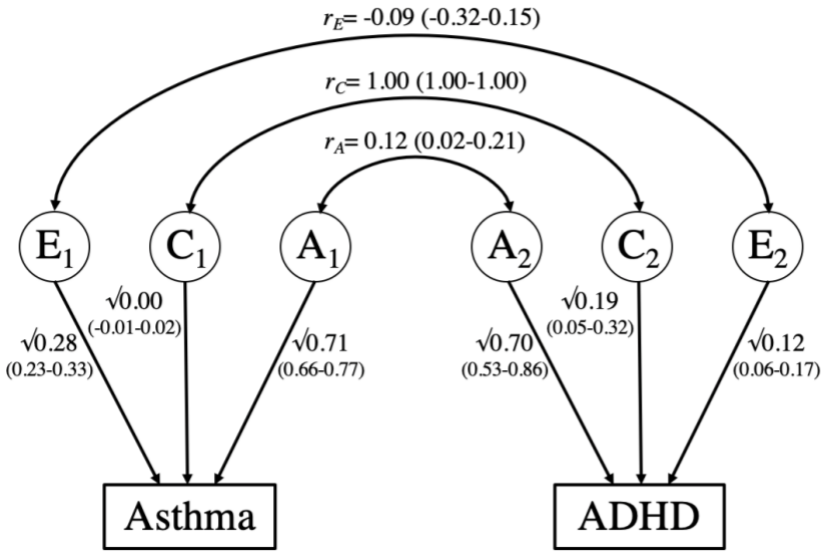

Figure 5.2.3.2 Path parameter estimates for the ACE model presented for one twin.

The figure illustrates cross-trait paths within one individual. Rectangles in the bottom indicate total variances for asthma and ADHD, standardized to the fixed value of 1. Circles represent different latent variables of A, C and E, each having a variance of 1. Numbers under the square root signs represent the percentage of variance accounted by each component for asthma and ADHD, respectively. Curved double arrows above indicate correlations between A (r_A), C (r_C) and E (r_E) across asthma and ADHD. Within parentheses are 95% confidence intervals of estimated parameters.

5.3 STUDY III: ADHD AND PREMATURE DEATH

5.3.1 Background

Individuals with ADHD present higher risks of adversities that correlate with premature death, including conduct disorder (CD),[130,217] substance use disorders (SUD),[218,219] injuries[134] and suicidal behaviors.[138] However, little is known about if ADHD is directly associated with premature death and if psychiatric comorbidities would affect the association. A Danish

register-based study reported increased all-cause mortality risks in ADHD, with unintentional injury as the leading cause of death.[143] The authors also found that the association was stronger when comorbid CD and/or SUD were present. Nonetheless, cause-specific mortality risks and potential roles of various psychiatric comorbid disorders remained unclear. In Study III, we investigated if ADHD was associated with all-cause and cause-specific mortality risks, and explored if number and type of psychiatric comorbidities (early-onset vs later-onset comorbid psychiatric disorders) would affect the association.

5.3.2 Methods

We obtained the study cohort from MBR, including all individuals born in Sweden between 1983 and 2009, who were alive and residing in Sweden on their 1-year birthday or January 1, 2001 (from when outpatient data was available), whichever came later. We followed the cohort up until death, emigration, or December 31, 2013 (whichever came first). We used Cox proportional hazard regression models to estimate the mortality risks, with attained age as the underlying time-scale. ADHD was the main exposure. ADHD and psychiatric comorbidities were treated as time-varying variables.

5.3.2.1 ADHD and risk of premature death

We compared the all-cause and cause-specific mortality risks between individuals with and without ADHD, and then separately analyzed the association in childhood and adulthood to test the potential effects of having ADHD in different age groups.

5.3.2.2 Psychiatric comorbidity with ADHD and risk of premature death

Since death events in childhood were limited, this analysis was restricted to adults. First, we analyzed if number (0, 1, 2, 3, or ⩾4) of psychiatric comorbidities would affect the mortality risks, comparing individuals with and without ADHD. Second, we looked at the mortality risks of having each specific psychiatric comorbidity within the ADHD group. Last, we investigated how early-onset and later-onset psychiatric comorbidities affected all-cause as well as cause-specific mortality risks by comparing individuals with and without ADHD. This was done by stepwise adjusting early-onset and later-onset psychiatric comorbidities.

5.3.3 Results

Unintentional injuries and suicide were the leading causes of death in ADHD. We found that ADHD was significantly associated with all-cause mortality risks (HR, 3.94; 95% CI, 3.51-4.43) and the association was much stronger in adulthood (4.64; 4.11-5.25) compared with childhood (1.41; 0.97-2.04); higher number of psychiatric comorbidities with ADHD presented higher risks of premature death (HR for individuals with only ADHD, 1.41 [95% CI, 1.01-1.97]; HR for those with ⩾4 comorbidities, 25.22 [95% CI, 19.60-32.46]).

Among adults, individuals with ADHD presented higher mortality rates due to natural causes compared to those without ADHD (3.44 vs. 1.13 per 10 000 person-years; Table 5.3.3) and

the association was significant before adjusting for any psychiatric comorbidity (HR, 2.68; 95% CI, 1.95-3.67). However, the association attenuated to non-significant when early-onset psychiatric disorders were further adjusted in the model (HR, 1.32; 95% CI, 0.94-1.85). For unnatural cause-specific mortality risks, the association was stronger (HR, 5.93; 95% CI, 5.17-6.81), and slightly attenuated when adjusting for early-onset comorbidities (HR, 5.33; 95% CI, 4.59-6.20), but attenuated substantially when adding later-onset comorbidities in the model (HR, 1.57; 95% CI, 1.35-1.83). Moreover, the association remained significant for unintentional injuries (HR, 2.14; 95% CI, 1.71-2.68) and other external causes (HR, 1.75; 95% CI, 1.23-2.48), but not for suicide (HR, 1.13; 95% CI, 0.88-1.45).

	ADHD Group		Non-ADHD		Adjustment, HR (95% CI)			
					Covariate		Comorbidity	
Cause of Death	No. of Deaths	Mortality Rate per 10 000 Person-Years[a]	No. of Deaths	Mortality Rate per 10 000 Person-Years[a]	Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
All	369	21.87	3452	3.69	5.65 (4.99-6.39)	5.00 (4.41-5.67)	3.87 (3.37-4.44)	1.48 (1.29-1.70)
Unnatural	311	18.44	2388	2.55	6.79 (5.92-7.78)	5.93 (5.17-6.81)	5.33 (4.59-6.20)	1.57 (1.35-1.83)
Unintentional injury	133	7.88	1105	1.18	6.80 (5.72-8.30)	5.89 (4.82-7.20)	5.85 (4.71-7.27)	2.14 (1.71-2.68)
Suicide	120	7.11	941	1.01	5.81 (4.61-7.32)	5.28 (4.18-6.66)	4.08 (3.15-5.29)	1.13 (0.88-1.45)
Other external	58	3.44	328	0.35	10.26 (7.44-14.13)	8.28 (5.99-11.45)	7.82 (5.51-11.10)	1.75 (1.23-2.48)
Natural	58	3.44	1052	1.13	2.93 (2.14-4.01)	2.68 (1.95-3.67)	1.32 (0.94-1.85)	1.01 (0.72-1.42)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio.

[a] ADHD and comorbid disorders were time-varying exposures while calculating mortality rates (per 10 000 person-years).

[b] Adjusted for year of birth and sex.

[c] Adjusted for model 1 covariates, birth weight, maternal age at birth, parental educational level, and parental employment status.

[d] Adjusted for model 2 covariates and early-onset disorders including conduct disorders, autism spectrum disorder, and intellectual disability.

[e] Adjusted for model 3 covariates and later-onset disorders including substance use disorder, depressive disorder, bipolar disorder, anxiety disorder, schizophrenia, personality disorder, and eating disorders.

Figure 5.3.3 Early- and later-onset psychiatric comorbidity with ADHD and risk of premature death in adults.

5.4 STUDY IV: ADHD MEDICATION AND PREMATURE DEATH

5.4.1 Background

ADHD is associated with increased mortality risks, especially due to unnatural causes including suicide and unintentional injuries.[143,220] ADHD medication treatment has been reported with efficacy in not only alleviating core symptoms of ADHD, but also decreasing the risks of adversities including SUD, depression, suicide, and injuries.[149] However, it is unclear how ADHD medication would affect the mortality risks in individuals with ADHD. Also, various factors such as concern over side effects and long-term efficacy hinder the initiation and continuation of ADHD medication,[221-225] leaving the disorder being under treated in most countries including Sweden.[226-229] In Study IV, we investigated how initiation and continuation of ADHD medication associated with all-cause and cause-specific mortality risks in individuals with ADHD, to provide evidence of great clinical relevance for guiding management of ADHD after diagnosis.

5.4.2 Methods

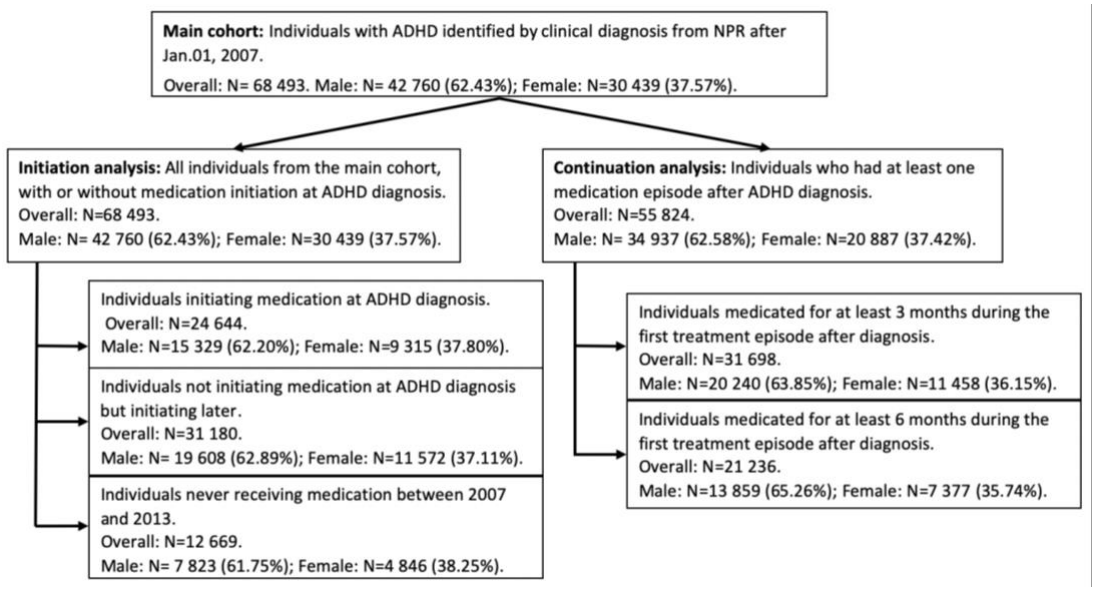

Figure 5.4.2.1 Flow-chart of cohort selection and sample sizes.

We obtained a cohort of 68 493 individuals born between 1973 and 2009, diagnosed with ADHD between January 01, 2007 and December 31, 2013 using linkage of Swedish national registers, and followed them from ADHD diagnosis until death, emigration or up to two years. Cohort selection and sample sizes are shown in Figure 5.4.2.1. We separately investigated the potential effects from ADHD medication initiation and continuation on all-cause and cause-specific death. Deaths due to natural causes were limited and we did not analyze the association for natural cause-specific mortality risks. Follow-up setting for the initiation and continuation analysis is illustrated in Figure 5.4.2.2. Between-individual Cox regression models were used to compared the mortality risks between the treated and untreated person-times.

5.4.2.1 Initiation analysis

We used the main cohort and looked at the all-cause and unnatural cause-specific mortality risks between individuals who initiated vs. who did not initiate ADHD medication treatment at ADHD diagnosis. The follow-up was censored at the first switch of treatment status, so that we only compared the treatment vs. non-treatment person-times right after ADHD diagnosis.

5.4.2.2 Continuation analysis

We identified a sub-cohort with individuals who were continuously medicated at least 3 months, with follow-up starting from 3 months after ADHD medication initiation. Follow-up time was reset to zero when the medication was re-started after discontinuation, so that we compared only the continuation and discontinuation person-times.

5.4.2.3 Sensitivity analysis

We tested if the treatment effects were time-varying or stable across prolonged treatment periods by censoring follow-up at 6 months and 1 year, respectively. For the continuation analysis, we re-ran the analysis among those who were continuously treated for at least 6 months, to test if longer treatment before continuation would differ from shorter treatment.

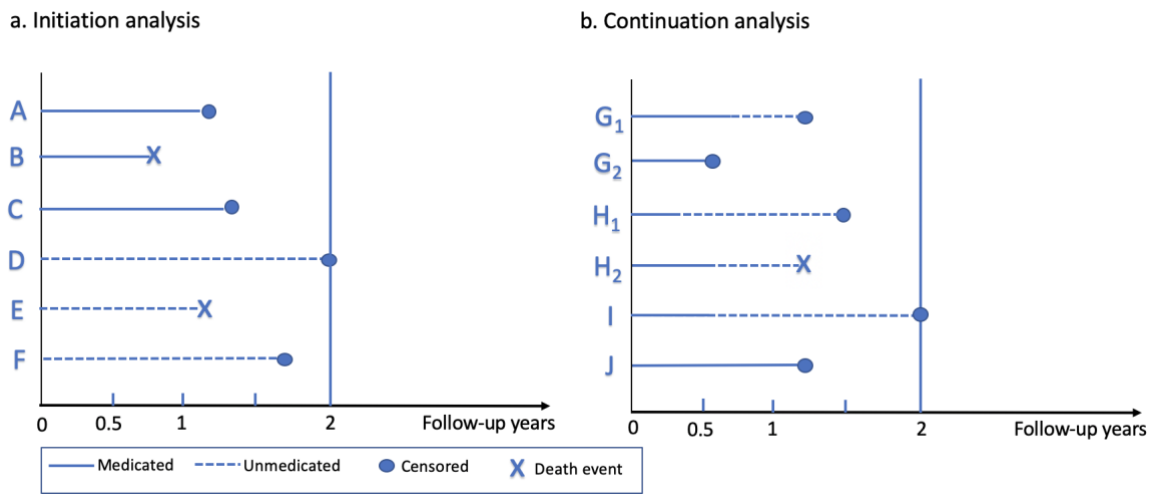

Figure 5.4.2.2 Follow-up setting for the initiation and continuation analysis

The figure shows how we set the time and follow-up for initiation and continuation analysis (with maximum follow-up of 2 years).

a. Initiation analysis: Different rows represent different individuals. Time zero was the time of cohort entry (time of ADHD diagnosis). Follow-up started at ADHD diagnosis, and ended at death, emigration, censoring up until 2 years of follow-up, or whenever the treatment status changed. For example, individual A started follow-up as initiating medication treatment at ADHD diagnosis, and then censored when A stopped medication. Follow-up beyond 2 years were censored and not included in the analysis (such as individual D).

b. Continuation analysis: Different rows may represent different continuation/discontinuation periods of the same individual. Time zero was either 3 or 6 months after the first medication prescription, or every time when the individual re-started medication after a period of discontinuation. Therefore, the initial 3 or 6 mongths of medication periods were excluded from analysis. Follow-up stopped at death, emigration, up until 2 years of follow-up, or whenever the individual re-started medication treatment. For example, individual G started follow-up with a period of continuing medication treatment (indicated as G_1 in the figure), followed by a period of discontinuation. Then the re-start of medication period was treated as another observation (indicated as G_2), until censored. Maximum time of censoring was 2 years after start of follow-up (such as individual I).

5.4.3 Results

5.4.3.1 ADHD medication initiation

The mortality rates among those who initiated medication treatment at ADHD diagnosis were lower than those who did not initiate medication, with the association being statistically significant for all-cause (adjusted HR [aHR], 0.31; 95% CI, 0.13-0.73) and unnatural cause-specific (aHR, 0.33; 95% CI, 0.14-0.80) morality risks. However, the associations were not significant for specific unnatural causes including suicide (aHR, 0.56; 95% CI, 0.16-1.96) and

unintentional injuries (aHR, 0.23; 95% CI, 0.05-1.10), although the mortality rates were also much lower in the treated group compared to the un-treated group.

5.4.3.2 ADHD medication continuation

Medication continuation was associated with substantially lower all-cause (aHR, 0.37; 95% CI, 0.24-0.57) and unnatural cause-specific (aHR, 0.42; 95% CI, 0.27-0.66) mortality risks compared to discontinuation. The associations remained statistically significant for specific unnatural causes including suicide (aHR, 0.45; 95% CI, 0.21-0.96) and unintentional injuries (aHR, 0.47; 95% CI, 0.23-0.96).

5.4.3.3 Sensitivity analysis

Results of censoring at 6 months and 1 year were similar to the main analysis when censoring at 2 years, although there were fewer death events, and no death due to unintentional injuries among the treated group when censoring at 6 months. Among those who were treated at least 6 months, the results were also consistent with the main analysis.

6 DISCUSSION

In this thesis work, we investigated the magnitude and potential mechanisms of the associations between ADHD and specific adverse outcomes including asthma and premature death using national register-based data in Sweden. In Study I and II, we found a robust association between asthma and ADHD, and the association was largely explained by shared genetic overlaps. In Study III and IV, we found that individuals with ADHD presented substantially increased risk of premature deaths with psychiatric comorbidities contributing to most of the excessive risks, and that ADHD medication may help lower the mortality risks. Our findings provided evidence for further research into ADHD related adverse outcomes, and have both clinical and public health implications for preventing or alleviating the burden of specific adversities.

6.1 ADHD AND ASTHMA

6.1.1 Main findings

In Study I, we combined a meta-analysis with a national population-based cohort study and tested the cross-sectional association between asthma and ADHD. The pooled unadjusted and adjusted ORs from the meta-analysis supported previous findings of the association,[95,96] and the results were robust across study settings. To clarify the potential confounding that most previous studies did not fully address, we summarized all covariates adjusted for in previous studies, systematically assessed their potential roles given the possible causal pathways between asthma and ADHD using a DAG, and then conducted the new population analysis by only adjusting for those categorized as confounders. The adjusted OR from the population study was comparable with the meta-analysis, providing more concrete evidence of the link between asthma and ADHD.

In Study II, we investigated the familial liability to asthma and ADHD, and used a twin modelling analysis to quantify the genetic and environmental influences as well as the genetic correlations. For the first time, we found that relatives of probands diagnosed with either asthma or ADHD have elevated risk of being diagnosed with the other. This was not consistent with previous sibling analyses that did not find evidence of familial co-aggregation between asthma and ADHD,[212,213] but statistical power in these two studies was extremely limited. Results from our twin modelling analysis indicated that the association between asthma and ADHD may be substantially explained by shared etiology, especially shared genetic risk factors, which was also supported by the pattern of associations across relatives in our familial-coaggregation analysis. The genetic correlation between asthma and ADHD estimated from our twin modelling was weak but robust and similar with results from a GWAS finding.[54] The size of the genetic correlation between these two highly heritable conditions indicate that only a small proportion of the total genetic underpinnings of asthma and ADHD is shared across disorders.

6.1.2 Interpretations and implications

Findings from Study I and II have important clinical and public health implications for both disorders, as well as for future research. The health burden attributed to asthma and ADHD is tremendous worldwide. Delayed diagnosis remains to be a challenge for both, and early detection and management predicted better prognosis.[131,132,230-232] Currently, practitioners dealing with asthmatic children and not aware of the link between asthma and ADHD may consider comorbid inattention, hyperactivity and impulsivity as asthma symptomatology or results from asthma treatment,[213] or a consequence of a psychological distress due to the fact of having a chronic medical condition,[91,233,234] thus missing an important opportunity to identify a neuropsychiatric condition for which effective treatments are available.[82,149,235] With improved awareness of the link between asthma and ADHD, clinicians can make more prompt decisions of referral for children with one disorder presenting suspicious symptoms of the other. Apart from within-individual presentation, family history of the other disorder can also serve as a sign of clinical referral due to the familial liability identified from Study II. For instance, practitioners seeing patients referred for ADHD, should query about personal and family history of symptoms of asthma, which may pin to the need of a prompt referral for specialist assessment of asthma, thus reducing the diagnostic delay for this condition. Our findings emphasize the importance of joint services where clinicians with expertise in developmental psychopathology and those specialized in allergic/atopic conditions may quickly and effectively interact to provide timely and high-quality care to patients with the double burden of developmental disorders (such as ADHD) and medical conditions (such as asthma). As a result, early diagnosis and treatment can substantially help with lowering the overall health burden improving the prognosis for both diseases. Although it is currently not feasible to prevent the onset of asthma and ADHD, early intervention and effective treatment of the disruptive behaviors related to ADHD symptoms among asthmatic children, for example, may improve the adherence to asthma treatment, as to decreasing the unnecessary health-care costs. Early diagnosis and treatment of ADHD, on the other hand, may substantially improve the quality of life and prevent severe adversities such as psychiatric comorbidities and premature deaths.

6.2 ADHD AND PREMATURE DEATH

6.2.1 Main findings

In Study III, we for the first time investigated the cause-specific mortality risks associated with ADHD, and explored the potential effects from number and types of psychiatric comorbidities. We found that ADHD in adulthood, later diagnosis of ADHD and more comorbid psychiatric comorbidities presented even higher mortality risks. Among adults, early-onset psychiatric comorbidities including ASD, ID and CD may explain most of the mortality risks due to natural deaths. For example, comorbid ADHD and ID had higher mortality risks compared to ADHD alone, and most deaths among individuals with such comorbidity were due to natural deaths. This was consistent with previous findings, with the possible explanation that ID related poor health behavior and self-care may impose the risk of preventable diseases such as respiratory infections and digestive diseases.[236,237] Comorbid

ADHD symptoms may further aggravate such effects. Later-onset psychiatric comorbidities such as SUD, depression, anxiety and schizophrenia, on the other hand, substantially explained the excessive mortality risks due to unnatural causes including suicide and unintentional injuries. Although ADHD was still associated with over 50% of increased unnatural cause-specific mortality risks after adjusting for all psychiatric comorbidities, the association largely attenuated for unintentional injuries and became non-significant for suicide. The twice higher risk of premature death due to unintentional injuries after adjusting for all psychiatric comorbidities may be explained by inattention and impulsivity symptoms in ADHD increasing the proneness to risky behaviors and the risk of severe unintentional injuries.[238,239]

In Study IV, we found that ADHD medication treatment was associated with lower mortality risks due to unnatural causes. Individuals who initiated ADHD medication treatment at diagnosis had lower all-cause and unnatural cause-specific mortalities compared to those who did not initiate medication, although the associations were not statistically significant for suicide and unintentional injuries in the main analysis. Previously there were concerns over ADHD medication regarding side-effects involving severe events such as sudden death and cardiovascular events which may increase the risk of premature death, [222,223,240] but no previous study reported statistically significant associations. Our results provided evidence against such concerns over potential side-effects as an important factor impeding initiation of ADHD medication.[241] Moreover, the mortality risks due to both suicide and unintentional injuries decreased by about 60% when comparing periods of medication treatment continuation with periods of discontinuation in our data. There have been controversies about whether and when to stop ADHD medication after a period of treatment due to concerns over long-term tolerance and decreased efficacy.[69,242,243] Our results were not in line with such concerns regarding premature death, with similar treatment benefits among individuals medicated for at least 3 months to those medicated for at least 6 months. Furthermore, we did not find an obvious decline of benefits from longer treatments up to 2 years, which is also evidence against the concern of decreased effectiveness after longer-term medication use.

6.2.2 Interpretations and implications

Results from Study III and IV indicate that individuals with ADHD suffer from increased risk of premature death, with different types of psychiatric comorbidities exerting different effects on the association. ADHD medication may be a possible way to lower the excessive mortality risks. Identification of psychiatric comorbidities, as well as proper initiation and continuation of medication treatment may help to prevent premature death in ADHD. Among specific psychiatric comorbidities, we found from Study III that comorbidity with SUD, depression, anxiety and bipolar disorders presented specifically higher risk of dying from suicide compared to ADHD only. Co-occurrences of ADHD and these disorders should then be prioritized for treatment in order to prevent suicide. Moreover, individuals with comorbid ADHD and ID presented lower risk of unintentional injuries probably due to the limited possibility of obtaining a driving license. Considering the increased risk of natural death

associated with early-onset psychiatric comorbidities, management of such comorbidities including ID may prioritize closer monitoring of somatic health conditions to prevent natural deaths. Undertreatment of ADHD remains a severe issue in most countries including Sweden (e.g., some patients with ADHD are not prescribed with ADHD medication treatment for a considerable amount of time after diagnosis),[226-229] and medication discontinuation rates are high among individuals with ADHD (i.e., rates reported as ranging from 13% to 64%[244]), which may have a negative impact on the prognosis.[16] In Study IV, almost 40% of cohort members did not initiate ADHD medication until about 5 months after ADHD diagnosis. A study among children and adolescents reported that longer interval between the first ADHD diagnosis and the first prescription of methylphenidate was associated with higher all-cause mortality risks, although the authors did not analyze the treatment effects of medication *per se* and did not have sufficient statistical power to investigate cause-specific mortality risks.[245] Nonetheless, our results in Study IV did point out that proper ADHD medication treatment may help alleviating the excessive mortality risks associated with ADHD and preventing premature deaths among individuals with ADHD.

6.3 STRENGTHS AND LIMITATIONS

6.3.1 Strengths

Studies in this thesis work provided significant evidence on clearly defined research questions with both research and clinical/public health relevance. Our findings could facilitate the understanding of both the magnitude and mechanisms of specific associations between ADHD and specific adverse outcomes, and have important implications for preventing severe adversities. Large scale data sets based on national registers were extracted with prospectively collected information on socioeconomic data and health related information for cohort members. Thoroughly designed analysis plans generated robust results with causal inference frame work considered by adjusting for relevant covariates in the statistical models.

Previous studies provided controversial findings regarding the association between asthma and ADHD, and available meta-analyses with limited evidence could not provide conclusive results and failed to address potential confounders that may bias the association. In Study I, our meta-analysis included 49 studies and substantially extended the evidence on an association between asthma and ADHD from previous meta-analyses. Meta-regression showed that the pooled estimates were robust across study settings, year of study, participants age distribution and study continent. We also obtained unpublished data by contacting authors of the included studies and therefore gathered more evidence. More importantly, we were able to systematically assess the potential confounding and adjust for possible confounders in the Swedish national register-based population analysis, providing a rigorously validated link between asthma and ADHD on the population level. In Study II, we obtained the largest family data ever used to investigate the familial liability to asthma and ADHD, and were able to quantify the genetic overlaps between clinically diagnosed asthma and ADHD for the first time. The findings of shared genetic overlaps also provided important implications for future research on not only the biological pathways between ADHD and

asthma or other allergic conditions in general, but also other observed somatic comorbidities with ADHD such as obesity or clinically diagnosed eating disorders.

Evidence on ADHD associated mortality risks had been scarce as the relatively low incidence of premature death among individuals with ADHD requires large sample size with long-term follow-up. Furthermore, no previous studies had the resources to clarify the cause-specific mortality risks and the potential roles of various psychiatric comorbidities. Our work in Study III and IV largely improved the understanding of the all-cause and cause-specific mortality risks associated with ADHD. By identifying different number and types of psychiatric comorbidities, and adjusting for them in a stepwise manner in Study III, we were the first to clarify the potential mediating effects from specific comorbidities on specific death causes. In Study IV, we were also the first to have the data for investigation of the specific effects from ADHD medication treatment initiation and continuation on cause-specific mortality risks in ADHD, providing significant results for guiding clinical practice. We adopted a new-user design, and tested if the potential treatment effect was time-varying or time stable, as well as if longer treatment presented different results compared to shorter treatment before discontinuation. We also conducted multiple sensitivity analyses in both Study III and IV to test the robustness of our results and to extend the generalizability of our findings.

6.3.2 Limitations

There were limitations in each study of the thesis work that should be taken into consideration when interpreting the findings. Although with large sample size and comprehensive information, the Swedish national registers do not always have perfect coverage and may have the issue of misclassification. For instance, the prevalence of ADHD is usually underestimated in the register data as individuals with mild ADHD may not always seek for professional help at all or until the symptoms and impairments became severe enough, resulting in either misclassification or delayed diagnosis. Moreover, diagnosis from NPR were mostly recorded in outpatient register which was initiated in 2001, and we do not have data on medication treatment before the start of PDR from July, 2005. There are also other specific limitations in each study that should be mentioned.

In Study I, heterogeneity across the studies included in the meta-analysis was significantly high, indicating that the overall pooled estimation may not appropriately represent all individual studies, although heterogeneity decreased in the sub-group analyses. Publication bias was detected, and the quality rating for some studies indicated poor representativeness. In the population-based analysis, false-negative misclassification was possible among those without diagnosis of asthma or ADHD, although this may have underestimated the association instead of overestimation. Furthermore, we did not aim to test the longitudinal association between asthma and ADHD in either the meta-analysis or the population-based analysis. The main reason is that asthma as a somatic condition with more noticeable symptoms may usually precede ADHD in diagnosis, but this temporality does not necessarily mean later ADHD associated with early asthma should be interpreted as a causal link.

In Study II, we could not completely rule out the possibility of direct causality between asthma and ADHD, since the overall association and phenotypic correlation was weak in magnitude and we could not make conclusive judgements on the environmental contributions to the comorbidity. In fact, we did observe slightly attenuated ORs when adjusting for asthma or ADHD in the outcome person in the familial co-aggregation analysis and a weak and non-significant correlation for non-shared environmental factors in the ACE model, indicating possibly weak causality between asthma and ADHD. The previously raised hypothesis of asthma and other allergic reactions producing inflammatory cytokines and then affecting the development of ADHD may be possible and should be tested in more appropriately designed experiments.[92,246] Vertical pleiotropy from the same genes is also possible, as the genetic variants causing allergic conditions, and then ADHD, with possible mediation of the inflammatory pathophysiology.

In Study III, we could not fully address the cause-specific mortality risks in childhood due to limited death events, and we had to restrict the analysis of psychiatric comorbidities among adults. The follow-up window in our data was relatively short, and we should rely on future studies with even larger sample size and longer follow-up window to investigate this issue in childhood. While investigating the mortality risks, we did not account for ADHD medication treatment. Considering the reported benefits of ADHD medication treatment on adversities associated with premature death,[149] the true mortality risks caused by ADHD may be even larger than reported in our data.

In Study IV, the number of death events were limited in most of our analyses, which may explain some of the non-significant associations. Second, unmeasured confounding may have important contributions to the results. Larger differences in disease severity between the treated and un-treated groups may have masked the potential treatment benefits in the initiation analysis, although this may have been less of an issue in the continuation analysis. Third, we did not investigate specific reasons of medication initiation or discontinuation. Contraindications of both initiating and continuing ADHD medications such as psychiatric or somatic conditions may also be important confounders. Fourth, the current results did not address questions regarding long-term treatment effects of ADHD medication, for example if baseline treatment or extended cumulative treatment associates with mortality risks years later.[149]

For both Study III and IV, deaths due to natural causes were rarer compared to unnatural deaths, making it difficult to further clarify the specific natural causes such as infectious or nervous system diseases in Study III, or to investigate the treatment effects on natural cause-specific mortality risks in Study IV. However, unnatural deaths consistently accounted for most of the deaths and mortality risks in ADHD, indicating that management on adversities associated with unnatural deaths should be prioritized. Moreover, as observational studies, our work may not be interpreted as established causal effects from ADHD or ADHD medication treatment on mortality risks. For example, an alternative explanation for the reduced mortality risks during continued medication treatment might be better adherence to

general health service and better self-control and management in individuals undergoing persistent medication.

6.4 ETHICAL CONSIDERATIONS

The studies conducted as above used individual level information on personal history of birth, education, occupation, emigration, health and death identified and extracted from Swedish national registers. The unique PIN we used to link through different registers was encoded by register holders and designated to each individual in our cohorts, and it is not possible for researchers to track back to the individual's personal identity. Linkage of data across registers obtained approval by the Regional Ethical Review Board in Stockholm in 2013 and the approval will be updated as required. Regardless of this fact, an ethical issue may occur since according to the previously valid Personal Data Act in Sweden (PUL) and the recently adopted European General Data Protection Regulation (GDPR), register data is still sensitive personal data, and strict rules should be obeyed to while conducting relevant research.

While forming a research question and gathering the data for analysis, potential gains regarding the positive implications from the study findings are always weighed against potential harms, and only the most relevant information to the research questions were extracted and analyzed. We were specifically careful in reporting our results, pointing out both strengths and limitations of our work, and we did not impose any interpretations of our results to be stigmatizing for specific groups of individuals. For example, we found a population-level association between asthma and ADHD, but this conclusion does not mean all individuals with asthma will develop ADHD or vice versa. Also, the identified genetic overlap between the two disorders does not justify the possible prejudice that asthma and ADHD would definitely co-aggregate in the family. Our intention and focus were to emphasize the awareness of the link between two of the mostly diagnosed diseases in childhood and therefore to tackle the challenge of delay in diagnosis and associated health burden. In Study III, our findings indicate individuals with ADHD may suffer from increased risk of premature death due to suicide, but this should never be interpreted as ADHD would definitely lead to suicide death, nor to imply social stigma of risky behavior and higher risks of having other psychiatric comorbidities on individuals with ADHD. Again, the focus was to improve the awareness of the issue, so as to attract more proper resources to prevent premature deaths. Such considerations and interpretations were presented both in the constituent papers and the communicating materials when interviewed by public media.

Another issue that may also jeopardize integrity of the research, which may exist in any projects in academic world, is the possibility of any form of misconduct. Throughout the thesis work, source datasets were anonymized and maintained on a protected server. Data extraction and analysis process were documented according to the data management and archiving policies formulated by the department to guarantee reproducibility of study results.

7 CONCLUSIONS

In summary, findings from this thesis work support that individuals with ADHD are at increased risk of adverse outcomes including somatic conditions such as asthma and severe adversities such as premature death. Shared genetic factors largely explained the association between asthma and ADHD, indicating the significance of detecting within-individual and family history of either disorder for preventing delayed diagnosis of the other condition. This also shed light on the general link between allergic or inflammatory conditions and psychiatric disorders, and provided a possible way to understand the etiology of comorbidity between ADHD and other somatic diseases. Moreover, psychiatric comorbidities and medication treatment play crucial roles in understanding the mechanisms of ADHD associated mortality risks. Identification of specific psychiatric comorbidities and implementing proper treatment strategies should be prioritized in preventing premature deaths among individuals with ADHD.

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冬日宴，热酒一杯歌一遍。

再拜陈三愿：

一愿高堂康健，

二愿膝下承安，

三愿如同梁上燕，岁岁常相伴。

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