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DEPRESSION IN YOUTH AND ADULTS: ETIOLOGY, OUTCOMES, AND COMORBIDITIES

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Depression in youth and adults: etiology, outcomes, and comorbidities

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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"Without data, you're just another person with an opinion"

W. E. Deming

POPULAR SCIENCE SUMMARY OF THE THESIS

Depression is a common and serious mental health condition. It causes a wide variety of symptoms, such as feeling hopeless and sad, and losing interest or pleasure in hobbies and activities. To be diagnosed with depression, symptoms must last for at least two consecutive weeks. At its worst, this mental condition can lead to suicide.

Current research suggests that depression is caused by a combination of genetic, physiological, environmental, social, and psychological factors. Nevertheless, many aspects regarding its causes, consequences and relation to other diseases are still largely unknown.

Sweden provides unique opportunities for medical research. The country supports a universal and tax-funded health care system, and a long history of national registries. Through the use of a personal identity number (*personnummer*) assigned to every resident at birth or immigration, linkage between these registers is possible, allowing aggregation of demographic, medical and other information on the entire Swedish population. Throughout this process, sensitive data of participating individuals is protected.

This unique source of large-scale data enables the development of scientific knowledge on important areas in which other study designs may be unethical or difficult to implement, including origins and long-term health outcomes of psychiatric disorders.

BODY AND MIND ARE CLOSELY LINKED

In the first study of this thesis, children and adolescents with depression were found to be at increased risk of physical illnesses and early death.

We gathered medical information for nearly 1.5 million people born in Sweden and followed them up to age 31. More than 37,000 children and teenagers were diagnosed with depression between ages 5 and 19.

Compared to their peers without a depression diagnosis, people with depression had increased risks for 66 of the 69 medical conditions that we explored, including self-harm, sleep disturbances, type 2 diabetes, thyroid disorders, liver problems, and kidney diseases. Furthermore, they were almost 6 times more likely to die prematurely by any cause, and 14 times more likely to die by suicide. These risks diminished but persisted even after taking into account other psychiatric disorders, including substance use disorder, that were diagnosed in some individuals with depression.

Although further research is needed to establish whether and to what extent depression in youth is causing these adverse health outcomes, this study brings awareness to the issue of pediatric depression, the burden of this disease, and to the importance of the mental-physical health relationship.

INFECTIONS IN CHILDREN DO NOT INCREASE THE RISK OF DEPRESSION AND SELF-HARM

Many studies suggest a link between infections and psychiatric disorders, including depression. Since childhood represents a sensitive developmental time during which the central nervous system and the immune system are still immature, it may be possible that infections in early life could have a greater influence on the risk of depression and self-harm.

In the second study of this thesis, we followed more than 1.5 million individuals from birth up until age 31. Of these, 338,251 (22.5%) experienced early-life infections, 67,630 (4.5%) received a diagnosis of depression, and 25,651 (1.7%) were diagnosed with or died by self-harm.

Severe infections during childhood were associated with a 22% increased risk of depression and 29% increased risk of self-harm. However, these risks almost disappeared when accounting for other factors linked to both physical and mental health, such as a family history of mental disorders and low parental education and income.

These findings show that childhood infections do not seem to be related to later depression and self-harm. Instead, other factors shared between family members appear to increase risks of infections, depression and self-harm, highlighting the importance of identifying and screening for these familial influences in childhood.

THE ROLE OF GENETICS IN THE LINK BETWEEN DEPRESSION AND ENDOCRINE-METABOLIC DISORDERS

In a third study, we explored in more detail the relationship between depression and various endocrine and metabolic diseases. Over 2.2 million people were included, of whom more than 118,000 received a diagnosis of depression. A number of endocrine and metabolic disorders were explored: hypothyroidism, hyperthyroidism, type 1 diabetes, type 2 diabetes, obesity, and polycystic ovarian syndrome. Compared to their peers without endocrine-metabolic conditions, people with these diseases had 2-fold increased risk of depression.

Siblings of individuals with an endocrine-metabolic disorder were also at higher risk of depression, compared to siblings of those without. This suggests that genetic and environmental risk factors shared between family members play a role in the co-occurrence of these mental and physical disorders.

Specifically, we found that vulnerability for depression and for certain endocrine-metabolic conditions such as type 2 diabetes, obesity, and polycystic ovarian syndrome share some of their genetic risk. Conversely, environmental factors were predominantly involved in the association between depression and type 1 diabetes. This indicates that the link between depression and different endocrine-metabolic disorders may be driven by different mechanisms.

This study enhances the understanding of the association between depression and physical illnesses, and underscores the importance of screening for depression symptoms in patients with endocrine-metabolic conditions and *vice versa*.

THE IMPORTANCE OF SLEEP IN THE RELATIONSHIP BETWEEN DEPRESSION AND SELF-HARM

Given the established link between sleep problems, depression and suicidal behavior, we explored whether sleep treatment could be associated with a lower rate of self-injury in young people with and without psychiatric disorders.

In Sweden, melatonin is the most commonly prescribed drug for sleep disturbances in young patients, and its use has dramatically increased in recent years. For the period under consideration in this study, melatonin was only available on prescription.

Using information on all prescribed drugs in Sweden, more than 25,500 children and teenagers who initiated melatonin treatment were identified. Over 87% had at least one psychiatric disorder, mainly attention-deficit hyperactivity disorder, anxiety disorders, depression, or autism spectrum disorder.

The risk of self-harm steadily increased in the months preceding melatonin prescription and decreased thereafter. This was particularly evident among teens with depression and/or anxiety disorders, with girls displaying greater rates than boys.

After excluding antidepressant users, who could have displayed lower risk of self-injurious behavior due to these other medications, the risk of self-harm in the month following melatonin-treatment initiation still decreased by 54% among girls with psychiatric disorders, compared to the last unmedicated month.

This study did not account for a possible role of non-pharmacological treatments (e.g., psychotherapy) and it cannot establish whether melatonin directly causes a decrease in self-harm rates among these patients. However, these findings support the hypothesis that sleep interventions may be beneficial to reduce pediatric self-injurious behavior.

CONCLUSION

This thesis provides new insights into the origins and health outcomes associated with depression, raising awareness about this serious mental condition, which affects a considerable proportion of the population, including many teenagers. Our findings may be of importance to guide patients, clinicians and policy makers in making informed decisions, and underscore a critical need for treatment and for long-term support in this vulnerable population.

ABSTRACT

Depression is a common and debilitating mental disorder characterized by low mood, loss of interest in activities, and long-lasting functional impairment. It is a worldwide psychiatric illness with a wide range of ages of onset, and it occurs about twice as often in women than men. However, most large observational studies have focused on adult populations, leaving pediatric depression largely unexplored. Depressive disorder is linked to poorer physical health and increased comorbidity and mortality, particularly by suicide. This mental condition is the result of a complex interaction between environmental, social, genetic, physiological, and psychological influences, with many risk factors and underlying mechanisms still unknown. This thesis leverages epidemiological statistics and the availability of nationwide registers in Sweden to enhance the understanding of depression in children, adolescents, and adults, exploring adverse health outcomes, psychiatric and somatic comorbidities, potential risk factors, and melatonin treatment for sleep disturbances.

In *Study I*, we described the association of pediatric depression with a wide range of subsequent somatic conditions and premature death, while also exploring the potential role of psychiatric comorbidities. Compared to the general population, individuals diagnosed with depression during youth displayed higher risks for 66 of the 69 somatic diagnoses under investigation (including self-harm, endocrine and metabolic disorders, and sleep disturbances), as well as elevated risks for mortality, particularly for death by intentional self-harm. When adjusted for psychiatric comorbidity, associations were attenuated but persisted. This study provides new insights into the relationships between psychiatric and somatic disorders among a young population, increasing awareness about the burden of pediatric depression and providing a foundation for future research.

In *Study II*, we investigated the link between early-life infections and the risks of depression and self-harm during adolescence and early adulthood. Increased risks of the outcomes were observed among individuals exposed to childhood infections, compared to the rest of the population. When adjusting for familial influences, risks were considerably attenuated and no strong association persisted. Our findings show that childhood infections may not be involved in the etiology of later depression and self-harm, and highlight the importance of identifying these genetic and environmental risk factors shared between family members, which represent potential targets for interventions.

Study III explored the underlying factors contributing to the comorbidity of depression and endocrine-metabolic disorders. A family design was applied to investigate the familial co-aggregation of these medical conditions, while quantitative genetic modeling was used to quantify the relative contribution of genetic and environmental influences to the familial liability. We found evidence of shared etiology to the co-occurrence of depression and endocrine-metabolic conditions, which was primarily due to genetics for non-autoimmune conditions, and to unique environmental factors for autoimmune disorders, especially for type 1 diabetes. These findings expand current knowledge on the etiological sources of these

comorbidities, which could guide future research aiming at identifying underlying pathophysiological mechanisms.

In *Study IV*, we examined whether melatonin use in children and adolescents with sleep disturbances was associated with a reduced risk of self-harm and unintentional injuries. Risks of the outcomes were assessed in periods before and after melatonin-treatment initiation, among youth with and without psychiatric disorders, and across sexes, injury types, psychiatric disorder diagnoses, and age groups. Melatonin-use initiation was associated with reduced risks of self-harm among adolescent females with depression and anxiety disorders, suggesting that sleep interventions may be an important component to reduce risk of self-injurious behavior in this pediatric population.

In conclusion, this thesis contributes to the understanding of depression in youth and adults, highlighting its extensive comorbidity and burden of disease, and posing quality-of-life and public health challenges. Our findings underscore an urgent need for screening, prevention, and early intervention of depression, particularly in young patients, as well as for adequate health care resources to treat this mental illness and its psychiatric and somatic comorbidities.

LIST OF SCIENTIFIC PAPERS

I. **Leone M**, Kuja-Halkola R, Leval A, D'Onofrio BM, Larsson H, Lichtenstein P, Bergen SE. Association of Youth Depression With Subsequent Somatic Diseases and Premature Death. *JAMA Psychiatry*. 2021 Mar 1;78(3):302-10.

II. **Leone M**, Kuja-Halkola R, Leval A, D'Onofrio BM, Larsson H, Lichtenstein P, Bergen SE. Association of severe childhood infections with depression and intentional self-harm in adolescents and young adults. *Brain, Behavior, and Immunity*. 2022 Jan 1;99:247-55.

III. **Leone M**, Kuja-Halkola R, Leval A, Butwicka A, Skov J, Zhang R, Liu S, Larsson H, Bergen SE. Genetic and Environmental Contribution to the Co-Occurrence of Endocrine-Metabolic Disorders and Depression: A Nationwide Swedish Study of Siblings. *(Submitted)*

IV. **Leone M**, Lagerberg T, Butwicka A, Kuja-Halkola R, Leval A, Larsson H, D'Onofrio BM, Bergen SE. Melatonin use and the risk of self-harm and unintentional injuries in youths with and without psychiatric disorders. *(Manuscript)*

These articles are referred to by their Roman numerals throughout the text, and are presented in full at the end of this thesis.

SCIENTIFIC PAPERS NOT INCLUDED IN THE TEHSIS

I. Du Rietz E, Brikell I, Butwicka A, **Leone M**, Chang Z, Cortese S, D'onofrio BM, Hartman CA, Lichtenstein P, Faraone SV, Kuja-Halkola R. Mapping phenotypic and aetiological associations between ADHD and physical conditions in adulthood in Sweden: a genetically informed register study. *The Lancet Psychiatry*. 2021 Sep 1;8(9):774-83.

II. Rajula HS, Manchia M, Agarwal K, Akingbuwa WA, Allegrini AG, Diemer E, Doering S, Haan E, Jami ES, Karhunen V, **Leone M**, Schellhas L, Thompson A, van de Berg SM, Bergen SE, Kuja-Halkola R, Hammerschlag AR, Järvelin MR, Leval A, Lichtenstein P, Lundstrom S, Mauri M, Munafo MR, Myers D, Plomin R, Rimfeld K, Tiemeier H, Ystrom E, Fanos V, Bartels M, Middeldorp CM. Overview of CAPICE—Childhood and Adolescence Psychopathology: unravelling the complex etiology by a large Interdisciplinary Collaboration in Europe—an EU Marie Skłodowska-Curie International Training Network. *European child & adolescent psychiatry*. 2021 Jan 20:1-1.

CONTENTS

LIST OF ABBREVIATIONS

A	Additive genetic influences
ATC	Anatomical Therapeutic Chemical
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
C	Shared environmental influences
CDR	Cause of Death Register
CI	Confidence interval
CTCT	Cross-twin cross-trait correlations
DAG	Directed acyclic graph
DSM	Diagnostic and Statistical Manual of Mental Disorders
E	Unique environmental influences
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
GWAS	Genome-wide association study
h^2	Heritability
HR	Hazard ratio
ICC	Intra-class correlation
ICD	International Classification of Diseases
IR	Incidence rate
IRR	Incidence rate ratio
LISA	Longitudinal integrated database for health insurance and labour market studies
MBR	Medical Birth Register
MDD	Major depressive disorder
MGR	Multi-Generation Register
NPR	National Patient Register
OR	Odds ratio
PIN	Personal identification number
PDR	Prescribed Drug Register
PUL	The Personal Data Act in Sweden

RCT	Randomized controlled trial
SEM	Structural equation modelling
SES	Socioeconomic status
SSRI	Selective serotonin reuptake inhibitor
TPR	Total Population Register
TRD	Treatment-resistant depression
WHO	World Health Organization
YLD	Years lived with disability

1 BACKGROUND

1.1 MAJOR DEPRESSIVE DISORDER

Low mood, sadness and depressive feelings are normal reactions to difficult life experiences, such as distress and bereavement. However, when these feelings lead to a long-lasting functional impairment, a clinical diagnosis of major depressive disorder (MDD) may arise. Depression is a debilitating psychiatric disorder that is characterized by a cluster of symptoms lasting at least two consecutive weeks and involving depressed mood, markedly diminished interest or pleasure, changes in cognition, and vegetative symptoms, such as sleep and appetite disturbances.[1] Additionally, MDD is common, has a significant and negative impact on quality of life, and can affect individuals in early life and for sustained periods, thereby leading to persistent disability. In 2015, the global burden of depression accounted for 7.5% of all Years Lived with Disability (YLD), making this mental disorder the single largest contributor to non-fatal losses in health and functioning in both developed and developing countries.[2] A recent systematic analysis describing the global burden of several mental disorders ranked depression as the second leading cause of YLD in 2019.[3] Future trends in global health expect depression to remain a top contributor to the global disease burden.[4] Moreover, the health impact of depression extends beyond daily functioning and quality of life. In fact, depressive disorder is associated with poor physical outcomes and suicide, which further inflates its total burden.[5-7] Hence, depression is a major public health problem and involves substantial human, social, and economic costs.[8]

1.2 DIAGNOSTIC ASSESSMENT AND SYMPTOMS

The tenth edition of The International Classification of Diseases (ICD-10), which is the main diagnostic system used in Europe, defines depression as an episode lasting a minimum of two weeks, and it classifies this as mild, moderate, or severe.[9, 10] According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), an individual will be diagnosed with major depressive disorder (MDD) when suffering from at least five of the nine defined major depression symptoms, over a minimum period of two consecutive weeks.[11] Thus, there are many unique symptom combinations that a person can experience to meet these criteria, which emphasizes the broadness of the current diagnostic system. Some symptoms characterizing MDD overlap with those of bipolar disorder and schizophrenia. Therefore, in order to be diagnosed with MDD, it is required that a patient does not meet the criteria for either of these disorders.

Some MDD symptoms are entirely opposite to each other (e.g. weight loss and weight gain, or insomnia and hypersomnia), leading to the possibility that patients with very different clinical profiles and underlying biological mechanisms could receive the same diagnosis of MDD.[12] This highlights the extensive heterogeneity of this mental disorder.

In children and adolescents, the DSM-5 criteria for assessing MDD are the same as for adults, with the exception that depressed mood can be identified as irritable mood, and that changes in weight and appetite can be observed as failure to make expected weight gains.[13]

In recent years, evidence has accumulated supporting the hypothesis that, for many psychiatric phenotypes, diagnoses represent the extreme end of continuously distributed traits in the population.[14] Therefore, while relying on categorically defined diagnoses may provide information on the more severe cases, exploring milder traits of these disorders may expand the current knowledge on psychiatric phenotypes in the general population.

1.3 EPIDEMIOLOGY

Depression has a 12-month prevalence of ~6% and a lifetime prevalence of ~16%, meaning that approximately 1 in 6 people develop the disorder during their lifetime.[15] It presents at a wide range of ages-of-onset (peak risk period 16-43 years, with a median age of onset at ~25 years).[15, 16] Before puberty, depressive disorder has an estimated prevalence of 1%-3% and an equal distribution in boys and girls. During adolescence, the prevalence rises to 3%-9%, with females showing a higher risk compared to males.[13, 17] In adults, depression occurs about twice as often in women than in men.[18]

1.4 DISEASE COURSE

The course of depression varies considerably between individuals in terms of chronicity and remission. A history of childhood trauma has been identified as an impactful risk factor for the development of depression, and it has also been associated with chronicity and poorer prognosis of MDD.[19] Early age of onset, increased symptom severity, psychiatric comorbidities, and longer duration of a previous depressive episode are other factors associated with a poorer clinical course of depression.[20] Duration of and remission from an MDD episode differ widely: the mean MDD episode duration varies between 3 and 7 months, with 50-90% of patients recovering within 1 year.[21, 22] Persistence of residual symptoms and functional impairment is often observed after MDD remission.[23] Moreover, approximately 90% of individuals in remittance will experience depression recurrence in their lifetime.[24]

1.5 ETIOLOGY

As with other psychiatric disorders, depression has a multifactorial etiology, with several environmental and genetic factors implicated in its development and clinical course. However, the extent to which these risk factors, as well as their interaction, affect the development and clinical course of depression is still largely unknown.

1.5.1 Environmental risk factors

Stressful life events, parental psychiatric history, low socioeconomic status (SES), low social support, cardio-metabolic diseases, obesity, sleep disturbances, and childhood adversities (e.g., physical and sexual abuse) are some of the consistently reported environmental determinants of MDD.[25-28]

A growing body of research suggests the involvement of inflammatory pathways in the etiology of depression.[29-31] Inflammation is generally inherent to medically-related immune insults but also to 'sterile' stressors. These are psychological stressors that activate key inflammatory pathways, increasing the circulating levels of pro-inflammatory cytokines.[32, 33] Essentially, the body mounts an immune response against a threat to the subject (i.e., a 'sterile' insult), rather than against a pathogen. Stress-induced inflammatory signals can be transmitted to the brain, where they may interact with neurotransmitters and neurocircuits, influencing the risk for depression and non-responsiveness to available antidepressant treatments.[29, 34]

Immune dysregulation is not always present in depression, and not everyone exposed to increased inflammation develops depression.[34, 35] Thus, immune-depression may be restricted to particular subgroups of depressed persons. Previous research indicates that individuals who experienced certain stressful life events, such as childhood adversity, show higher levels of inflammatory biomarkers, increased inflammatory responses to psychosocial stressors, and higher risk of developing depression.[32, 36-38] Moreover, recent studies have proposed the existence of an 'immune-metabolic depression' dimension characterized by metabolic dysregulations.[39, 40]

With regards to medically-related immune insults such as viral and bacterial infections, growing evidence suggests a link between these inflammatory events and subsequent mood disorders.[41] However, there is a lack of large longitudinal studies exploring whether there exists a critical period in life when exposure to infections may increase susceptibility to depression.[42] Childhood or adolescence may encompass sensitive time points during which infections could be more damaging. In fact, during the developmental years, the maturing immune system exhibits an increased vulnerability to insults compared to the fully matured immune system of adults. Consequently, early-life infections may lead to the impairment of specific biological systems involved in the etiology of depression. In *Study II* of this thesis, we investigated the association of childhood infections with later depression and self-harm.

1.5.2 Genetic risk factors

Heritability (h^2) is a measure of how differences in a phenotypic trait within a population can be explained by the genetic variation between individuals in that population. Heritability estimates range from 0 to 1 (where a higher value indicates that the variability in a given trait among people is mainly due to genetic factors over environmental ones). Estimates are specific to populations and the environments they experience, and they can differ over time as circumstances change. Research designs involving twins are one way to estimate the heritability of traits. This is, by comparing a trait in identical twins (who share 100% of their genetic variation) versus fraternal twins (sharing on average 50% of their co-segregating alleles) an estimate of that trait's heritability can be calculated, and genetic and environmental contributions for that specific phenotype can be disentangled.[43] To determine which genes are likely to influence a specific trait, molecular genetic approaches are necessary. Genome-wide association studies (GWAS) examine changes in single nucleotide polymorphisms (SNPs) between individuals with a particular trait under investigation (cases) versus people without

that trait (controls).[44] Markers that differ in frequency between cases and controls are likely to play a role in the etiology of the trait.

From twin studies, the heritability of depression is estimated to be approximately 31–42%;[45] however, this genetic component has remained difficult to identify at a single-nucleotide polymorphism level for a number of reasons. First, depression has lower heritability compared to other psychiatric conditions, such as schizophrenia (h^2=64–81%)[46] and bipolar disorder (h^2=60%).[47] Second, as with all complex traits, depression is highly polygenic, involving many genetic variants with small effect. Therefore, in order to identify genetic loci associated with this psychiatric condition, a particularly large number of patients is required.[44] Moreover, its widespread phenotypic heterogeneity may limit the possibility to capture replicable information on the genetic basis of MDD.[48] In fact, the considerable clinical and etiological heterogeneity results in reduced statistical power as the genetic effect size distribution could be diluted. Additionally, misclassification of controls could further reduce the power to detect association in genetic studies.[49] Finally, there is a possibility that MDD risk is also influenced by other factors, such as gene-environment interaction, rare mutations, and copy number variations, which are not captured in GWAS.[50-54]

A meta-analysis of the three largest GWASs of depression was able to identify 102 independent genetic variants, 87 of which were replicated in an independent sample.[54] In addition to revealing etiological insights, these results can be leveraged for further types of research. In particular, the GWAS summary statistics could be used to calculate polygenic risk scores (PRS) and provide a measure of individual genetic liability for depression. PRS are calculated as the count of GWAS-identified risk alleles for a given phenotype, weighted by their effect size and summed across the genome.

1.6 COMORBIDITY AND ADVERSE HEALTH OUTCOMES

1.6.1 Psychiatric comorbidity

The term comorbidity refers to the occurrence within the same patient of two or more medical conditions at the same time or sequentially. Depression is known to be associated with several other mental illnesses, especially anxiety disorders, substance use disorder, neurodevelopmental disorders, and bipolar disorder.[55-58] Apart from environmental factors that may influence the risk of developing multiple mental illnesses, evidence also points in the direction of a shared genetic liability among psychiatric disorders: the so-called general psychopathology factor (or P factor).[59] Depression comorbid with other mental disorders has been shown to be associated with more severe health outcomes compared with MDD patients with few or no coexisting conditions.[60] Investigating the role of psychiatric comorbidity may provide new insights into the relationship of depression with somatic health decline, as well as with mortality.

1.6.2 Somatic conditions

Prior research indicates that extensive somatic comorbidity among depressed patients is the rule rather than the exception.[61, 62] For example, a close relationship between sleep disturbances and depression has been established, especially among youth, with sleep problems likely to be both symptoms of and contributors to depression.[63-65] A possible genetic overlap between insomnia and depression has also been recently described.[66] Moreover, several studies have shown that MDD substantially increases the risk of diabetes mellitus, cardiovascular diseases, and cancer, among other disorders.[67-71] One major factor that could confound the association between depression and somatic diseases is lifestyle. In fact, MDD patients have been reported to be generally unhealthier, exhibiting increased levels of smoking, drinking, and physical inactivity.[72] Nevertheless, several studies have been conducted in which such potential confounders have been adjusted for, with results consistently suggesting that increased comorbidity risks are not simply explained by lifestyle differences.[61] Although it should be noted that a residual impact of these factors may still exist due to the difficulty in measuring such behaviors in detail, a direct link between depression and incident somatic conditions could still exist, with a number of underlying biological dysregulations that have been proposed as potential mediators for such association. In particular, a consistent body of research suggests that metabolic and immune-inflammatory dysregulations could be the driving forces behind the relationship between depression and the development of certain somatic diseases.[61] Genetic pleiotropy could represent a contributing factor to the development of such co-occurring disorders. This is, when certain conditions/traits share genetic risk variants conferring a disposition for both disorders/traits in the same individual.

1.6.3 Mortality and suicide

In addition to several somatic and psychiatric disorders, patients suffering from depression are at substantially increased risk of all-cause mortality,[7] suicidal intent, and completed suicide compared to the general population.[73] It is estimated that up to 50% of the worldwide suicides per year occur within a depressive episode,[74] and that the risk of death by suicide among MDD patients is almost 20-fold higher compared to the general population.[73]

As most previous studies have focused on adult populations, the association between youth depression, somatic conditions, and premature death is largely unexplored. In *Study I*, we investigated the relationship of youth depression with subsequent diagnoses of several somatic diseases and mortality, while controlling for psychiatric comorbidity. *Study IV* explored whether melatonin-use for the treatment of sleep problems was associated with a decreased risk of suicidal behavior and unintentional injuries among a pediatric population with and without psychiatric disorders.

1.7 TREATMENT

To date, several treatment options are available for the management of depression symptoms, including psychotherapy and pharmacological treatments. Psychotherapy represents the first treatment option in individuals experiencing mild depressive episodes. Patients with moderate-

to-severe depression are usually treated with medication or, when possible, with psychotherapy and medication combined.[75] Selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed antidepressants since these drugs are associated with fewer side effects compared to other pharmacological strategies.[76] Serotonin–noradrenaline reuptake inhibitors (SNRIs), and noradrenaline and specific serotonergic antidepressants (NASSAs) are mostly prescribed in patients unable to take SSRIs. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are older types of medications and rarely recommended for patients nowadays.[77]

In children and adolescents, current Swedish guidelines – Socialstyrelsen (National Board of Health and Welfare), SfBup (Swedish Society for Child and Adolescent Psychiatry) and Läkemedelsverket (Swedish Medical Products Agency) – recommend psychosocial treatment as the primary option.[78] Patients should be evaluated after 4-8 weeks, and if no improvement has occurred, pharmacological treatment should be initiated. In cases of severe depression, clinicians should consider pharmacological treatment at an earlier stage (i.e., after 1-2 weeks). SSRIs are the first-line medication choice for youth: fluoxetine (from age 8) and escitalopram (from age 12) are the drugs for pediatric depression approved by the U.S. Food and Drug Administration (FDA).[13] In Sweden, fluoxetine is the first treatment option, followed by escitalopram and setralin. Other classes of antidepressants such as mirtazapine, bupropion and duloxetine are generally used when SSRIs have proven insufficient, or to augment an SSRI.

Although several options are available for the treatment of this mental disorder, conventional antidepressant therapies are not effective in approximately one third of patients.[79] Treatment-resistant depression (TRD) is a clinical concept and is typically used to describe MDD patients who failed to respond to trials of antidepressant drugs with adequate doses and duration. Several definitions of TRD have been proposed for clinical and research purposes, some of which also include information on resistance severity.[80] Nevertheless, all current definitions consistently refer to the failure of at least two adequate treatment attempts during the same depressive episode.

Evidence suggests that, compared to other MDD patients, individuals with TRD are at greater risk for adverse outcomes, including substance use disorder and all-cause mortality (mainly from suicide and accidents).[81, 82] Currently, TRD patients are primarily treated with a combination of approaches including pharmacotherapy, psychotherapy and electroconvulsive therapy (ECT). Pharmacological strategies for TRD involve higher antidepressant dosage (double or triple), switching to another antidepressant of the same or different class, combination of treatments, and augmentation with non-antidepressant drugs such as lithium or atypical antipsychotics.[83-86] Several emerging therapeutics for TRD have been introduced in recent years, including repetitive transcranial magnetic stimulation (rTMS), intranasal esketamine, and hallucinogens such as psilocybin and ayahuasca.[87-90]

2 RESEARCH AIMS

2.1 OVERARCHING AIM

The overarching aim of this thesis was to investigate potential risk factors, adverse health outcomes, and comorbid disorders of clinically-ascertained depression in children, adolescents, and adults.

2.2 STUDY-SPECIFIC AIMS

Study I: To explore the association of youth depression with subsequent diagnoses of numerous somatic diseases and premature mortality, and to estimate the role of psychiatric comorbidities.

Study II: To examine the association of severe childhood infections with later depression and self-harm, exploring the role of specific groups of infections, possible sensitive periods, and the effect of familial influences.

Study III: To describe patterns of familial co-aggregation between depression and endocrine-metabolic disorders, and to quantify the contribution of genetic and environmental factors to their co-occurrence.

Study IV: To estimate the risk of self-harm and unintentional injuries in periods preceding and following melatonin-treatment initiation among youth with and without psychiatric disorders, and across sexes, injury types, psychiatric disorder diagnoses, and age groups.

3 DATA SOURCES AND MEASURES

3.1 SWEDISH NATIONAL REGISTERS

All studies in this thesis make use of several Swedish population-based registers (**Figure 3.1.1**), which provide nationwide prospective data on a large population, with long and virtually complete follow-up as well as censoring information.[91, 92] Linkage between the different registers is enabled through the use of a unique ten-digit personal identity number (PIN), which is assigned at birth or immigration to each resident in Sweden by the National Tax Board since 1947.[93] The PIN is a vital component in Swedish society and an essential tool for health research purposes. It enables to keep records of population statistics, migration, taxation, education, income, social security, etc., as well as to trace patients and their medical records, allowing efficient handling of referrals and promoting the medical care of individual patients.

Register linkages for medical research purposes in handled by the government agencies responsible for collection and storage of national data, such as Statistics Sweden and the National Board of Health and Welfare. Data are then distributed to the researcher pseudonymized (rather than anonymized), where the Swedish personal identity number is replaced by a key (i.e., a serial number); the key could be traced back to the original PIN through a key file, which is stored at the government agency responsible for the data matching. This is essential in registry-based research since it allows for clarification of improbable data and additional linkage, while ensuring that all data are de-identified and not recognizable at an individual level by the researcher.

Thus, thanks to its universal and tax-funded health care system, long history of national population-based registries, and unambiguous data linkage, Sweden provides unique opportunities for medical research.

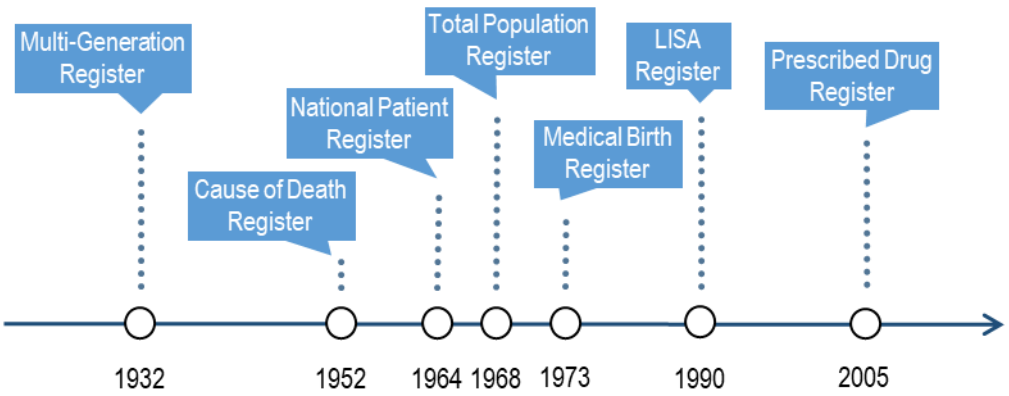

Figure 3.1.1. *Timeline of the Swedish registers used in this thesis work*

The Total Population Register (TPR) – The TPR was established in 1968 and it includes demographic information on all Swedish residents, including place and date of birth, date of death, sex, civil status, and migration within, to, and from Sweden.[94]

The Multi-Generation Register (MGR) – Within the TPR, the MGR provides data on biological and adoptive parents of all Swedish residents born from 1932 and alive from 1961 onwards. The MGR can be used to identify family relationships.[95]

The Cause of Death Register (CDR) – This register contains information on date and cause of death for all Swedish residents since 1952;[96] this data can be used for censoring purposes as well as for investigating all-cause and cause-specific mortality. Underlying causes of death are coded according to the Swedish International Classification of Disease (ICD) system, which is adapted from the World Health Organization (WHO) ICD classification system.[97]

The Medical Birth Register (MBR) – The MBR includes prenatal, perinatal, and postnatal information related to 98-99% of all pregnancies and births in Sweden since 1973.[98, 99] Among others, this register contains data on stillbirths, neonatal deaths, and congenital malformation identified at birth.

The National Patient Register (NPR) – The NPR was launched in 1964 when the National Board of Health and Welfare began collecting data on somatic hospital discharges (**Figure 3.1.2**). It reached complete national coverage for inpatient care in 1987, with information on psychiatric diagnoses since 1973.[100] Data on outpatient visits to specialist clinics are available from 2001, with approximately 80% national coverage. The NPR does not include data on primary health care (i.e., basics of care provided by general practitioners). The register contains patient-related information, data about caregiver (hospital and department), administrative data, including dates of admission and discharge, and medical data, including primary and secondary diagnoses coded according to the relative version of the ICD system; ICD-8 (1969-1986), ICD-9 (1987-1996), ICD-10 (1997-2013). The diagnostic validity and reliability of the NPR is high, with a positive predictive value of 85–95% for most diagnoses within the inpatient register,[100] and only around 1% of diagnoses with missing personal identification numbers.[101] With respect to diagnoses of psychiatric disorders, excellent validity has been described for tic disorder, obsessive-compulsive disorder,[102] and bipolar disorder,[103] while the validity is fair to moderate for diagnoses of depression,[104] schizophrenia,[105] and substance use disorder.[106]

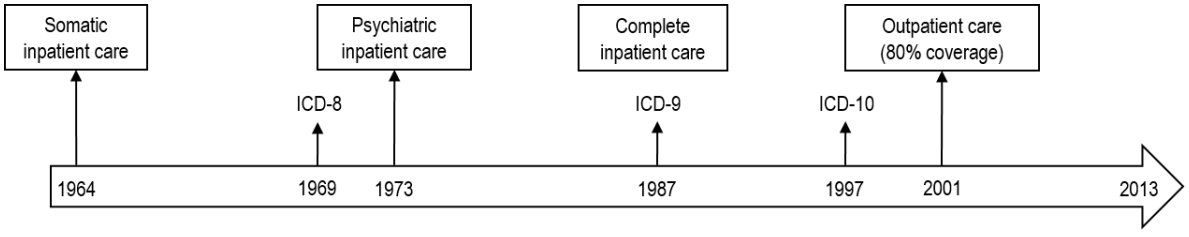

Figure 3.1.2. *Timeline of data included in the National Patient Register and of the ICD versions*

The Prescribed Drug Register (PDR) – The PDR was established on July 2005 and covers all dispensed pharmaceuticals from outpatient and primary health care for all Swedish residents, according to the Anatomical Therapeutic Chemical (ATC) classification system.[107] The register contains information on prescribing and dispensing date, dispensed amount, dosage, etc.; it does not include data on over-the-counter medications, medications used in hospitals, or on the indication for treatment. The proportion of PDR entries with invalid or missing personal identification numbers is less than 2%.[108]

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) – The LISA register keeps information on education, income, and occupation for all individuals aged 16 years or above since 1990, and all individuals aged 15 years or above since 2010.[109]

3.2 MAIN MEASURES

3.2.1 Depression

In all studies, depression was defined as receiving at least one primary or secondary diagnosis of depression within inpatient or outpatient care, using the following *ICD* codes from the National Patient Register: ICD-8 code 300.4; ICD-9 codes 296B and 311X; and ICD-10 codes F32 and F33. In *Study II*, further cases were identified via dispensations of antidepressants in the PDR (ATC code: N06A).

3.2.2 Self-harm

In *Study I*, *Study II*, and *Study IV*, we used the NPR to identify hospitalizations and specialist clinic contacts for intentional self-harm using the ICD-9 code E95, and the ICD-10 codes X60-X84 and X87.0. *Study I* and *Study II* also included information on death by self-harm as the primary cause, using the Cause of Death Register.

3.2.3 Mortality

Study I explored all-cause and cause-specific mortality (**Table 3.2.3**) using data from the CDR.

Table 3.2.3. *Specific causes of death considered in Study I*

Mortality cause	**ICD Version**	**Diagnostic code**
Intentional self-harm	ICD-8	E950-E959
	ICD-9	E950-E959
	ICD-10	X60-X84, Y87.0
Other external causes mortality (excludes intentional self-harm)	ICD-8	800-999, E800-E899, E900-E949, E960-E999
	ICD-9	797-799, 800-999, E800-E899, E900-E949, E960-E999
	ICD-10	V01-X59, X85-Y86, Y87.1-Y89
Natural-cause mortality	ICD-8	000-799
	ICD-9	001-796
	ICD-10	A00-R99

3.2.4 Other psychiatric disorders

Table 3.2.3 shows the ICD codes used when exploring psychiatric comorbidities (in *Study I* and *Study IV*) and parental history of mental illnesses (in *Study II*).

Table 3.2.3. *Diagnostic classification of psychiatric disorders considered in this thesis*

Type of psychiatric disorder	ICD version	Diagnostic code	Study
Any psychiatric disorder	ICD-8	290-315	Study I Study II Study IV
	ICD-9	290-319	
	ICD-10	F00-F99	
Schizophrenia and schizoaffective disorder	ICD-9	295A-X	Study I
	ICD-10	F20, F25, F23.1-F23.2	
Substance use disorder	ICD-9	291A-291F, 291W, 291X, 292A-292C, 292W, 292X, 294A, 304A-304G, 304W, 304X, 305A-305H, 305X	Study I Study IV
	ICD-10	F10-F19	
Bipolar disorder and mania	ICD-9	296A, 296C-296E, 296W, 296X	Study I Study IV
	ICD-10	F30, F31	
Depression	ICD-9	296B, 311	Study IV
	ICD-10	F32, F33	
Anxiety disorders (includes obsessive-compulsive disorder)	ICD-9	300A, 300C, 300D	Study I Study IV
	ICD-10	F40-F42	
Stress-related disorders (includes post-traumatic stress disorder)	ICD-9	308, 309	Study IV
	ICD-10	F43	
Eating disorders	ICD-9	307B, 307F	Study IV
	ICD-10	F50.0-F50.3, F50.9	
Intellectual disabilities	ICD-9	317, 318A-318C, 319	Study I Study IV
	ICD-10	F70-F79	
Autism spectrum disorder	ICD-9	299A, 299B, 299W, 299X	Study I Study IV
	ICD-10	F84.0, F84.1, F84.5	
Attention-deficit hyperactivity disorder	ICD-9	314A, 314B, 314C, 314J, 314W, 314X	Study I Study IV
	ICD-10	F90, F90.0, F90.1, F90.8, F90.9	
Tic disorders (includes Tourette syndrome)	ICD-9	307C	Study IV
	ICD-10	F95	

3.2.5 Somatic conditions

Specific ICD codes used to define medical conditions in all studies of this thesis can be found in the **Appendix Table**.

3.2.6 Socioeconomic status

In *Study II*, we explored the role of parental socioeconomic status (SES) in the association of childhood infections with depression and self-harm. SES was defined using the following data from the LISA register:

i. Highest parental educational attainment; levels were grouped as:
    1. Primary and lower secondary (up to 9 years, compulsory)
    2. Upper secondary (up to 3 years)
    3. Postsecondary (up to 3 years of university education)
    4. Postgraduate (4 or more years of university education)
ii. Maternal and paternal unemployment from age 0 to 18 of the child
iii. Maternal and paternal financial support from birth through age 18 of the child
iv. Maternal and paternal disposable income, which was divided into quartiles and calculated as the average between ages 9 and 11 of the child to account for year-to-year fluctuations

In *Study III*, we use parental educational attainment as an indicator of SES, defined as low (primary school, lower, and upper secondary school) or high (≥1 year of university).

3.2.7 Melatonin

Study IV explored melatonin treatment in children and adolescents (ATC code from the PDR: N05CH01). During the follow-up of this study, melatonin was available in Sweden only as a prescription medicine (i.e., not available over the counter) and fully refundable by the health care system for the pediatric population.

4 METHODS

4.1 STUDY DESIGNS

All four studies included in this thesis use observational study designs. Observational studies can be used to investigate the associations between certain exposures and outcomes when other study designs, such as randomized control trials (RCT), cannot be conducted for ethical, financial or logistic reasons. In observational studies, the problem of confounding which arises from the lack of randomization of the exposure can be reduced by adopting statistical models that allow for adjustments.[110] Nordic countries represent a gold mine for this type of research due to their long history of national population-based registries. Moreover, unambiguous data linkage and virtually free health care allow for longitudinal studies of large-scale populations, where data collection costs are minimized, and selection bias can be reduced or eliminated. This allows prospective follow up of nationwide samples, exploring their changes in health and social situation with time.[92]

4.1.1 Cohort studies

In a cohort study, a group of individuals is followed over a period of time, during which the occurrence of a disease (or any outcome of interest) is measured. Each cohort member is followed up until the time of the outcome or censoring, which may occur at the end of the study period or when a person is no longer under observation (e.g., death –if this is not the outcome of interest– or emigration). Within the cohort, individuals are clustered into two or more groups based on some common characteristics, such as ethnicity or an exposure. For example, participants can be split into exposed and unexposed, depending on whether they experience the exposure event under investigation. The aim of a cohort study is usually to compare the outcome rates or risks among these groups. In every study, several aspects need to be addressed, including inclusion and exclusion criteria, definitions of exposures and outcomes, and how to measure rates or risks.[110]

4.1.2 Family-based studies

4.1.2.1 Familial co-aggregation studies

Familial co-aggregation studies explore whether familial influences, of both genetic and non-genetic origin, play a role in the co-occurrence of multiple traits. This can be accomplished by investigating the degree of clustering of two or more traits within families.[111, 112] Compared to unrelated individuals, members of the same family share a higher amount of genetic and environmental factors. Therefore, a higher occurrence of trait A in relatives of individuals with trait B, compared to relatives of individuals without trait B, may suggest that genetic and/or environmental factors shared by family members are involved in the etiology of the co-occurrence of traits A and B.

When including multiple types of relatives, familial co-aggregation studies can also provide insights on the relative importance of genetic and non-genetic factors influencing the co-

aggregation of traits. For example, if the strength of the association between two traits among relatives increases along with the increasing degree of genetic sharing, the importance of genetic influences for the association of these traits can be suggested.

In *Study III*, we assessed the familial co-aggregation between depression and endocrine-metabolic disorders across full- and half-siblings, to test for the presence of shared familial liability for the co-occurrence of these disorders.

4.1.2.2 Quantitative genetic modeling

Once the familial liability to the co-occurrence of multiple traits has been established, it is possible to quantify the relative contribution of genetic and environmental factors using quantitative genetic modeling.[43, 113] The most common approach utilizes the different degree of genetic sharing between monozygotic (MZ) and dizygotic (DZ) twins. MZ twins are genetically identical, while DZ twins share on average 50% of their segregating alleles. Furthermore, both MZ and DZ twins are assumed to share 100% of common environmental influences. By comparing concordance rates of the trait(s) of interest between MZ and DZ twin pairs, it is possible to understand whether genetic influence is important for that trait (or co-presentation of multiple traits). For example, a stronger correlation for a trait within MZ twin pairs compared to DZ twin pairs (intra-class correlation, ICC) suggests a genetic contribution to variation in the trait; higher correlation between trait A for twin 1 and trait B in twin 2 (cross-twin cross-trait correlations, CTCT) among MZ twins compared to DZ twins indicates that the covariation between the traits of interest is influenced by overlapping genetic effects.

Similarly, it is possible to compare full- and maternal half-siblings, who share 50% and 25% of their segregating genes, respectively, and can be assumed to share their common environmental factors, given that they grow in a similar prenatal environment and are often reared in the same household.[114] This approach has the advantage of increasing sample size and, therefore, statistical power, allowing the investigation of relatively rare disorders. Moreover, using siblings can improve the generalizability of the findings since they may be more representative of the general population compared to twins.

In *Study III*, structural equation modelling (SEM, described in section 4.2.3) was used to decompose the observed variation and covariation of depression and various endocrine-metabolic disorders into the genetic and non-genetic influences, by comparing full- and maternal half-siblings.

4.1.3 Within-cluster comparison

In observational studies, the problem of confounding leads to systematic differences between exposed and unexposed. Observed confounders can be adjusted/controlled for by stratification or using regression models; however, many confounders may be difficult to measure, or even unknown. To overcome this limitation, one strategy is to examine the exposure-outcome association within clusters in which some confounders are (approximately) constant, such as the whole genome when comparing identical twins, socioeconomic status when comparing

people from the same neighborhoods, etc. Thus, this design enables adjustment for cluster-constant confounders, because within clusters there cannot be imbalances in such confounders across exposure levels. In other words, within-cluster comparison ensures that exposed and unexposed are conditionally exchangeable for cluster-constant confounders.

An illustration of within-cluster analysis is given in the directed acyclic graph (DAG) illustrated in **Figure 4.1.3**. In the DAG, *X* and *Y* refer to exposure and outcome in two members of a cluster; *C* represents cluster-varying confounders (e.g., sex, birth year, etc.); and *U* indicates cluster-constant confounders. The aim of within-cluster analysis is to control for *U*.

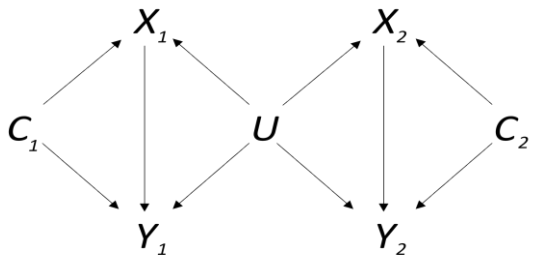

Figure 4.1.3. *Directed acyclic graph representation of the within-cluster analysis*

4.1.3.1 Within-sibling comparison

In within-sibling comparisons, the cluster is a set of genetically related individuals; therefore, by comparing differentially exposed siblings in terms of the outcome of interest, it is possible to control for confounding shared by the siblings (e.g. genetic, environmental, and socioeconomic factors).[115] In *Study II*, this approach was used to adjust for unmeasured familial confounding when investigating the association of childhood infections with later depression and self-harm.

4.1.3.2 Within-individual comparison

In the within-individual analysis, the same individual is compared to him- or herself under two different levels of the exposure; this enables adjustment for all unmeasured confounders that are constant within the individual over time (e.g., genetic background and early life risk factors).[116] This design was used in *Study IV* to examine the association of melatonin-treatment initiation with self-harm and unintentional injuries.

4.2 STATISTICAL METHODS

4.2.1 Regression models

4.2.1.1 Cox proportional hazard regression

Cox proportional hazard regression is a statistical method used to analyze survival, or time-to-event, data. With this model, it is possible to estimate the hazard ratio (HR) of specific outcomes in exposed individuals compared to unexposed, while controlling for potential confounders and for the selected underlying timescale. Moreover, Cox regression allows time-

varying covariates to be modeled.[117] In *Study I*, *Study II*, and *Study III* we use Cox proportional hazard regression with attained age as the underlying timescale (i.e., we compared individuals of the same age) to determine the HRs of i) somatic medical conditions and mortality in patients with youth depression compared with individuals who did not suffer from depression early in life; ii) depression and self-harm in individuals exposed to severe infections during childhood compared to the rest of the population; iii) endocrine-metabolic disorders in individuals with depression (and *vice versa*) compared to individuals without the exposure disorder; and the HRs of the outcome disorder in siblings of individuals with and without the exposure disorder.

4.2.1.2 Logistic regression

Logistic regression is a statistical model used to analyze the odds of a binary outcome (0/1). In these analyses, the measure of association between the exposure and outcome is given by the odds ratio (OR). Odds are defined as the probability of an event to occur dived by the probability of that event not to occur. An OR is the ratio between odds of an event in one group (e.g. exposed) and odds of the same event in a comparison group (i.e. unexposed). Logistic regression estimates the change in the log-odds of the outcome for every unit increase in the exposure variable, while controlling for confounding and assessing effect modification (i.e., interaction between variables). Logistic regression was used in *Study III* to compare whether results were differing from the ones estimated using Cox proportional hazard regression models.

4.2.1.3 Poisson Regression

Poisson regression is used to model the number of times that an event of interest has occurred over a period of time. The outcome measures are the incidence rate (IR), which is the number of events per unit of time in a well-defined population, and the incidence rate ratio (IRR), which is the ratio of the incidence rate among the exposed portion of the population and the incidence rate in an unexposed group. Poisson regression assumes that the outcome follows a Poisson distribution with constant rate of event occurrence over time.[118] An offset term can be included to account for the differential length of follow-up between individuals.

4.2.2 Cluster-robust variance estimation

This technique is used to obtain standard errors corrected for deviations from model assumptions, such as homoscedasticity and independence of rows of data.[119] In *Study I*, *Study II*, and *Study III* some individuals included in the cohorts were related (e.g., biological siblings), violating the assumption of independence. Therefore, we identified individuals who shared the same biological mother and used cluster-robust variance estimation to produce robust standard errors and adjust the precision of the estimated regression coefficients.

4.2.3 Structural equation modeling

Structural equation modeling (SEM) is a statistical method combining factor and regression analyses used to describe the relative contribution of the latent (unmeasured) constructs that are assumed to underpin the observed data.[120] In quantitative genetics, SEM can be applied to

compare correlations across MZ and DZ pairs (or across full- and half-sibling pairs) and decompose the variation in a measured trait/phenotype into variation attributable to the following three latent variables: additive genetic factors (A); shared environmental factors (C), which are non-genetic components making siblings similar; and non-shared environmental influences (E), which are factors making sibling dissimilar, including measurement error.

Assuming that the latent components are independent from each other, the variance (V) in a phenotype (p) consists of the variances of A, C, and E:

$$V(p) = V(A) + V(C) + V(E)$$

Therefore, the proportion of variance of each latent component represents the influence of genetic or environmental factors on the phenotypic variation. For example, the relative contribution of additive genetics (i.e., narrow-sense heritability, or h^2) can be calculated as the share of phenotypic variation explained by A:

$$h^2 = \frac{V(A)}{V(p)}$$

Comparison of correlations across full- and half-sibling pairs are based on the following assumptions: A-factors correlate at 0.50 between full-siblings and 0.25 between half-siblings, as they share 50% and 25% of their co-segregating alleles, respectively; C-factors correlate at 1 across all siblings; E-factors correlate at 0 across all siblings.

In a multivariate model, it is possible to estimate the relative contribution of A, C, and E to the total variance of more than one phenotype as well as to the covariance between the phenotypes.[121] A bivariate model was used in *Study III* to calculate the extent to which the same genetic factors are involved in two traits (i.e., the genetic correlation), and to estimate the relative genetic, shared environmental, and non-shared environmental contributions to the phenotypic correlations between depression and various endocrine-metabolic disorders. The proportion of phenotypic covariation between two traits explained by genetic effects is referred to as bivariate heritability.

5 RESULTS

5.1 STUDY I: ASSOCIATION OF YOUTH DEPRESSION WITH MEDICAL CONDITIONS AND MORTALITY

In this study of almost 1.5 million Swedish individuals, youth depression was associated with a wide range of subsequent medical conditions and with premature death.

5.1.1 Descriptive characteristics of the study cohort

Table 5.1.1. *Demographic and descriptive characteristics of the study cohort* [122]

Characteristic	No. (%)		P value[a]
	Unexposed (1 450 779 [97.5%])	Exposed (37 185 [2.5%])	
Sex			
Male	749 773 (51.7)	12 136 (32.6)	<.001
Female	701 006 (48.3)	25 049 (67.4)	
Birth year			
1982-1985	340 813 (23.5)	3666 (9.9)	<.001
1986-1989	394 870 (27.2)	9176 (24.7)	
1990-1993	437 952 (30.2)	14 808 (39.8)	
1994-1996	277 144 (19.1)	9535 (25.6)	
Age at first recorded diagnosis of depression, mean (SD), y			
Male	NA	16.7 (2.1)	
Female	NA	16.7 (1.8)	
Age at first recorded diagnosis of depression, age group, y			
5-11	NA	483 (1.3)	
12-16	NA	14 394 (38.7)	
17-19	NA	22 308 (60.0)	
Psychiatric comorbidities			
Attention-deficit/hyperactive disorder	37 669 (2.6)	7530 (20.3)	
Male	24 565 (65.2)	3254 (43.2)	<.001
Female	13 104 (34.8)	4276 (56.8)	
Autism spectrum disorder	15 139 (1.0)	3248 (8.7)	
Male	10 361 (68.4)	1677 (51.6)	<.001
Female	4778 (31.6)	1571 (48.4)	
Intellectual disability	12 529 (0.9)	867 (2.3)	
Male	7446 (59.4)	385 (44.4)	<.001
Female	5083 (40.6)	482 (55.6)	
Mania and bipolar disorder	7550 (0.5)	2932 (7.9)	
Male	2614 (34.6)	663 (22.6)	<.001
Female	4936 (65.4)	2269 (77.4)	
Schizoaffective disorder and schizophrenia	1850 (0.1)	455 (1.2)	
Male	1172 (63.4)	197 (43.3)	<.001
Female	678 (36.6)	258 (56.7)	
Substance use disorder	63 687 (4.4)	7911 (21.3)	
Male	36 096 (56.7)	2743 (34.7)	<.001
Female	27 591 (43.3)	5168 (65.3)	
Anxiety disorders	66 240 (4.6)	17 047 (45.8)	
Male	25 527 (38.5)	4571 (26.8)	<.001
Female	40 713 (61.5)	12 476 (73.2)	

Abbreviation: NA, not applicable.

[a] Significance testing of differences between males and females in the exposed group (except birth year, for which the difference between birth-year groups in the exposed was tested) used the Pearson χ^2 test.

A total of 37,185 patients (2.5% of the population; 67.4% female) was diagnosed with depression between ages 5 and 19, with a mean age at first recorded diagnosis of depression at 16.7 years. 60% of these patients had their first depression diagnosis between ages 17 and 19.

Compared with the general population, the youth-depression group had a higher prevalence of other psychiatric disorders, particularly anxiety disorders (45.8% [73.2% females]), substance use disorder (21.3% [65.3% females]), and attention-deficit hyperactivity disorder (20.3% [56.8% females]).

1% of patients with youth depression died during the follow-up compared to 0.4% individuals who died in the non-depressed group. Intentional self-harm was the leading cause of death among those with youth-depression (62.2%), followed by other external causes of death (25.8%).

5.1.2 Absolute risks

The absolute risk difference of a specific disease within 12 years from the first diagnosis of depression during youth ranged from -0.2% for arthropathies among males, to 23.9% for the broader category of injuries among females.

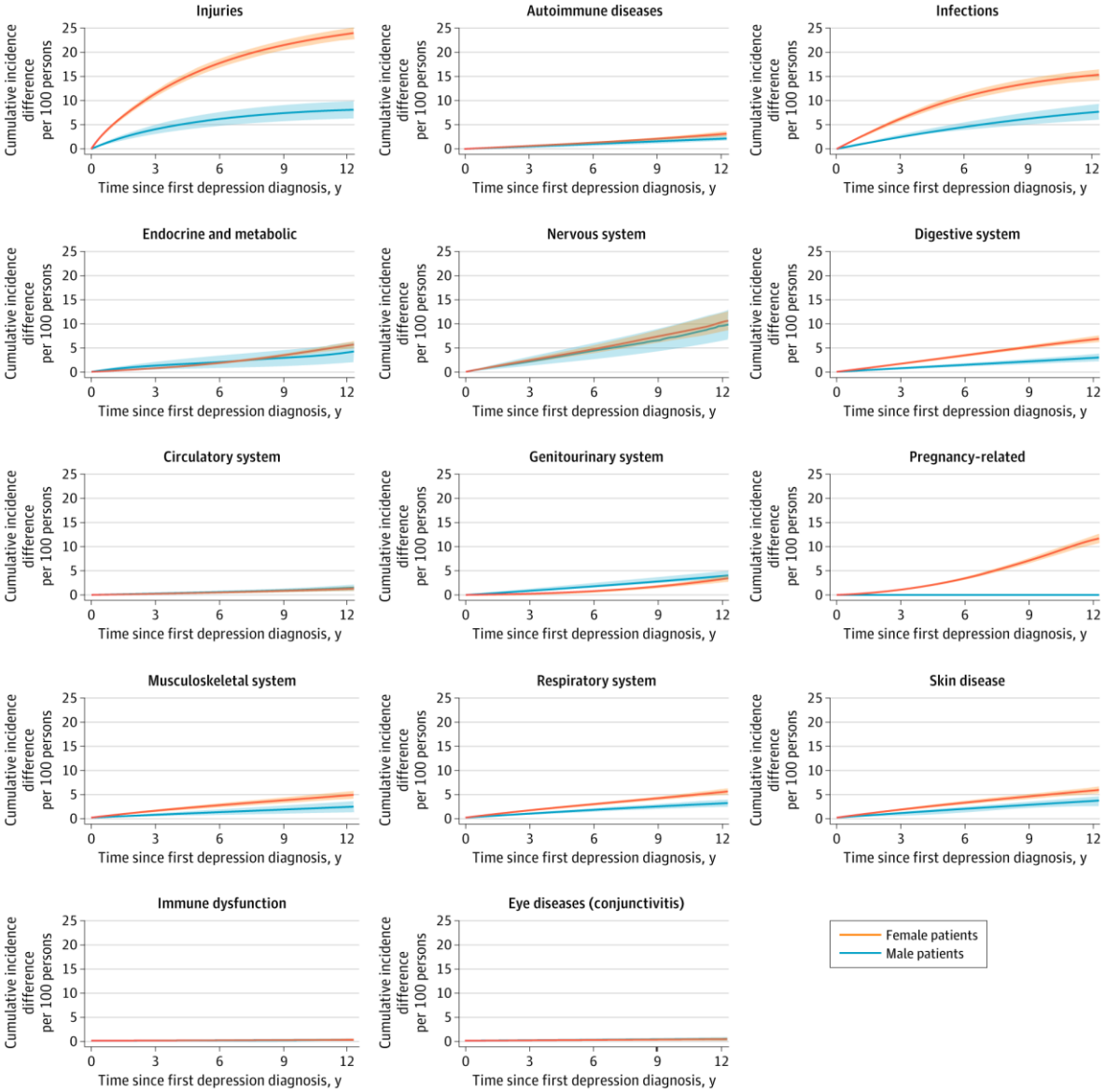

Figure 5.1.2. *Absolute risk differences for various medical conditions after a first diagnosis of depression during youth* [122]

5.1.3 Relative risks

Youth-depression patients had higher relative risks of being diagnosed with 66 of the 69 explored somatic diseases at any time subsequent to their first depression diagnosis. Most associations were attenuated but persisted after adjusting for psychiatric comorbidity.

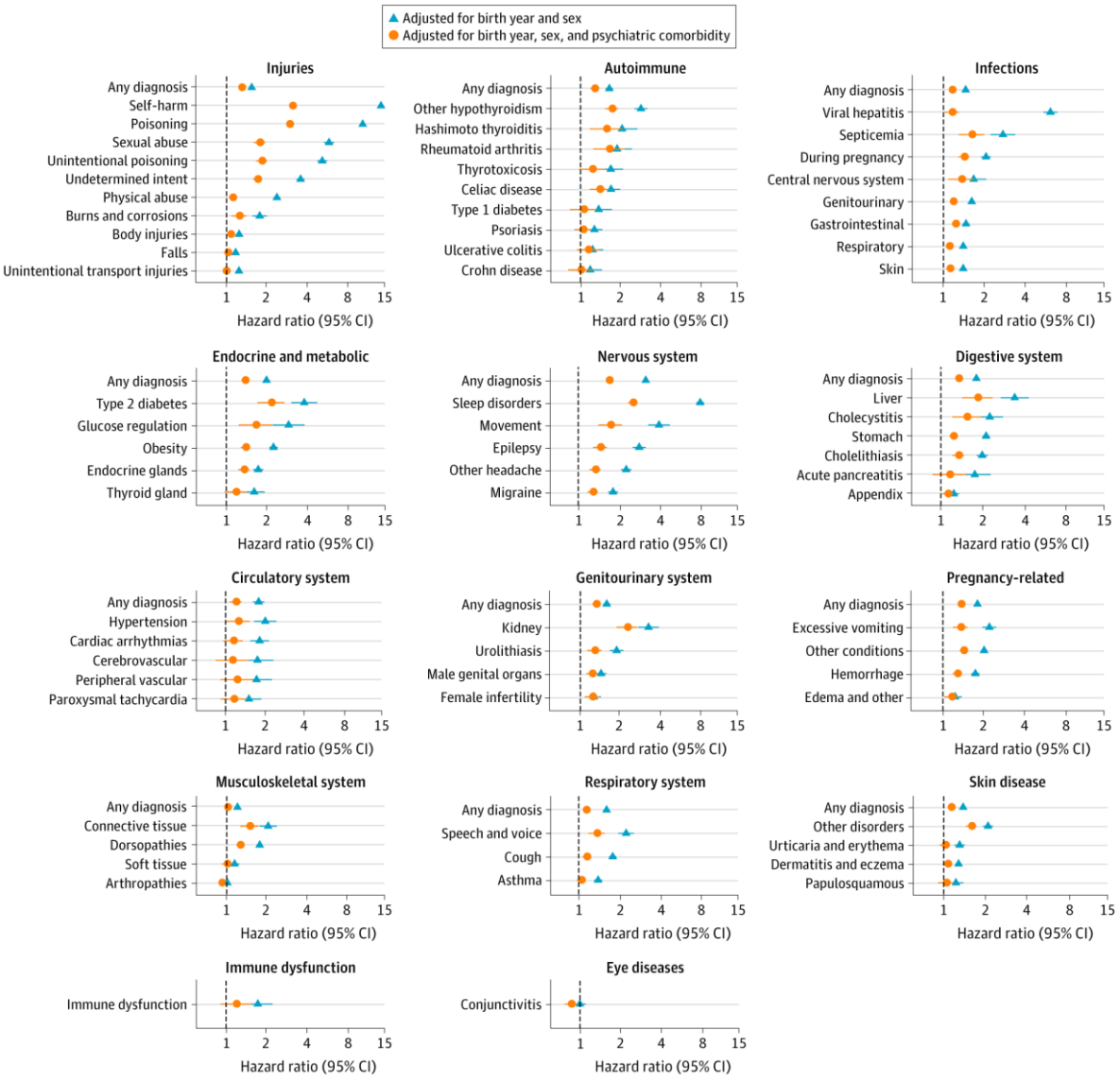

Figure 5.1.3. *Risk of somatic diagnoses subsequent to clinically ascertained youth depression* [122]

5.2 STUDY II: ASSOCIATION OF CHILDHOOD INFECTIONS WITH LATER DEPRESSION AND SELF-HARM

In this population-based register study, genetic and environmental factors shared between siblings explained the association of childhood infections with later depression and suicide.

5.2.1 Descriptive characteristics of the study cohort

Table 5.2.1. *Number of individuals exposed and unexposed to childhood infections among the total cohort of 1,506,070 and among patients with depression or self-harm* [123]

	Unexposed to Infection No. (%)	Exposed to Infection No. (%)	*P* value [a]
Any Infection			
Total cohort	1,167,819 (77.5)	338,251 (22.5)	NA
Depression	50,553 (4.3)	17,077 (5.0)	<.001
Self-harm	18,946 (1.6)	6,705 (2.0)	<.001
Nervous System Infections			
Total cohort	1,497,400 (99.4)	8,670 (0.6)	NA
Depression	67,194 (4.5)	436 (5.0)	.02
Self-harm	25,478 (1.7)	173 (2.0)	.04
Gastrointestinal Infections			
Total cohort	1,402,310 (93.1)	103,760 (6.9)	NA
Depression	62,063 (4.4)	5,567 (5.4)	<.001
Self-harm	23,390 (1.7)	2,261 (2.2)	<.001
Genitourinary Infections			
Total cohort	1,471,697 (97.7)	34,373 (2.3)	NA
Depression	65,662 (4.5)	1,968 (5.7)	<.001
Self-harm	24,930 (1.7)	721 (2.1)	<.001
Respiratory Infections			
Total cohort	1,298,494 (86.2)	207,576 (13.8)	NA
Depression	57,288 (4.4)	10,342 (5.0)	<.001
Self-harm	21,551 (1.7)	4,100 (2.0)	<.001
Sepsis			
Total cohort	1,501,063 (99.7)	5,007 (0.3)	NA
Depression	67,371 (4.5)	259 (5.2)	.02
Self-harm	25,564 (1.7)	87 (1.7)	.89
Skin Infections			
Total cohort	1,471,188 (97.7)	34,882 (2.3)	NA
Depression	65,982 (4.5)	1,648 (4.7)	.03
Self-harm	24,995 (1.7)	656 (1.9)	.01

Abbreviation*: NA, not applicable.*

Note*: [a] Significance testing of differences between exposed and unexposed individuals among the depression and the self-harm group, using the Pearson χ^2 test.*

5.2.2 Absolute risks

Childhood infections were associated with increased absolute risks of depression (Figure 5.2.2.1) and self-harm (Figure 5.2.2.2). For example, compared to the general population, individuals exposed to any childhood infection displayed an absolute risk difference of 2.42% [95% CI, 0.41–4.43%] of being diagnosed with depression up until age 31, and 0.73% [95% CI, −2.05% to 3.51%] of self-harm. This means that, if we had followed every individual until age 31, more than 36,000 and 10,000 patients exposed to early-life infection would be later diagnosed with depression or self-harm, respectively, compared to the rest of the cohort. There was no major difference when investigating exposure to specific groups of infections.

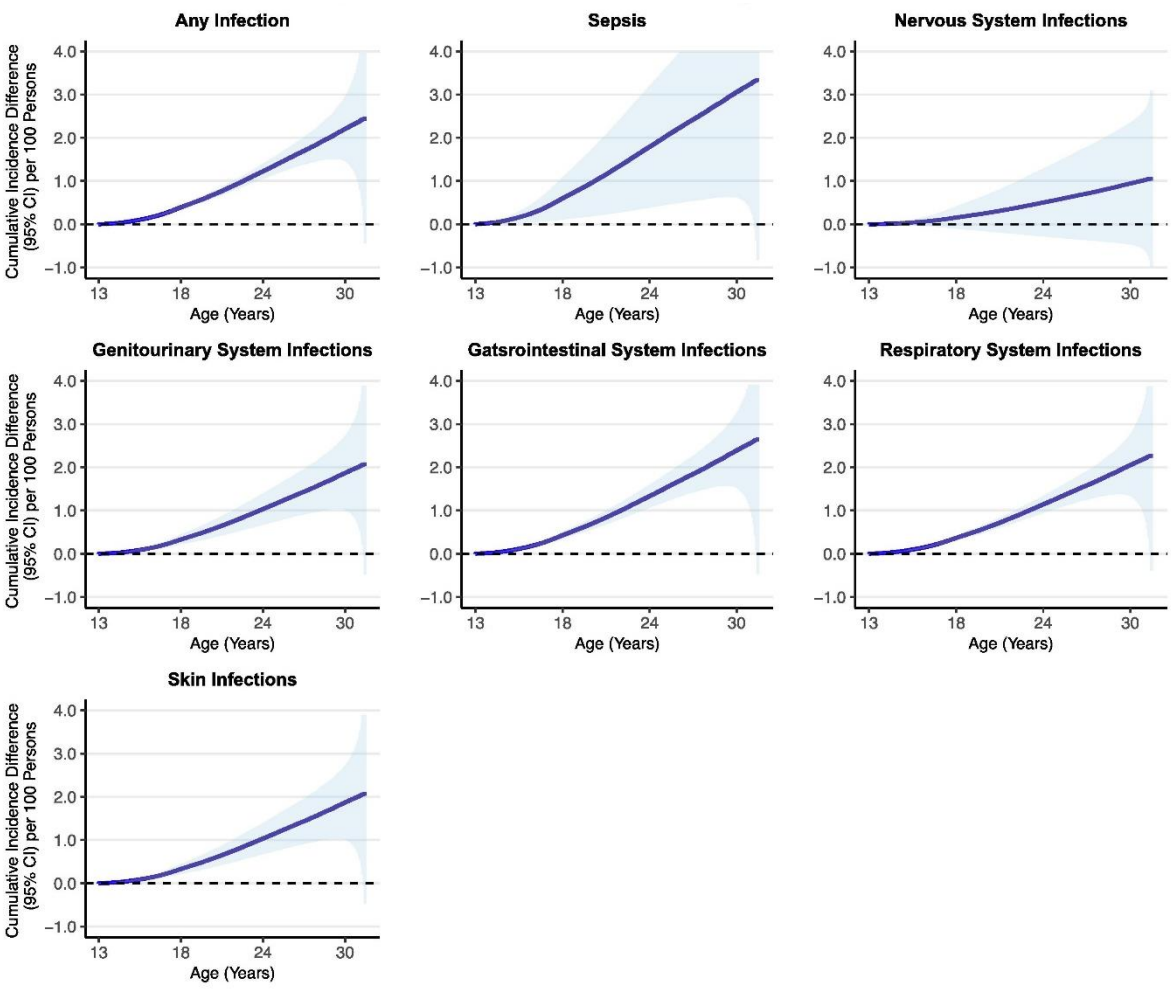

Figure 5.2.2.1. *Absolute risk differences for adolescent or early-adulthood depression after severe infections during childhood* [123]

Note: *Each panel shows the time-specific risk differences (calculated as the difference between cumulative incidences among children exposed and unexposed to severe infections) of depression from age 13 years up until age 31 years, following exposure to specific groups of infections during childhood. Some CIs are cut from the plots for visual purposes.*

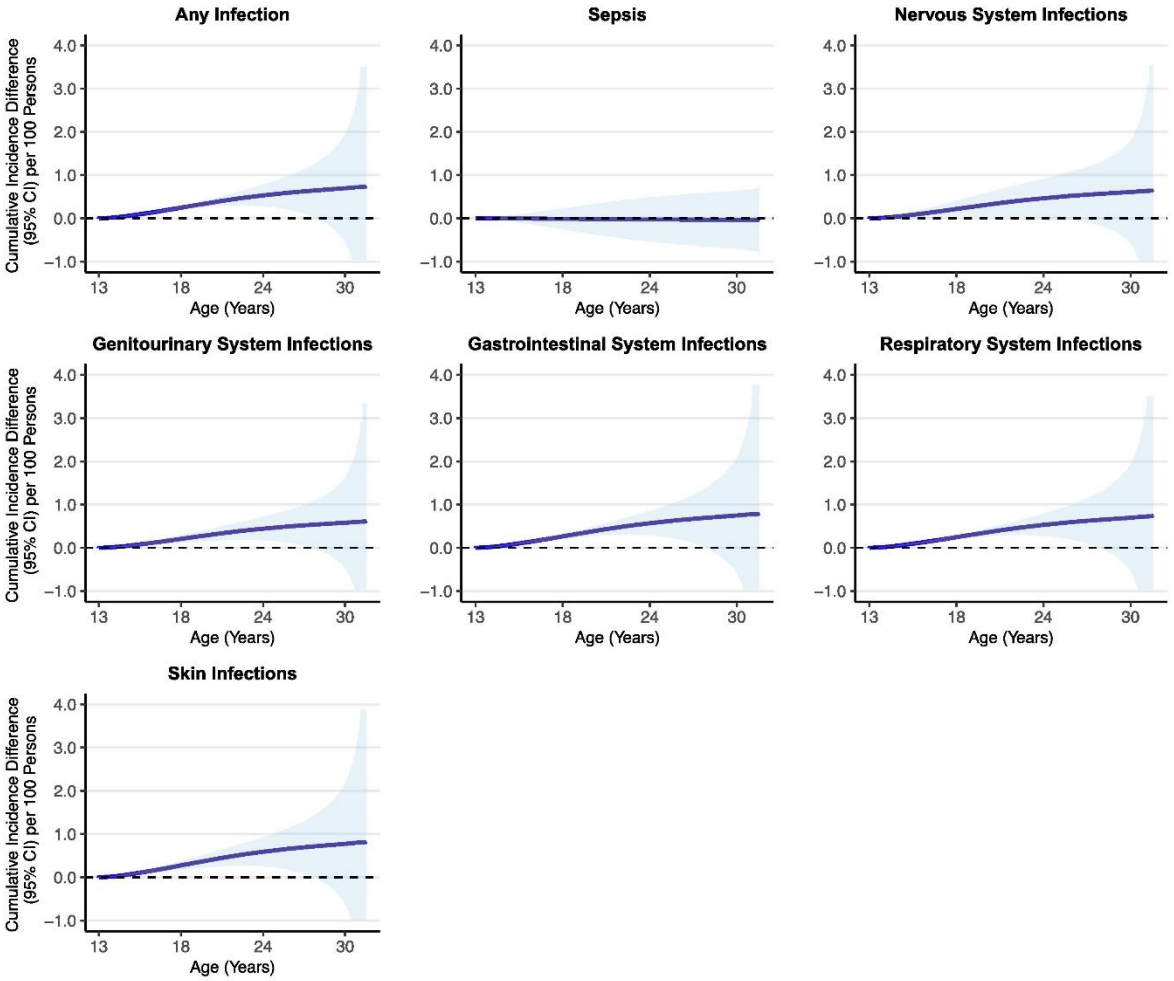

Figure 5.2.2.2. *Absolute risk differences for adolescent or early-adulthood depression after severe infections during childhood* [123]

Note: *Each panel shows the time-specific risk differences (calculated as the difference between cumulative incidences among children exposed and unexposed to severe infections) of self-harm from age 13 years up until age 31 years, following exposure to specific groups of infections during childhood. Some CIs are cut from the plots for visual purposes.*

5.2.3 Relative risks and familial influences

Childhood infections were associated with increased risk of depression and intentional self-harm. When controlling for parental history of psychiatric disorders and socioeconomic status (SES), all associations were attenuated. Finally, when adjusting for unmeasured factors shared between family members by comparing siblings discordant for early-life infection exposure, no strong association persisted.

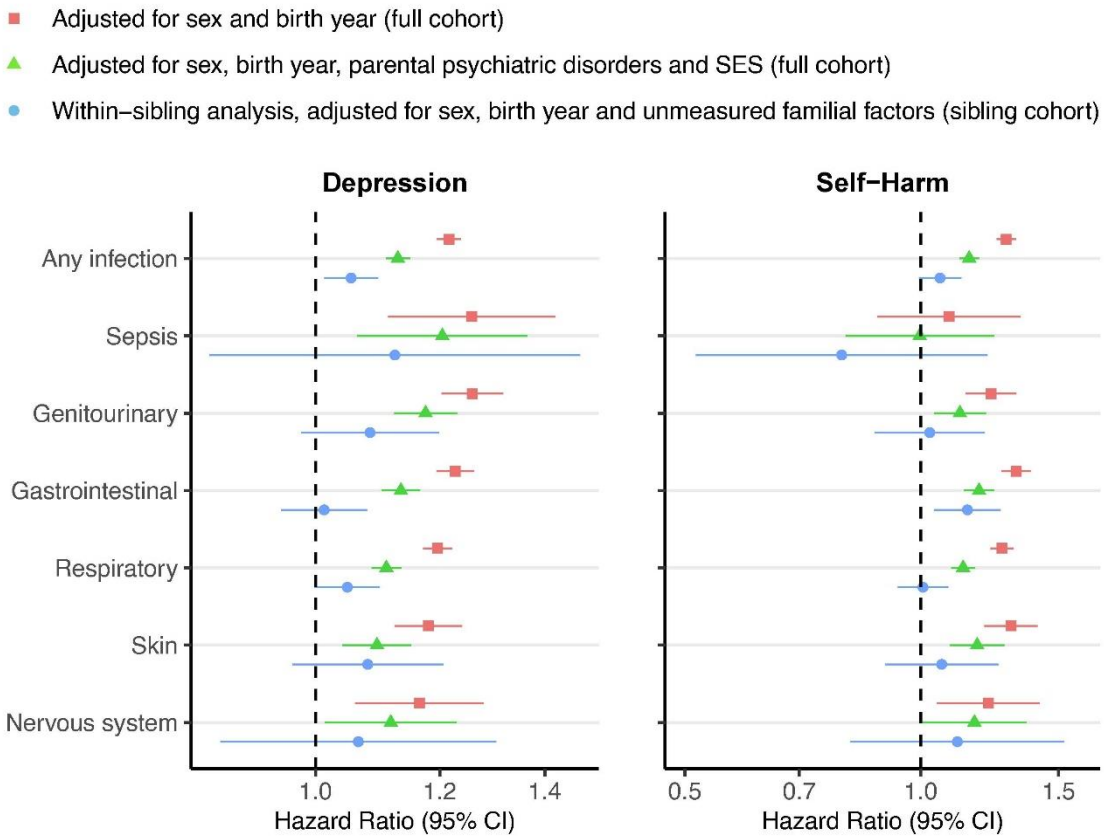

Figure 5.2.3. *Risk of depression and self-harm in adolescents and young adults subsequent to childhood infections* [123]

Note: *Relative risks of depression (left) and self-harm (right) between ages 13 and 31, following exposure to specific groups of infections during childhood. Hazard Ratios and 95% confidence intervals were estimated via Cox proportional hazards regression model with attained age as the underlying timescale. Three models are compared: i) adjusted for birth year and sex (red squares), including the full cohort of 1,506,070 individuals; ii) further adjustment for parental psychiatric disorders and SES (green triangles), including the full cohort of 1,506,070 individuals; iii) within-sibling analysis adjusted for birth year and sex (blue circles), only including differentially exposed full-siblings. The within-sibling design allows adjustment for unmeasured familial risk factors (i.e., genetic and environmental factors shared by siblings).*

5.3 STUDY III: FAMILIAL LIABILITY TO DEPRESSION AND ENDOCRINE-METABOLIC DISORDERS

In this nationwide register-based study, depression and endocrine-metabolic disorders co-aggregated in families, primarily due to shared genetics in the case of non-autoimmune conditions, and to unique environmental factors in the case of autoimmune disorders, especially type 1 diabetes.

5.3.1 Descriptive characteristics of the study cohort

A total of 2,263,311 participants (48.8% female) were followed-up for a median [IQR] time of 27 [22, 34] years. Compared to the general population, individuals with depression had a higher prevalence of endocrine-metabolic disorders, especially hypothyroidism and obesity.

Table 5.3.1. *Demographic and descriptive characteristics of the study cohort*

Characteristics	No Depression 2,145,260 (94.8)	Depression 118,051 (5.2)
Sex		
Female	1,030,975 (48.1)	74,326 (63.0)
Male	1,114,285 (51.9)	43,725 (37.0)
Age at first recorded diagnosis of depression, mean (SD), year		
Female	NA	23.2 (6.3)
Male	NA	23.8 (6.3)
Age at first recorded diagnosis of depression, age group, year		
4-12	NA	1,027 (0.9)
13-16	NA	14,123 (12.0)
17-20	NA	30,114 (25.5)
21-25	NA	30,889 (26.2)
26-30	NA	22,823 (19.3)
31-40	NA	15,422 (13.1)
Endocrine and metabolic disorders		
Any autoimmune condition	37,733 (1.8)	4,720 (4.0)
Autoimmune hypothyroidism	17,993 (0.8)	2,892 (2.4)
Graves' diseases	4,951 (0.2)	489 (0.4)
Type 1 diabetes	17,507 (0.8)	1,737 (1.5)
Any non-autoimmune condition	55,925 (2.6)	8,080 (6.8)
Type 2 diabetes	5,431 (0.3)	1,049 (0.9)
Obesity	41,305 (1.9)	6,126 (5.2)
Polycystic ovarian syndrome [a]	12,397 (1.2)	1,675 (2.3)

Abbreviations: *SD, standard deviation; NA, not applicable.*

Note: *Data are presented as number (%) of individuals unless otherwise indicated.* [a] *When investigating polycystic ovarian syndrome, only female individuals were included (N = 1,105,301, of which 74,326 [6.7%] received a diagnosis of depression).*

5.3.2 Association and familial co-aggregation analyses

Compared to the general population, individuals with endocrine-metabolic disorders displayed higher risks of depression. Increased risks extended to full-siblings of individuals with endocrine-metabolic disorders, suggesting that shared familial liability contributed to the co-occurrence of these conditions. No difference in depression risks was observed between full-, maternal half-, and paternal half-siblings of individuals with type 1 diabetes, potentially indicating that unique environmental factors may be underlying the association between the two disorders.

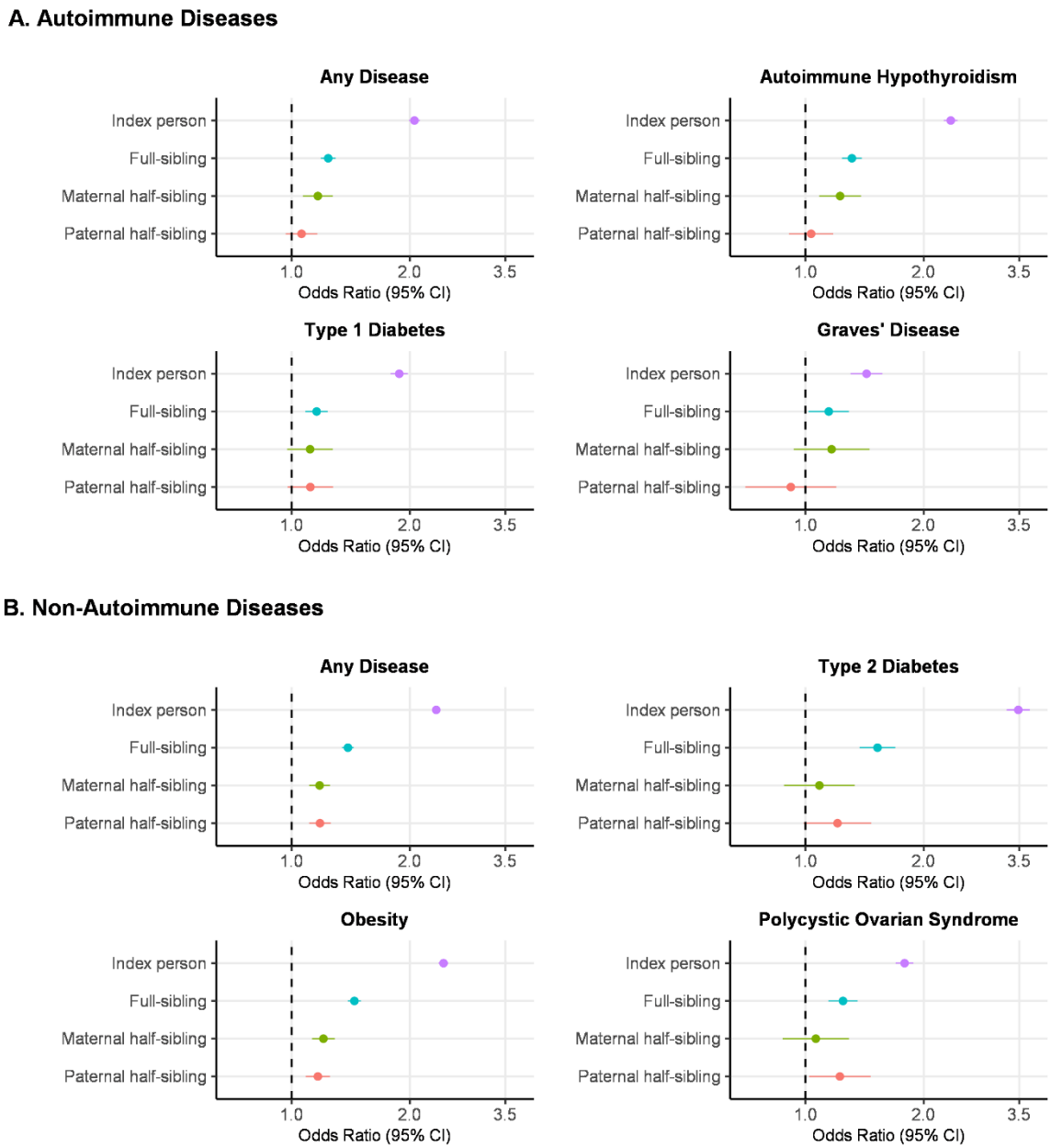

Figure 5.3.2. *Association and familial co-aggregation of depression and endocrine-metabolic disorders, grouped as autoimmune and non-autoimmune diseases*

5.3.3 Quantitative genetic analyses

The phenotypic correlations between depression and autoimmune conditions were mostly explained by non-shared environmental factors; particularly, no evidence of shared genetic influences emerged in the association between depression and type 1 diabetes. In contrast, shared genetic risk factors appeared to be the main influences underlying the correlations between depression and non-autoimmune disorders.

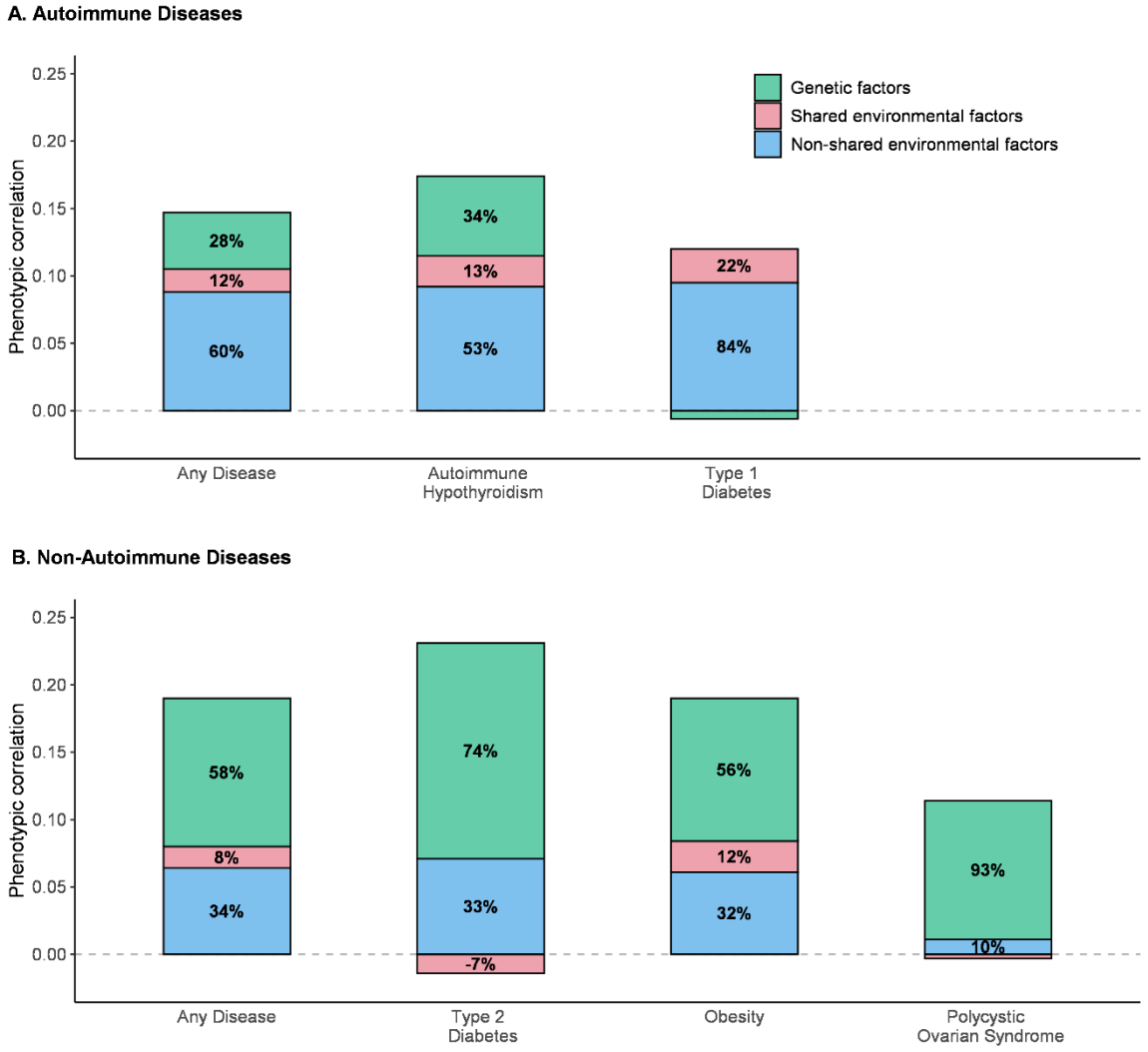

Figure 5.3.3. *Phenotypic correlations and contribution of additive genetic, shared, and non-shared environmental factors*

5.4 STUDY IV: MELATONIN USE AND THE RISK OF SELF-HARM AND UNINTENTIONAL INJURIES

In this Swedish register study of 25,575 children and adolescents who initiated a melatonin treatment between ages 6 and 18, females with psychiatric disorders displayed a reduced risk of intentional self-harm following melatonin-use initiation.

5.4.1 Descriptive characteristics of the study cohort

Females initiating melatonin-treatment were older than males, with a median [IQR] age of 15 [13-17], compared to 13 [9-16] in male individuals. A total of 87.2% participants received at least one psychiatric diagnosis by age 18. Attention-deficit hyperactivity disorder (ADHD) was the most prevalent diagnosis, particularly in males (53.9%; 66.5% male), followed by anxiety disorders (21.8%; 35.8% male) and depression (20.7%; 36.5% male).

Table 5.4.1. *Study cohort characteristics*

	Entire cohort		**Males**		**Females**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Study cohort	25,575	–	14,889	–	10,686	–
6-10 y at first melatonin prescription	6,840	(26.7)	5,021	(33.7)	1,819	(17.0)
11-14 y at first melatonin prescription	7,327	(28.7)	4,674	(31.4)	2,653	(24.8)
15-18 y at first melatonin prescription	11,408	(44.6)	5,194	(34.9)	6,214	(58.2)
≥1 psychiatric disorder between age 0-18	22,299	(87.2)	13,037	(87.6)	9,262	(86.7)
≥1 injury during follow-up	5,205	(20.4)	2,756	(18.5)	2,449	(22.9)
Body injuries	4,402	(17.2)	2,529	(17.0)	1,873	(17.5)
Falls	2,141	(8.4)	1,252	(8.4)	889	(8.3)
Intentional self-harm	1,053	(4.1)	212	(1.4)	841	(7.9)
Poisoning	938	(3.7)	219	(1.5)	719	(6.7)
Transport accidents	749	(2.9)	427	(2.9)	322	(3.0)
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age at first melatonin prescription, y	14	10-16	13	9-16	15	13-17
Age at first diagnosis of ADHD, y	11	8-15	10	8-14	14	10-16
Age at first diagnosis of ASD, y	11	8-15	11	7-14	13	9-16
Age at first diagnosis of depression, y	15	14-17	15	13-17	15	14-17
Age at first diagnosis of anxiety disorders, y	15	13-17	14	12-16	15	14-17

Abbreviations: *ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; y, years.*

5.4.2 Absolute risks

While the risks of body injuries (e.g., injuries to the head, shoulder, or wrist), falls, and transport accidents were comparable in the year before and after melatonin-treatment initiation, the IRs for self-harm and poisoning progressively increased during the last unmedicated months, peaking in the month immediately prior to medication initiation, and decreased right after. Females showed greater absolute risks than males.

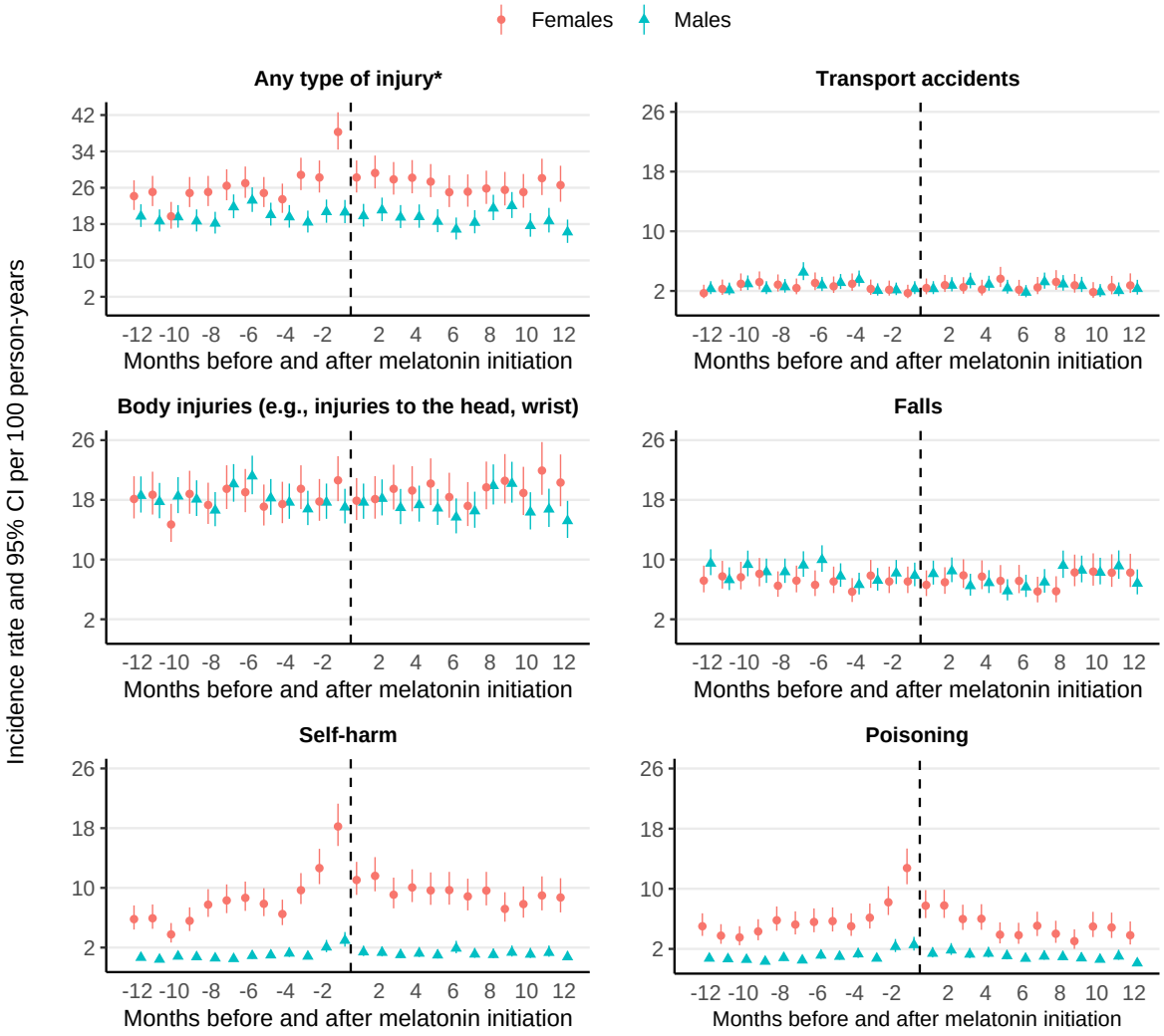

Figure 5.4.2. *Sex-specific incidence rate of different types of injuries in the year before and after melatonin-treatment initiation among children and adolescents with and without psychiatric disorders*

Note: **Y-axis range wider compared to other plots' range due to visualization purposes.*

5.4.3 Relative risks and sensitivity analysis

Compared to the last unmedicated month, the 12 months post medication initiation had decreased relative risks for self-harm and poisoning.

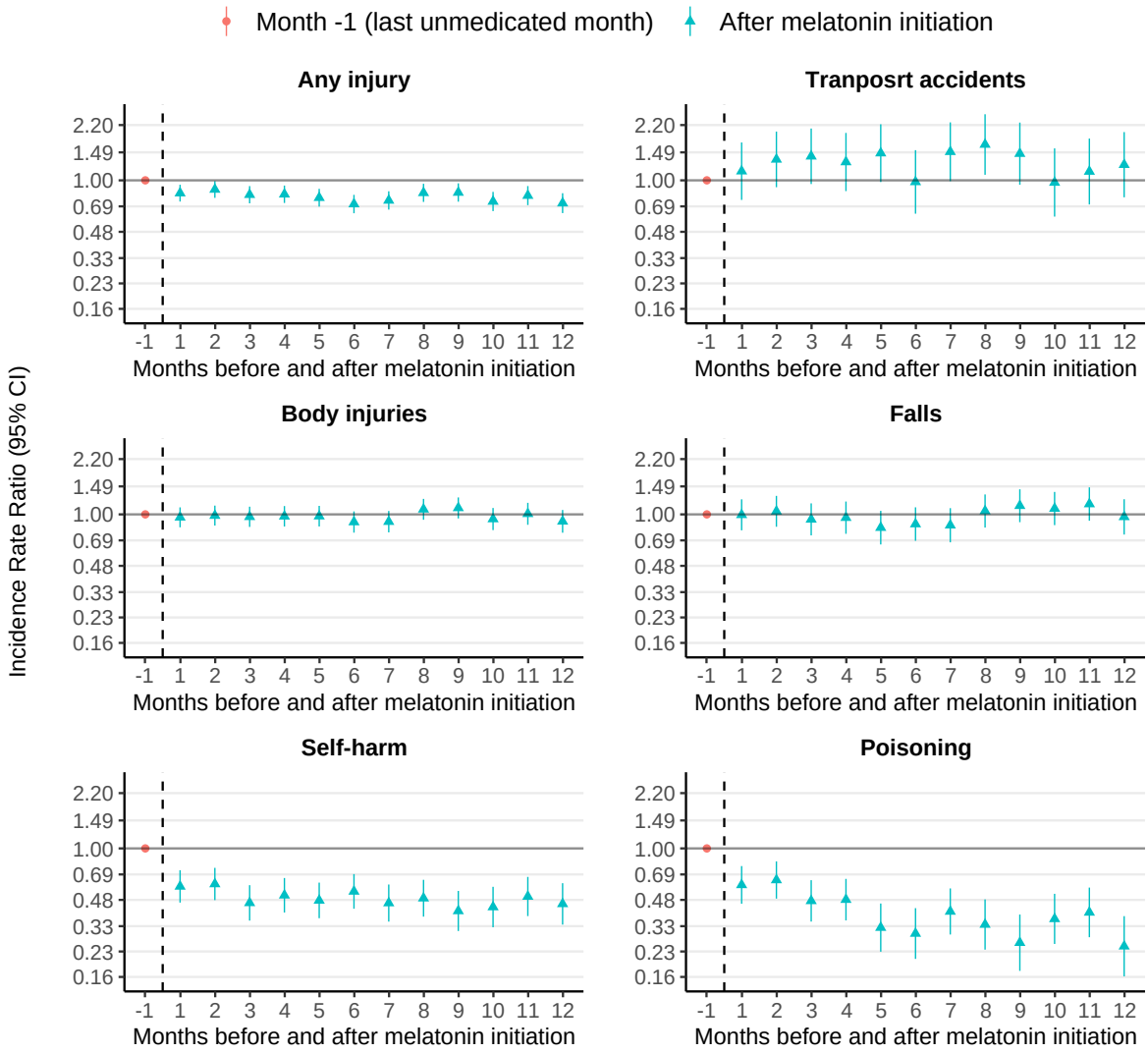

Figure 5.4.3. *Within-individual incidence rate ratios of injuries among children and adolescents in the 12 months after first melatonin initiation, using month –1 as the reference category*

These risk patterns were found to be driven by adolescent females with psychiatric disorders, especially depression and anxiety disorders.

Statistically significant decreased risks still persisted after excluding antidepressant users, with an IRR for self-harm among adolescent females with psychiatric disorders of 0.46 (95% CI, 0.27-0.76) in the month following melatonin-treatment initiation compared to the last unmedicated month.

6 DISCUSSION

6.1 MAIN FINDINGS AND IMPLICATIONS

The main findings of this thesis support that depression is related to a wide range of somatic conditions, including self-harm, infections, endocrine-metabolic disorders, and sleep disturbances. When exploring whether exposure to early-life infections could be linked to later depression and self-harm, we found no strong association after accounting for familial factors, suggesting that childhood infections may not be involved in the etiology of these adverse health outcomes. Further investigation of the comorbidity between depression and endocrine-metabolic conditions revealed that most of these associations are partly due to shared genetic influences, which could guide future research aiming to identify specific mechanisms contributing to risk of endocrine-metabolic disorders in people with depression and *vice versa*. Finally, given the established link between sleep disturbances, depression, and suicidal behavior, we explored whether treatment for sleep problems could be linked to a lower rate of injury in a young population with and without psychiatric disorders. Our findings show that melatonin use for the treatment of sleep disorders is associated with a decreased risk of self-harm in adolescent females with mental conditions, especially depression and anxiety disorders.

6.1.1 Depression and adverse health outcomes

In *Study I*, we observed increased risks of several medical conditions and of early death among individuals with youth depression compared to the general population. In particular, youth depression was a strong risk factor for sleep disorders and infections, as well as self-harm and other injuries, especially in females, and endocrine-metabolic disorders such as obesity and hypothyroidism, predominantly in males. In both sexes, depression was associated with all-cause mortality and all cause-specific mortalities, especially death by intentional self-harm. Adjusting for psychiatric comorbidity, particularly for substance use disorders and anxiety disorders, attenuated all the risks, indicating a substantial contribution of these co-occurring disorders to adverse outcomes. Nevertheless, associations of depression with various somatic diseases and premature mortality persisted, indicating that diagnoses of these comorbid disorders cannot fully explain the correlations.

This study presents new evidence of a link between youth depression, several diseases, and premature mortality, providing information on the role of different psychiatric comorbidities. Our findings suggest that young patients suffering from depression should be carefully monitored, even into their adult years, for self-harm behavior and potential health problems across numerous diagnostic domains.

6.1.2 Familial confounding explains the association between childhood infections and later depression and self-harm

In light of previous research reporting associations between infections, inflammation, and the immune system with increased risks of depression and suicide, *Study II* explored whether these

links exist when the exposure to infections happens during early developmental ages. This was based on the hypothesis that childhood could represent a sensitive time period during which infections may be more harmful, for example by disrupting central nervous system and immune system maturation, and impairing biological mechanisms involved in the development of depression and self-harm.

In an initial analysis adjusted for demographic characteristics (underlying age, sex, and birth year), severe childhood infections were associated with increased absolute and relative risks of later depression and intentional self-harm. Nevertheless, these associations attenuated when controlling for measured familial risk factors (i.e., parental history of mental illnesses and low SES), and further decreased when adjusting for unmeasured familial influences by comparing siblings discordant for exposure to infections; in this last model, no strong association persisted. These results suggest that measured and unmeasured familial risk factors, which may be of genetic and non-genetic origin, are linked to children's poor physical and mental health, potentially through biological and/or psychosocial mechanisms.

While these findings do not rule out a weak association between severe childhood infections and the observed outcomes, they do not provide strong evidence for a causal role of childhood infections in the etiology of later depression and self-harm. Moreover, this study highlights the importance of adjusting for familial confounding in similar observational studies, as well as of identifying the genetic and environmental risk factors shared between family members which appear to be common causes of both childhood infections and later depression and self-harm.

6.1.3 Shared etiology between depression and endocrine-metabolic disorders

In *Study III*, we further explored the comorbidity of depression and several endocrine-metabolic disorders. We reported convergent results across two complementary approaches: familial co-aggregation analysis and quantitative genetic modeling. First, we found evidence of a familial liability to the co-occurrence of these disorders: an increased risk of depression was observed in individuals with endocrine-metabolic diseases, compared to the general population, as well as in siblings of individuals with endocrine-metabolic conditions, compared to siblings of individuals without these disorders. Second, we disentangled genetic and environmental contributors to these comorbidities and found that, while the co-presentation of depression and type 2 diabetes, obesity, and polycystic ovarian syndrome were largely explained by shared genetic influences, the correlation between depression and type 1 diabetes was mainly due to non-shared environmental factors.

In line with prior research, this study suggests that shared biological mechanisms, such as immuno-inflammatory and metabolic dysregulations, may underlie the comorbidity of depression and some endocrine-metabolic disorders (i.e., type 2 diabetes, obesity, and polycystic ovarian syndrome) by increasing the risks of both conditions, and/or by acting as mediating factors in the causal link between these disorders. In contrast, the absence of shared genetics in the association between type 1 diabetes and depression may reflect the existence of

a direct link between these conditions through mediating factors (e.g., biological and psychosocial mechanisms connected to type 1 diabetes, including inflammation, cerebral damage, as well as stress and burden of this lifelong condition that is often diagnosed early in life and that requires a complex management regime for both patients and their families), and/or environmental factors influencing the risk of both conditions.

Overall, our results suggest that clinicians should be aware of increased risks of depression in individuals with endocrine-metabolic disorders and *vice versa*, and be vigilant for comorbid symptoms. Information on family history of these disorders may help identify risk factors for their co-occurrence. Furthermore, our findings indicate that different etiologies exist for these comorbid conditions, and highlight the need for tailored treatment strategies for individuals with co-occurring depression and different comorbid endocrine-metabolic conditions. This study also provides a useful foundation for future research aimed at identifying and targeting the biological mechanisms and modifiable risk factors underlying the co-presentation of endocrine-metabolic disorders and depression.

Altogether, findings from *Studies I*, *II*, and *III* have extended the boundaries of knowledge regarding the relationships between depression and somatic illnesses. *Study I* and *Study III* reaffirm the importance of collaboration between mental and somatic health professionals to comprehensively manage both psychiatric and somatic disorders and improve patient outcomes.

6.1.4 Melatonin use is associated with a decreased risk of self-harm

In *Study IV*, we estimated absolute and relative risks of injuries in the year prior to and following melatonin-treatment initiation in a pediatric population with and without psychiatric disorders. We found that the risk of intentional injury steadily increased in the months preceding melatonin-treatment initiation, peaking in the month immediately prior medication, and decreased thereafter. Analyses stratified by sex, age at melatonin-treatment initiation, and psychiatric comorbidities show that this risk pattern was mainly driven by female adolescents with depression and/or anxiety disorders. In this patient group, the relative risk of self-harm was attenuated in the year following medication initiation, compared to the last unmedicated month. Results were stable even after excluding antidepressant users, indicating that this medication did not entirely explain our results.

Although melatonin prescription could be an indicator that these young patients may also be receiving non-pharmacological treatments as well as closer monitoring from clinicians and care-givers, our results support the hypothesis that improving youth's sleep may be an important component to reduce self-injurious behavior in this pediatric population.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Measures

All work included in this thesis relies on register data, which involves several limitations that should be taken into account when interpreting the findings of these studies. First, information on outpatient care and dispensed pharmaceuticals is only available from 2001 and mid-2005, respectively, leading to a possible loss of early diagnoses and prescriptions for the youngest individuals in our studies. Second, using hospitalization and specialist care information from the NPR to identify psychiatric and somatic diagnoses may lead to mainly capturing the most severe cases, limiting the generalizability of the findings. This can be particularly true in the case of depression and other mental illnesses, given that the majority of psychiatric consultations for adult patients occurs in primary health care (~80%).[124] An additional concern of not being able to identify patients with mild symptoms who were diagnosed by general practitioners or who never seek help is that these individuals will inappropriately be classified as "unexposed", which could lead to an underestimation of the effect estimates when comparing participants with and without depression. Nevertheless, it is important to note that diagnoses of psychiatric and somatic disorders given to children and adolescents are well captured in the NPR, since it is standard for the pediatric population to be referred to specialist health care, including general pediatrics and child psychiatry clinics.

In *Study II*, we attempted to identify mild and moderate forms of depression by adding information on antidepressants from the Swedish Prescribed Drug Register. However, since we did not have information on prescription indications, there could have been misclassification of some depression patients given that a high proportion of these medications are indicated for other medical conditions.[124-126]

With regards to the diagnostic validity of depression in the NPR, this has been reported to be fair to moderate (Cohen's kappa –κ– of 0.32; 88% full agreement with patients' medical records),[104] meaning that there could be a few instances where participants coded as depression patients did not meet the criteria for that diagnosis. In this scenario, one possible solution to decrease misclassification is to include only patients with at least two recorded depression diagnoses, although this approach has the disadvantage of reducing sample size and, therefore, statistical power.

Diagnoses of depression for children and adolescents have not been yet validated in Swedish registers. Nevertheless, this has been recently examined in the Danish Psychiatric Central Research Register.[127] The authors of this study reported a satisfactory diagnostic validity of pediatric depression (overall agreement of 72.8% between raters and ICD-10 diagnoses in the register), which increased steadily over the last two decades, and which was higher for patients treated with antidepressants but lower for patients diagnosed in the emergency department. Given the similarity between Denmark and Sweden, the findings from this study support the use of data from the Swedish NPR and PDR to identify children and adolescents with depression.

Another limitation when measuring depression from national registers is that no information on symptoms is available, which prevents research on depression subtypes.

In *Study IV*, we used melatonin prescriptions as proxies for treatment of sleep disorders in children and adolescents. Although we were able to capture all melatonin dispensations within the country, we couldn't establish treatment compliance. Also, others factors that could have influenced our results were not considered, including non-pharmacological treatments (e.g., psychotherapeutic and behavioral interventions) or prescriptions of other types of hypnotic drugs (e.g., z-drugs and sedating antihistamines), although medicines other than melatonin are rarely prescribed to the pediatric population due to side effects and risks of overdose.[128]

Finally, the generalizability of our findings outside Sweden may vary. For example, this is likely to be high for other Nordic countries, which have similar demographics as well as virtually free and equal access to health care; however, patterns of psychiatric and somatic comorbidity may vary in other countries, particularly in those with different health care and socioeconomic structures.

6.2.2 Methods

In *Studies I, II*, and *III* we used Cox proportional hazards regression model, which assumes that risks are constant over follow-up time. However, this is rarely the case, making the interpretation of results challenging when a single HR (averaged over the duration of the study's follow-up) is reported. In other words, the average HR may be uninformative because the distribution of events during the follow-up is not taken into account and, therefore, the effect magnitude may substantially differ depending on the duration of follow-up.[129] A naïve alternative would be to estimate period-specific HRs in an attempt to capture the potentially time-varying magnitude of the effect; however, period-specific HRs have a built-in selection bias.[130, 131] To overcome these limitations, in *Study II* we allowed the follow-up time to increase by 1 year and estimated time-updated HRs. In this way, we explored how a consecutively increased follow-up time could influence the HRs.

Another aspect to take into consideration in time-to-event analyses is the handling of competing risks, which are events preventing the outcome of interest from occurring. For example, when studying outcomes other than mortality, death is an event that competes with the events of interest. Ignoring competing risks may lead to biased estimates of the cumulative incidence risks (i.e., absolute risks). Our studies, however, included relatively young cohorts, meaning that the impact of death as a competing risk may have been minimal.

Study I relied on diagnostic records to explore the risks of somatic disorders following youth depression. However, the timing of diagnoses does not provide definitive information about when health problems occurred, encouraging caution when interpreting the findings.

Study III assumes that full- and maternal half-siblings share common aspects of rearing environment to the same degree (i.e., equal environment assumption), which may be an over simplification. However, previous studies using Swedish tax records showed that nearly all

full- and maternal half-siblings were registered to the same household while growing up.[114] Other key assumptions of quantitative genetic analyses used in *Study III* are that assortative mating does not make full-siblings share more than 50% of their segregating alleles, that genetic influences operate additively, and that there are no correlations or interactions between genes and environment.[132]

Studies II and *IV* used within-cluster comparison to adjust for cluster-constant confounders. In these models, only clusters with variation in the included covariates are informative for the analysis, which may affect the generalizability of the findings and the precision of the estimates. Additionally, the design assumes no carryover effects within the cluster. For example, in the case of the within-sibling design used in *Study II*, exposure and outcome status of one individual should not influence exposure and outcome status of his/her siblings. When this assumption does not hold, carryover effects may lead to bias.[133] In this regard, there is the possibility that exposure to childhood infections in one individual could have affected the infection status of the siblings, although this was less probable when analyzing non-contagious infections. Furthermore, two common sources of bias in the sibling-comparison design have been described: confounding by factors not perfectly shared by siblings, and random measurement error related to exposure measurement.[115] The first source of bias relates to the fact that, although within-cluster comparison controls for all factors shared by the members of a cluster, this design does not adjust for confounders that vary within the cluster. For example, in *Study II* characteristics of the parents and/or of the offspring related to birth, such as parental age at childbearing or birth weight, may increase vulnerability to both infections during childhood and later depression or self-harm. The second source of bias, random measurement error of exposure, could lead to greater attenuation of within-pair associations than corresponding unpaired associations, even in the absence of confounding. Thus, results from sibling comparisons should be interpreted in light of these limitations.

Study IV used a within-individual approach to adjust for time-constant confounders when comparing the risk of injury preceding and following melatonin-treatment initiation. Similar to the limitations of *Study II*, in *Study IV* we could not adjust for time-varying factors around the initiation of medication use, such as non-pharmacological treatments (e.g. psychotherapy). In addition, this design assumes that the outcome of interest does not affect whether a person receives the medication,[134] which is likely to be violated in *Study IV* since it can be expected that some patients were prescribed melatonin because of a self-harm event (i.e., confounding by indication). Consequently, risk reduction calculated using the last unmedicated month as the reference period may be biased downward (i.e., stronger risk reduction than it actually is), since the occurrence of a self-harm event may have selected individuals into medication treatment. However, given that self-harm and sleep disturbances are closely associated,[135] it is plausible that patients will receive treatments for sleep problems in temporal proximity to a self-injurious event; therefore, using the last unmedicated month as the reference category may be more relevant than using other prior months.

Other limitations related to the within-individual approach used in *Study IV* are: i) the assumption that prior events do not affect the occurrence of further events may not hold, given that previous suicide attempts are risk factors for later attempts;[136] ii) it was not possible to investigate the risk of self-harm among patients who had no prior history of such events preceding treatment initiation; iii) individuals who died by injury prior to medication initiation could have not been included in the study because this design requires participants to have survived until melatonin-treatment initiation, possibly leading to upward-biased estimates (i.e., lower risk reduction than the actual amount).

6.3 FUTURE DIRECTIONS

Many questions regarding the etiology and pathophysiology of depression remain unresolved. One of the highest priorities in the field should be to dissect the heterogeneous clinical picture of depression, for example by examining symptom profiles, age at first onset, severity, recurrence, duration of depressive episodes, genetic background, psychiatric and somatic comorbidity, and treatment response. In addition, identifying the underlying mechanisms responsible for gender differences in prevalence, incidence, and course of depression is of particular importance.

Research relying on national registers will benefit from including primary care data, which will enable identification of patients with less severe forms of somatic and psychiatric disorders, enhancing the generalizability of the findings and reducing diagnostic misclassification.

Overall, such research efforts may elucidate the etiological complexity of depression, facilitating the discovery of specific biological pathways associated with certain symptom patterns or subtypes of a disorder, and contributing to the development of better prevention strategies and personalized treatments for patients.

6.4 ETHICAL CONSIDERATIONS

6.4.1 Project overview

All studies included in this project use data from several Swedish national registers, which have been linked using the unique personal identification number (PIN) assigned to every Swedish resident. Linkage of data across registers was approved by the Regional Ethical Review Board in Stockholm in 2013, and the approval has been updated as required.

6.4.2 Research with registers

Medical research involving human subjects should be conducted only when no other alternative means or methods exist to achieve similar results, and only if human rights are guaranteed at all times.[137] Although most registry-based research does not involve direct contact with the study participants, these types of studies rely on the handling of personal data (which encompasses all types of information that directly or indirectly relate to an identifiable living individual) and sensitive personal data (e.g., medical records). Therefore, in line with the Personal Data Act in Sweden (PUL) and the European General Data Protection Regulation

(GDPR), several ethical aspects need to be taken into account, and strict rules should be followed while conducting research. First of all, there is a risk of breaching the identity and infringing upon the integrity of the research subjects, if the data would be accessed by non-researchers or used inappropriately. As a consequence, before a new research project is initiated it is essential to carefully weigh its potential benefit against risks and costs associated with the use of personal sensitive data. Processing of this data should always follow basic principles such as, lawfulness, fairness and transparency, purpose limitation, and data minimization. Additionally, every precaution should be considered in order to protect privacy and confidentiality of the study participants and their personal information at all times. One way to ensure this is through the use of pseudonymized data, which enables linkage of subject individuals to new data and to different registers with the use of a key (i.e. a serial number) rather than the PIN. In this way, all data are de-identified and not recognizable at an individual level. Usually, researchers have no access to the original PIN since the key file is stored elsewhere, most of the time at the government agency owning the data. Another way to minimize potential harm is by guaranteeing that confidential data are properly stored and not accessible to non-researchers. Moreover, throughout the entire study, research documentation should be kept at all stages to facilitate the researchers' work, to minimize the risk of illegal handling and loss of data, and to meet legal requirements and local guidelines.[94]

Another ethical issue relates to informed consent. As it stands today, no prior informed consent from the study participants is required when conducting medical research on data from registers. Although this could be considered a breach of privacy, it should be taken into account that processing personal data is allowed when the research is necessary in order to perform a task in the public interest. In fact, it could be argued that epidemiological studies benefit the population as they support public health and provide guidelines for healthcare.[92]

6.4.3 Psychiatric epidemiology

Research in the area of psychiatry should take into consideration the protection of human rights and dignity of people suffering from mental disorders. As this area is still stigmatized, especially in some countries, it is essential to conduct psychiatric research and communicate its findings in a sensitive way in order to increase awareness and acceptance, promote inclusion and diversity, and decrease blame and stigma for affected families.

6.4.4 Communication of results

It is crucial to consider the most appropriate way to clearly disseminate research findings in a meaningful and informative way among the scientific community, clinicians, affected patients, the press, and the general public. For example, it should be carefully communicated that associations estimated in observational studies do not necessarily imply causation, since in most cases these study designs do not enable to establish a cause-and-effect relationship between two events or variables. Also, when conveying findings on genetic liability to psychiatric and somatic disorders it is critical that genetic influences are not interpreted as deterministic. Overall, adequate science communication is of critical importance to avoid

misinformation and misunderstandings, which can have unfortunate medical and public policy consequences or damage public trust in science.

7 CONCLUSIONS

The work presented in this thesis provides new insights into childhood, adolescent, and adult depression. We showed that individuals receiving a diagnosis of depression at an early age display increased risks of extensive later comorbidity and mortality, particularly death by self-harm, highlighting the significant contribution of this mental disorder to the burden of disease.

Familial confounding explained the association between childhood infections and later depression and self-harm, suggesting that exposure to early-life infection may not be involved in the etiology of later depression and self-harm, and emphasizing the importance of identifying these familial risk factors, which may serve as targets for interventions.

Partially overlapping etiological factors, of genetic and non-genetic origin, were found to explain the comorbidity between depression and various endocrine-metabolic disorders, which could guide future research aiming at identifying pathophysiological mechanisms and key targets for prevention and treatment.

Finally, we showed that melatonin treatment for sleep problems in youth appeared to considerably decrease the risk of self-harm among females with depression and anxiety disorders, supporting the hypothesis that improving sleep may be an important component for reducing self-injurious behavior in this pediatric population.

Overall, these studies underscore the urgent need for prevention and early intervention of depression in young patients, as well as for adequate health care resources to manage and treat this mental illness and its psychiatric and somatic comorbidities.

8 APPENDIX

Appendix Table. *Diagnostic classification of the somatic diseases examined in this thesis*

Type of disease	ICD Version	Diagnostic code
Infections		
Gastrointestinal	ICD-8	000-009, 014, 039.92, 127.99, 522.50, 527.30, 528.00, 528.30, 540.00-540.99, 562.00, 562.19, 566.00-566.01, 567.00-567.02, 569.00, 572.99, 577.01
	ICD-9	001-009, 014, 123, 127, 129, 136E-F, 522E, 522H, 526E, 527D, 528A, 528D, 540A-X, 562-B, 566, 567-C, 569F, 575A
	ICD-10	A00-A09, B68, B69, B70, B71, B77-B82, B83.8, K04.4-K04.7, K10.2, K11.3, K12.1, K12.2, K35, K57, K61, K63.0, K65, K81, M02.1, T62.9
Septicaemia	ICD-8	038.00-038.99, 782.9
	ICD-9	038A-X, 785F
	ICD-10	A40-A41
Genitourinary	ICD-8	016, 054.02, 090-099, 590.00-590.99, 595.00-595.02, 597.00, 599.02, 601.00, 604.00, 604.01, 607.30, 611.00, 611.01, 612.01-614.99, 616.00-616.03, 620.00-620.99, 622.00-622.19, 629.40
	ICD-9	016, 054B, 090-099, 112B-C, 131A, 590-X, 597A, 595-X, 597W, 599A, 601-D, 603B, 604A, 604X, 607B-C, 608A-E, 611A, 614-X, 615A-X, 616-X
	ICD-10	A18.0-18.1, A50-64, A70-74, B37.3-37.4, N10-12, N13.6, N15.1, N15.9, N30-30.3, N30.8-30.9, N34-34.1, N39.0, N41-41.3, N43.1, N45.0-45.9, N48.1-48.2, N49-49.9, N61, N70-76.8, N98.0
Skin infections	ICD-8	017.01-017.09, 050-057, 110-111, 680.00-680.90, 681.00-682.99, 684.00-684.09, 686.00-686.98
	ICD-9	017A, 031B, 050-057, 074D, 091D, 110-111, 112D, 681-682X, 683, 684, 685-686X, 680A
	ICD-10	A18.4, A20.0, A22.0, A26.0, A31.1, A32, A36.3, B00-B09, B35-36, B37.2, B43.0, B43.2, B45.2, B46.3, B55.1, L00-L08, L30.3, L70.0
Viral hepatitis	ICD-8	070
	ICD-9	070A-X
	ICD-10	B15-B19
Central nervous system	ICD-8	013.00-013.99, 027.01, 036.00, 040.00-043.99, 045.00-046.99, 052.00, 054.04, 062.00-065.99, 071.99, 072.01, 075.02, 079.20, 084.00, 094.00-094.98, 320.00-320.80, 320.88-320.99, 322.00-322.03, 392.99, 474.99
	ICD-9	006F, 013-X, 036A-B, 045-049X, 052B, 053A, 054D, 055A, 056A, 071, 072B-C, 090E, 094-X, 320-X, 321A, 321B-H, 321W, 323A, 323C-D, 324-X, 392-X
	ICD-10	A06.6, A17-17.9, A20.3, A22.8, A32.1, A39.0, A80-89, B00.3-00.4, B01.0-01.1, B02.0-02.1, B05.0-05.1, B06.0, B26.1-26.2, B37.5, B38.4, B43.1, B45.1, B46.1, B50.0, B57.4, B58.2, B60.2, B69.0, B83.2, G00-00.9, G01, G02.0-02.8, G04, G04.2, G04.9, G05.0, G05.1, G05.2, G06.0-6.2, G07, I02-02.9
Respiratory	ICD-8	010-012, 020.10, 460.99, 461.00-461.09, 462.01, 462.02, 462.09, 463.01, 463.09, 464.01-464.09, 465.99, 466.99, 470.99-473.99, 480.99, 481.99-482.98, 483.99-486.09, 490.99-491.09, 501.99, 502.00-503.09, 508.00-508.03, 510.01-510.09, 511.10, 513.99, 519.92
	ICD-9	010-012W, 031A, 033-034B, 052A, 055B, 112E, 122B, 460-466, 466-B, 473-X, 475, 480-X, 481-482X, 483, 485, 486, 487-W, 490, 491B, 510-X, 511B, 513-B
	ICD-10	A15-16, A20.2, A21.2, A22.1, A31.0, A37, A38, A48.1, B00.2, B01.2, B05.2, B27, B37.1, B39-42, B44, B45.0, B46.0, B58.3, B59, J00-J22, J32, J34.0, J35.0, J36, J37, J39.0-39.1, J40-42
Infections related to pregnancy	ICD-8	630.00-630.09, 635.00-635.99
	ICD-9	646F, 646G, 646W, 674D
	ICD-10	O23, O26.4, O85-O86
Immune dysfunction		
Disorders involving the immune mechanism	ICD-8	135.97-135.99, 275.10, 275.98, 289.00-289.99
	ICD-9	135, 273A-C, 277G, 279, 289W
	ICD-10	D80-D89

Appendix Table. *Diagnostic classification of the somatic diseases examined in this thesis (continued)*

Type of disease	ICD Version	Diagnostic code
Autoimmune diseases		
Other hypothyroidism	ICD-8	243.99, 244.00-244.09
	ICD-9	243, 244D, 244W, 244X
	ICD-10	E03
Thyrotoxicosis (includes Graves' disease)	ICD-8	242.00-242.20
	ICD-9	242A-X
	ICD-10	E05
Hashimoto's thyroiditis	ICD-8	-
	ICD-9	245C
	ICD-10	E06.3
Type I diabetes	ICD-8	250.00-250.09
	ICD-9	250A-X
	ICD-10	E10
Crohn's disease	ICD-8	563.00
	ICD-9	555A-X
	ICD-10	K50
Ulcerative colitis	ICD-8	563.10
	ICD-9	556
	ICD-10	K51
Psoriasis	ICD-8	696.00-696.19, 696.98
	ICD-9	696A-B, 696W
	ICD-10	L40
Rheumatoid arthritis	ICD-8	712.00-712.50
	ICD-9	714A-X
	ICD-10	M05-06
Coeliac disease	ICD-8	269.00
	ICD-9	579A
	ICD-10	K90.0
Endocrine and metabolic disorders		
Disorders of thyroid gland (excludes "Other hypothyroidism" and "Thyrotoxicosis")	ICD-8	240.00-241.99, 245.00-246.99
	ICD-9	240A-X, 241A-X, 245A-X, 246A-X
	ICD-10	E00-E02, E04, E06.0-E06.2, E06.4-E06.9, E07
Type II diabetes	ICD-8	250.00-250.09
	ICD-9	250A-X
	ICD-10	E11
Other disorders of glucose regulation and pancreatic internal secretion	ICD-8	251.01-251.09
	ICD-9	251A-X
	ICD-10	E15-E16
Disorders of other endocrine glands	ICD-8	246.99, 252.00-258.99, 269.90-269.99, 273.40, 626.99
	ICD-9	244X, 246X, 252A-X, 253A-X, 254A-X, 255A-X, 256A-X, 257A-X, 258A-X, 259A-X, 275E, 269X, 626W, 783E
	ICD-10	E20-E35
Obesity and other hyperalimentation	ICD-8	277.99, 278.99
	ICD-9	278A-W
	ICD-10	E65-E68
Nervous system diseases		
Extrapyramidal and movement disorders	ICD-8	306.20, 331.1-331.99, 333.00-333.99, 350.00, 733.90, 780.30-780.49, 781.60-781.69, 787.10
	ICD-9	333A-X, 344W, 351W, 781D
	ICD-10	G23-G26
Epilepsy	ICD-8	345.00-345.99
	ICD-9	333C, 345, 348D
	ICD-10	G40-G41
Migraine	ICD-8	346.00, 346.09
	ICD-9	346A-X
	ICD-10	G43
Other headache syndromes	ICD-8	305.98, 305.99, 346.01, 346.09, 791.99
	ICD-9	307W, 346C, 784A
	ICD-10	G44
Sleep disorders	ICD-8	306.40, 347.90-347.99, 519.90-519.98, 780.60, 783.20-783.29
	ICD-9	307E, 347, 348W, 349W, 780F, 786A
	ICD-10	G47

Appendix Table. *Diagnostic classification of the somatic diseases examined in this thesis (continued)*

Type of disease	ICD Version	Diagnostic code
Eye diseases		
Conjunctivitis	ICD-8	360.00-360.09
	ICD-9	372A-D, 372G
	ICD-10	H10
Circulatory system diseases		
Hypertensive diseases	ICD-8	400.00-404.99
	ICD-9	401-405
	ICD-10	I10-I15
Paroxysmal tachycardia	ICD-8	427.90-427.99
	ICD-9	427A-C, 427W
	ICD-10	I47
Atrial fibrillation and other cardiac arrhythmias	ICD-8	426.01-426.09, 427.90-427.99
	ICD-9	426A, 427D-E, 427G, 427W-X
	ICD-10	I48-I49
Cerebrovascular diseases	ICD-8	356.00-356.09, 430.90-430.99, 431.90-431.99, 432.00-432.99, 433.99, 434.99, 436.00-436.99, 437.99, 438.99, 440.20
	ICD-9	344W, 352G, 430, 431, 432A-X, 433A-X, 434A-X, 436, 437A-X
	ICD-10	I60-I69, G45, G46
Peripheral vascular diseases	ICD-8	421.00, 440.00-443.10, 443.88-443.99, 444.00-444.10, 444.40-444.99, 447.00-447.09
	ICD-9	421A, 440A-X, 441A-G, 442A-X, 443A-X, 444A-X, 447A-X
	ICD-10	I70, I71, I72, I73, I74, I77
Respiratory system diseases		
Asthma	ICD-8	493.00-493.09
	ICD-9	493A-X
	ICD-10	J45, J46
Cough and abnormalities of breathing	ICD-8	460.99, 519.91-519.98, 783.20-783.30, 783.60
	ICD-9	460, 784X, 786A-C, 786W-X
	ICD-10	R05, R06
Symptoms and signs involving speech and voice (e.g. dyslexia)	ICD-8	306.10, 780.70-780.79, 781.50-781.69, 783.50-783.59,
	ICD-9	315B, 784D-G, V40,
	ICD-10	R47-R49
Digestive system diseases		
Diseases of stomach and duodenum	ICD-8	531.00-537.08
	ICD-9	531-X, 532-X, 533-X, 534-X, 535-X, 536-X, 537-X, 569W
	ICD-10	K25-K31
Diseases of appendix	ICD-8	540.00-542.08
	ICD-9	540-X, 541, 542
	ICD-10	K35-K37
Liver disease	ICD-8	571.00-571.99, 573.00-573.09, 575.00-575.05
	ICD-9	571-X, 573D, 573W, 576B
	ICD-10	K70.0-K70.3, K70.9, K71, K73, K74, K76.0, K76.9
Cholelithiasis	ICD-8	574.00-574.09
	ICD-9	574-F
	ICD-10	K80
Cholecystitis, and other diseases of gallbladder and biliary tract	ICD-8	575.00-576.09
	ICD-9	575A-X, 576B-X
	ICD-10	K81-K83
Acute pancreatitis	ICD-8	577.00-577.09
	ICD-9	577A
	ICD-10	K85

Appendix Table. *Diagnostic classification of the somatic diseases examined in this thesis (continued)*

Type of disease	ICD Version	Diagnostic code
Skin and subcutaneous tissue diseases		
Dermatitis and eczema	ICD-8	686.00-686.99, 691.00-692.70, 692.90-692.99, 695.90-695.99, 696.30, 696.58-696.59, 697.98-697.99, 698.00-698.30, 698.91-698.99, 701.90-701.98, 705.90-705.99
	ICD-9	686W, 691A-W, 692A-X, 693A-X, 694W, 695W, 696D-F, 697X, 698A-D, 698W-X, 701W, 705W, 709W-X
	ICD-10	L20-L30
Papulosquamous disorders	ICD-8	110.00, 686.00-686.98, 693.99, 696.00-696.40, 696.98, 697.00, 697.98-697.99
	ICD-9	110A, 686W, 694D, 696A-E, 696W, 697A-B, 697W, 697X
	ICD-10	L40-L45
Urticaria and erythema	ICD-8	692.90-692.99, 695.00-695.20, 695.90-695.99, 708.90-708.99, 709.9
	ICD-9	693W, 695A, 695C, 695W-X, 708A-X, 709W
	ICD-10	L50-L54
Other disorders of the skin and subcutaneous tissue	ICD-8	136.01-136.09, 686.10-686.11, 695.20, 695.40, 695.90-695.99, 696.20-696.29, 701.00-701.01, 701.20-701.98, 709.00-709.09
	ICD-9	136A, 250H, 686B, 695C, 695E, 695W, 696C, 701A, 701D-F, 701W-X, 709B-E, 709W
	ICD-10	L90-L95
Musculoskeletal system and connective tissue diseases		
Arthropathies	ICD-8	711.00-712.00, 712.20-712.39, 713.00-713.09, 714.00-716.00, 723.90-724.99, 727.10, 727.70-727.99, 730.99, 732.99, 733.90-733.98, 736.99, 787.00-787.60
	ICD-9	710D, 711A, 711X, 712W-X, 714A-719, 726X, 727B, 728E, 728W-X, 733X, 734-736, 738W
	ICD-10	M00-M25
Systemic connective tissue disorders	ICD-8	136.01-136.09, 446.00-447.09, 686.90-686.98, 715.99-716.10, 717.98-717.99, 733.90-734.99
	ICD-9	136B, 446A-H, 447G, 447W, 710A-X, 716X, 725, 728G, 729D-E, 729X
	ICD-10	M30-M36
Dorsopathies	ICD-8	712.40, 713.10-713.20, 714.90-714.98, 715.99, 717.20-717.98, 720.00, 720.29, 722.00-722.09, 722.88, 723.00, 723.90-723.99, 725.00-726.99, 728.00-728.20, 728.40-728.70, 728.98-728.99, 733.90-733.98, 735.99, 756.10-756.20, 756.80
	ICD-9	720-724, 728E, 729C, 730A, 730C, 732A, 732W, 733A-B, 733X, 737A-D, 737W-X, 738E-G, 756B
	ICD-10	M40-M54
Soft tissue disorders	ICD-8	717.98, 732.99, 733.10-733.98, 787.10-787.20
	ICD-9	359X, 723H, 726X, 727A, 727D-X, 728A-D, 728W-X, 729B, 729W
	ICD-10	M60-M68
Genitourinary system diseases		
Moderate to severe renal disease	ICD-8	403.99, 404.99, 580.99, 581.99, 582.00-583.99, 590.00-590.02, 590.98-590.99, 593.10, 593.30
	ICD-9	403A-X, 404A-X, 580A-X, 581A-X, 582A-X, 583A-E, 583W-X, 584F, 590A, 590W, 599H
	ICD-10	I12, I13, N00-N05, N07, N11
Urolithiasis (calculus on kidney, ureter and lower urinary tract)	ICD-8	592.00-594.08
	ICD-9	592A-X, 593X, 594A-X
	ICD-10	N20-N21
Diseases of male genital organs	ICD-8	601.00-605.09, 607.00-607.98
	ICD-9	601A-D, 601W-X, 602A-X, 603A-X, 604A-X, 605, 607A-X, 608A-C, 608E-W
	ICD-10	N41-N49
Female infertility	ICD-8	628.00-628.01
	ICD-9	628A, 628C-X
	ICD-10	N97

Appendix Table. *Diagnostic classification of the somatic diseases examined in this thesis (continued)*

Type of disease	ICD Version	Diagnostic code
Diseases during pregnancy and perinatal period		
Oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium	ICD-8	634.9, 636.0, 637.0, 637.1
	ICD-9	642A, 642B, 642C, 642D, 642E, 642F, 642AG, 642H, 642X, 646B, 646C
	ICD-10	O10-O16
Haemorrhage in early pregnancy	ICD-8	632.00-632.99
	ICD-9	640A-X
	ICD-10	O20
Excessive vomiting in pregnancy	ICD-8	638.00-638.99
	ICD-9	643A-X
	ICD-10	O21
Maternal care for other conditions predominantly related to pregnancy	ICD-8	634.90, 636.00-636.09, 639.00-639.09, 639.9, 661.00-661.89
	ICD-9	646B-X, 648X, 669C, V45F
	ICD-10	O26
Injuries		
Injuries of different body regions	ICD-8	800.00-939.00, 950.00-959.92
	ICD-9	800-939X, 950-959X
	ICD-10	S00-T14
Burns and corrosions	ICD-8	940.00-949.91
	ICD-9	940-949
	ICD-10	T20-T32
Poisoning by drugs, medicaments, biological substances (includes overdose and wrong substance given or taken in error) & non-medicinals (e.g. alcohol etc.)	ICD-8	960.00-989.98
	ICD-9	005X, 960A-989X
	ICD-10	T36-T65
Physical abuse and assault	ICD-8	E961-E969
	ICD-9	995F, E961-E969
	ICD-10	T74.1, X85-Y09, Y87.1
Sexual abuse and assault	ICD-8	E960
	ICD-9	E960, V71F
	ICD-10	T74.2, Y05
Transport accidents	ICD-8	E800-E845
	ICD-9	E800-E849
	ICD-10	V01-V99, Y85
Falls	ICD-8	E880-E887
	ICD-9	E880-E888
	ICD-10	W00-W19
Accidental poisoning by noxious substances	ICD-8	E850-E877
	ICD-9	E850-E869
	ICD-10	X40-X49
Intentional self-harm	ICD-8	E950-E959
	ICD-9	E950-E959
	ICD-10	X60-X84, Y87.0
Event of undetermined intent	ICD-8	E980.9-E989.9
	ICD-9	E980-E989
	ICD-10	Y10-Y34, Y87.2

Note: *Study I* investigated all the disease listed in the Appendix Table;
Study II looked at the infection group (excluding viral hepatitis);
Study III focused on some endocrine and metabolic disorders;
Study IV explored injuries.

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