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RISK FACTORS AND HEALTH CONSEQUENCES OF OBSESSIVE-COMPULSIVE AND CHRONIC TIC DISORDERS

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ABSTRACT

Background: Obsessive-compulsive disorder (OCD) is a severe and heterogenous mental disorder characterized by intrusive thoughts, urges or images, followed by repetitive behaviors aimed to reduce the associated anxiety. Tic disorders are neurodevelopmental movement disorders consisting of recurring, involuntary, rapid, and sudden non-rhythmic motor movements or vocalizations. While OCD affects approximately 2% of the population and tic disorders affect about 1% of the population, a much smaller proportion of individuals seek help and come into contact with health services. Both disorders are associated with considerable distress and impairment. Little is known about the etiology and long-term health consequences of OCD and tic disorders. Tic-related OCD may constitute a biologically meaningful subtype of OCD but current evidence supporting this is incomplete.

Aims: The overarching aims of the studies in this thesis are:

- to synthesize the literature on potential environmental risk factors for OCD,
- to identify perinatal risk factors that may be in the causal pathway to OCD and tic disorders,
- to examine the validity of tic-related OCD as a potentially meaningful subtype of OCD, and
- to examine the risk of metabolic and cardiovascular disorders in individuals with OCD and tic disorders.

Methods: In study I we conducted a systematic review of potential environmental risk factors for OCD following the PRISMA guidelines.

In studies II and III, we used population-based birth cohorts to estimate the risk of OCD and tic disorders in individuals with a range of perinatal events, including maternal smoking during pregnancy, labor presentation, obstetric delivery, gestational age, birth weight, Apgar score, and head circumference, compared to the unaffected general population.

In study IV, we used a birth cohort to estimate the risk of OCD in relatives of individuals with OCD with and without comorbid tics, compared to relatives of unaffected individuals.

In studies V and VI, we used total population cohorts to estimate the risk of metabolic and cardiovascular disorders in individuals with OCD or tic disorders, compared to the unaffected general population.

Studies II, III, V, and VI applied sibling comparison designs to further control for shared familial confounding, and the role of other co-occurring psychiatric conditions was systematically evaluated. All studies adjusted for measured confounders.

Results: Including 128 studies of environmental risk factors for OCD, study I found that the methodological limitations of these studies precluded drawing strong conclusions. However,

the systematic review identified several promising areas of potential risk factors, which could be considered as reasonable starting points for further research.

Studies II and III found that several adverse perinatal events were associated with an increased risk of OCD and tic disorders, independent from measured confounders and unmeasured familial confounding. These perinatal events included breech presentation, cesarean section, preterm birth, low birth weight. Maternal smoking during pregnancy emerged as a potentially specific risk factor for OCD. A cumulative pattern was also found, whereby the greater the number of adverse perinatal events, the greater the risk for OCD and tic disorders.

Study IV found that relatives of individuals with tic-related OCD are at higher risk of having OCD themselves than relatives of individuals with non-tic-related OCD, independent of age at first OCD diagnosis. The same pattern was not observed, when we created additional subgroups based on other neuropsychiatric comorbidities, like ADHD or autism spectrum disorders (ASD). The results confirm the hypothesis that individuals with history of tics constitute a particularly familial subtype of OCD.

Studies V and VI found that both OCD and tic disorders are associated with increased risks of metabolic and cardiovascular disorders in general, and with obesity, type 2 diabetes mellitus, and circulatory system diseases in particular. The risks were considerably higher in individuals with tic disorders than in those with OCD, but were significantly reduced in the sibling comparisons.

Conclusions: Study I proposed a roadmap for future research of environmental risk factors for psychiatric disorders to improve upon the methodological limitations of previous studies. The road map emphasized using prospective longitudinal data at the population level, using standardized measures, and applying genetically informative study designs.

Following the plan suggested in study I, studies II and III found a range of perinatal risk factors for OCD and tic disorders, independent of familial confounding. Dose-response associations were also observed for the number of adverse perinatal events, in that the greater the number of events, the greater the risk for either disorder. This cumulative effect provides some hope that, in the future, it may be possible to derive environmental risk scores for these disorders.

Study IV found that tic-related OCD is a particularly familial subtype of OCD, supporting the validity of the DSM-5 tic-related OCD specifier. Identifying homogeneous subgroups of OCD may inform treatment selection, earlier detection, and future studies of OCD etiology, including ongoing gene-searching efforts.

Studies V and VI found that OCD and tic disorders are associated with increased risks for metabolic and cardiovascular disorders, independent of shared familial confounding. The results emphasize the importance of monitoring the long-term physical health of individuals with OCD and tic disorders. These results further suggest that lifestyle interventions may be required alongside other standard evidence based treatments to reduce the risk of premature mortality in these patients.

LIST OF SCIENTIFIC PAPERS

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II. **Brander, G.,** Rydell, M., Kuja-Halkola, R., Fernández de la Cruz, L., Lichtenstein, P., Serlachius, E., . . . Mataix-Cols, D. (2016). Association of perinatal risk factors with obsessive-compulsive disorder: a population-based birth cohort, sibling control study. *JAMA Psychiatry*, 73(11), 1135-1144. doi:10.1001/jamapsychiatry.2016.2095

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V. Isomura, K., **Brander, G.,** Chang, Z., Kuja-Halkola, R., Rück, C., Hellner, C., . . . Fernández de la Cruz, L. (2018). Metabolic and cardiovascular complications in obsessive-compulsive disorder: a total population, sibling comparison study with long-term follow-up. *Biological Psychiatry*, 84(5), 324-331. doi:10.1016/j.biopsych.2017.12.003

VI. **Brander, G.,** Isomura, K., Chang, Z., Kuja-Halkola, R., Almqvist, C., Larsson, H., . . . Fernández de la Cruz, L. (2019). Association of Tourette syndrome and chronic tic disorder with metabolic and cardiovascular disorders. *JAMA Neurology*, 76(4), 454-461. doi:10.1001/jamaneurol.2018.4279

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

VII. Pérez-Vigil, A., Fernández de la Cruz, L., **Brander, G.,** Isomura, K., Gromark, C., & Mataix-Cols, D. (2016). The link between autoimmune diseases and obsessive-compulsive and tic disorders: A systematic review. *Neuroscience & Biobehavioral Reviews*, 71, 542-562. doi:10.1016/j.neubiorev.2016.09.025

VIII. Fernández de la Cruz, L., Rydell, M., Runeson, B., D'Onofrio, B. M., **Brander, G.,** Rück, C., . . . Mataix-Cols, D. (2017). Suicide in obsessive-compulsive disorder: a population-based study of 36 788 Swedish patients. *Molecular Psychiatry*, 22(11), 1626-1632. doi:10.1038/mp.2016.115

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CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
AHA/NHLBI	American heart association/national heart, lung, and blood institute
ASD	Autism spectrum disorders
ATC	Anatomical therapeutic chemical
CI	Confidence intervals
DSM	Diagnostic and statistical manual of mental disorders
GABHS	Group-A beta-hemolytic streptococcal infections
GWAS	Genome-wide association study
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
ICD	International classification of diseases
IDF	International diabetes federation
LOE	*Lag om etikprövning* [Law on ethical vetting]
MESH	Medical subject heading
NPR	National patient register
OCD	Obsessive-compulsive disorder
PANDAS	Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections
PIN	Personal identification number
PPV	Positive predictive value
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PUL	*Personuppgiftslagen* [Personal information act]
SNP	Single-nucleotide polymorphism
SRI	Serotonin reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor

1 INTRODUCTION

Obsessive-compulsive disorder (OCD) and tic disorders, including Tourette syndrome and chronic motor or vocal tic disorders, are complex neuropsychiatric disorders of unclear etiology that often co-occur in the same individuals. We know that both disorders are familial and likely genetic, but the specific genes involved are yet to be identified. Large-scale gene searching efforts are currently underway, and identification of meaningful biological subtypes may help accelerate this process. It also seems clear that a substantial proportion of the liability to OCD and, to lesser extent tic disorders, is not of genetic origin. Little is known about the potential environmental risk factors that presumably interact with genetic risk factors to cause these disorders. Similarly, little is known about the long-term adverse health consequences associated with OCD and tic disorders. This is largely because it is often unfeasible to follow patients for several decades; the study of such distal health outcomes requires a long-term perspective.

The vast Scandinavian nationwide registers, which contain administrative records from entire populations 'from cradle to grave', and a wealth of high-quality healthcare data prospectively collected over several decades, provide unique opportunities to study environmental risk factors as well as the long-term consequences of these disorders.

The broad aims of this thesis were to investigate potential perinatal risk factors for OCD and tic disorders, to investigate whether tic-related OCD is a particularly familial subtype of OCD, and to investigate some of the potential long-term health complications following the onset of these disorders.

2 BACKGROUND

OCD is a mental disorder characterized by recurrent, persistent, and intrusive thoughts, urges, or images causing marked anxiety or distress. These, in turn, prompt repetitive behaviors or mental acts aimed at preventing or reducing the anxiety or the distress. The obsessions and compulsions are time-consuming and/or cause clinically significant distress or impairment. Tics are sudden, rapid, recurrent, non-rhythmic motor movements or vocalizations. Tic disorders are neurodevelopmental movement disorders including Tourette syndrome, characterized by multiple motor and vocal tics, and chronic (or persistent) tic disorder, characterized by multiple motor or vocal tics. For simplicity, henceforth both kinds of disorders will be referred to as "tic disorders". The frequency of the tics can wax and wane, but they need to have persisted for more than one year for a tic disorder diagnosis.[1] OCD and tic disorders have a severe negative impact on functioning in everyday life. Individuals with OCD or tic disorders experience lower quality of life than individuals without the disorders.[2,3] More specifically, both OCD and tic disorders have been associated with educational attainment difficulties, including being less likely to finish upper secondary school, finish a university degree, and finish a post-graduate degree, compared to those without the disorders.[4,5]. Further, OCD has been associated with increased risks of labor market marginalization, including higher rates of long-term unemployment, long-term sick-leave, and disability pension.[6]

Both OCD and tic disorders are relatively common psychiatric disorders. OCD has a reported lifetime prevalence of approximately 2%,[7] whereas the prevalence of tic disorders is about 1%.[8,9] However, these figures are based on epidemiological surveys and do not reflect the actual prevalence of help-seeking individuals, which is thought to be much lower.[10] Whereas the prevalence of OCD is similar in both males and females,[1] tic disorders are more common in males.[11] OCD is widely acknowledged to have two peaks of age at onset, one during childhood (mean age of 11-13), and another in early adulthood (mean age 23-25).[e.g.,12,13] By contrast, tic disorders are by definition childhood-onset disorders and the first symptoms typically first manifest in early childhood (typically between ages 4 and 6).[1,14] A great majority of OCD and tic disorders patients have other co-occurring psychiatric disorders. In OCD, the most common are other anxiety disorders (75.8%) and mood disorders (63.3%),[7] and as many as 29% of OCD patients have lifetime comorbid tic disorders.[15] In Tourette syndrome, the most common co-occurring disorders are OCD (66.1%) and attention-deficit/hyperactivity disorder (ADHD; 54.3%), followed by anxiety disorders (36.1%) and mood disorders (29.8%).[16]

Both OCD and tic disorders are familial disorders, meaning that relatives of individuals with either disorder are more likely to have that same disorder.[17,18] However, they are also familial cross-disorder, in that relatives of individuals with one of the disorders are more likely to have the other disorder,[19-23] suggesting some shared genetic etiology. Patients with OCD who also have a history of tic disorders have been observed to present with distinct clinical characteristics, compared to those without tic disorders. The co-occurrence of OCD and tic disorders in the same individual may represent a subtype of OCD, which led to the inclusion of a *tic-related OCD* specifier in the fifth edition of the Diagnostic and Statistical Manual of

Mental Disorders (DSM-5).[1,24] These differential features include tic-related OCD being linked to early age of onset,[21,25,26] a greater proportion of males,[15,20,26-28] and the course of the disorder being characterized by an early peak in the severity of the obsessive-compulsive symptoms, followed by an increased likelihood of remission,[29,30] compared to non-tic-related OCD. The symptoms in tic-related OCD have also been reported to include higher rates of symmetry and sexual/aggressive obsessions[26,28,31] and sensory phenomena preceding the compulsions.[15,32] While less supported, tic-related OCD has also been associated with a higher number of comorbidities[33] and higher rates of ADHD and autism than non-tic-related OCD.[31] Tic-related OCD could potentially guide choice of treatment, as some studies have reported that these patients may not respond to selective serotonin reuptake inhibitors (SSRIs).[34,35] However, other studies have not confirmed this.[36,37]

2.1 ETIOLOGY

The causes of OCD and tic disorders remain largely unknown. Controlled family studies have consistently found both disorders to be familial,[22,23,38-40] with first degree relatives of individuals with OCD being approximately 4–5 times more likely to have OCD themselves[18,40,41] and of individuals with tic disorders being 18-19 times as likely to have chronic tics themselves,[17,40] compared to relatives of unaffected controls. This risk decreases as the genetic distance to the relative increases,[17,18] strongly suggesting a genetic basis for the observed familiality. The genetic basis has been additionally supported by large population-based twin studies in nonclinical populations, particularly for OCD, finding that additive genetic effects contribute 38-40% and non-shared environmental effects contribute 50-52% to the variance of OCD.[42] In twin studies, the heritability estimates for tic disorders have been less consistent, with effects varying between 28% and 56%,[39,43-47] whereas in family studies the heritability has been estimated to be as high as 77%.[17] The broad range of estimates may be explained by the variations in methods of assessment, age groups, data collection, and definitions of tic disorders.

Thus, it seems clear that both OCD and tic disorders have some genetic basis. However, modestly sized genome-wide association studies (GWAS) have not been able to identify any single-nucleotide polymorphism (SNPs) firmly associated with OCD,[48] and only some promising but no definite SNPs for tic disorders.[49] Based on the encouraging results emerging from the genetics of schizophrenia and other mental disorders,[50-52] it is widely expected that a worldwide increase in sample sizes will return the first replicable set of risk genes for both disorders. Several worldwide efforts are currently ongoing to achieve such aim, and Scandinavian countries have a major role to play in such efforts.[53]

2.1.1 Environmental risk factors

Based on the current knowledge, it seems likely that neither disorder is fully explained by genetic factors. In OCD, at least half of the liability may not be of genetic origin, whereas in tic disorders, a smaller role of environmental risk may be expected, given the higher heritability of the disorder. Environmental risk factors for OCD and tic disorders, that may interact with genetic factors, are therefore as important to identify as genes, since some environmental factors may be more amenable for intervention or prevention strategies. Additionally, the identification of specific environmental risk factors for OCD and tic disorders may also facilitate future genetic research, as genes may not be sufficient to cause psychopathology but may be dependent on other necessary causes in the form of environmental factors.[54] On the other hand, genetic susceptibility may be a requirement for environmental factors to increase risks, but this conjecture requires empirical research.

A quick scan of the literature revealed that a number of potential environmental risk factors may be associated with increased risk for OCD and tic disorders. However, given the vast and methodologically heterogeneous nature of the literature, it was difficult to draw firm conclusions. At the time this thesis began, there were no systematic reviews of environmental risk factors for OCD, whereas there were a few reviews of risk factors for tic disorders.[55,56] Thus, a systematic review of the OCD literature seemed warranted prior to initiating empirical studies on the subject.

2.2 IS TIC-RELATED OCD A MEANINGFUL SUBTYPE OF OCD?

One potential obstacle for the identification of risk genes for OCD and tic disorders is the heterogeneity of these disorders.[57-61] There have been several approaches to dissecting OCD and tic disorders into more homogeneous subtypes.

Symptom dimensions have been studied mainly in OCD, but also in tic disorders. A meta-analysis of factor analyses of OCD symptoms found four dimensions consisting of symmetry, forbidden thoughts, cleaning, and hoarding symptoms.[62] Cluster analyses of tic disorders symptoms have also found dimensions, mostly consisting of combinations of the degree of complexity of the tics, whether they are vocal and, to some extent, which part of the body the tic involves.[63,64] The dimensions in both OCD and tic disorders have in turn been associated with other clinical characteristics, such as patterns of psychiatric comorbidity, familial patterns, neural correlates and treatment response,[63,65,66] albeit not consistently.

Subtyping based on comorbid psychiatric disorders have also been examined in both OCD and Tourette syndrome. For example, three classes of OCD have been identified, consisting of simple OCD, OCD with comorbid tics, and OCD with affective syndromes and panic disorder.[67] The main three classes of Tourette syndrome all included OCD or obsessive-compulsive symptoms.[61] Additionally, autism-related OCD[68] and early onset OCD[19,20] have

also been proposed subtypes of OCD. Of all these efforts, the most promising subtype of OCD is arguably the tic-related OCD subtype.[25]

Supporting the tic-related OCD subtype are three twin studies, finding modest genetic correlations between obsessive-compulsive symptoms and tics.[43,46,69] Recently, GWAS data was analyzed to estimate shared heritability between psychiatric disorders, finding a 0.43 genetic correlation between OCD and Tourette syndrome.[70] In a genome-wide analysis examining polygenic risk scores in OCD and Tourette syndrome, no significant polygenic signal was observed between the two disorders. However, it was observed that the polygenic risk scores of OCD increased when excluding individuals with both OCD and Tourette syndrome, despite the decrease in sample size.[71] In a previous study by the same team, the genetic correlation between the disorders increased when tic-related OCD cases were excluded.[72] These results may suggest that tic-related OCD possesses a different underlying genetic architecture than non-tic-related OCD. The genetic effects might even be stronger in tic-related OCD, compared to non-tic-related OCD, as has been further suggested by a few family studies indicating that tic-related OCD might be more familial than non-tic-related OCD.[20,22,40] However, these studies were generally limited by small samples from specialist clinics. Furthermore, tic-related OCD was not the main focus of these studies and did therefore not take potential confounding factors specific to tic-related OCD cases into account.

While there has been a considerable amount of work on the clinical features of tic-related OCD, there has yet to be a study investigating the validity of it being a meaningful subtype of OCD. If tic-related OCD would prove to be more familial than non-tic-related OCD, this would add to the evidence for tic-related OCD being a distinct subtype of OCD and, potentially, would inform future gene-searching efforts.

2.3 LONG-TERM HEALTH CONSEQUENCES

Both OCD and tic disorders have been associated with about double the risk of premature death, compared to individuals without the disorders.[73,74] Patients with OCD have also been reported to be almost 10 times more likely and patients with tic disorders more than four times more likely to die by suicide than the general population.[75,76] The mechanisms behind the increased risk of premature death from natural causes, however, have received little attention. One of the most plausible candidates contributing to mortality in tic disorders is metabolic syndrome, a collection of risk factors for metabolic and cardiovascular disorders, which has been associated with other psychiatric disorders[77,78] and in turn with increased mortality.[79-81] In a naturalistic Italian study of 104 OCD patients from a specialist clinic, metabolic syndrome was present in 21.2% and was further associated with long-term antipsychotic medication.[82] However, the small sample, clinical setting, cross-sectional design, and absence of a control group precludes any firm conclusions. In tic disorders, metabolic and cardiovascular symptoms have only been examined as potential side effects in the context of trials of psychiatric medication.[83-86] In previous studies, long-term use of psychiatric medication has been

associated with increased risk of metabolic syndrome.[87] Evidence-based pharmacological treatment for OCD includes high doses of serotonin reuptake inhibitors (SRIs),[88] while tic disorders are commonly treated with antipsychotic medication.[89,90] If individuals with OCD and tic disorders were to have an increased risk of metabolic syndrome, and other related adverse health consequences, there should be an additional emphasis on monitoring the general health of these patients and to implement interventions aimed at reducing health risks, something that has been neglected in these patient groups.

2.4 CONCLUSIONS AND RATIONALE

There are big gaps to be filled in understanding psychiatric disorders in general, and of OCD and tic disorders in particular. Whereas gene-searching efforts are well underway for both disorders, less emphasis has been put on identifying environmental risk factors for OCD and tic disorders. The identification of more homogeneous subgroups of individuals (e.g., tic-related OCD) might also facilitate more effective ways of finding risk factors for these disorders. While OCD and tic disorders are associated with considerable impairment, little is still known about the long-term effects on the physical health of the patients. Knowing specific long-term health consequences for people with OCD or tic disorders could inform intervention strategies beyond the treatment of the psychiatric symptoms. This thesis capitalizes on the wealth of information contained within the Swedish nationwide registers and aims to contribute to the understanding of the etiology and health consequences of OCD and tic disorders.

3 AIMS

The overarching aim of this PhD project was to fill in some of the gaps of knowledge about OCD and tic disorders, by investigating environmental risk factors and adverse health consequences of the disorders, and the validity of tic-related OCD as a particularly familial subtype of OCD.

The main aims of the individual studies in the thesis were:

Study I	To systematically synthesize the literature on potential environmental risk factors for OCD.
Studies II & III	To identify perinatal risk factors that may be in the causal pathway to OCD and tic disorders.
Study IV	To examine the validity of tic-related OCD as a potentially meaningful subtype of OCD.
Studies V & VI	To examine the risk of metabolic and cardiovascular disorders in individuals with OCD and tic disorders.

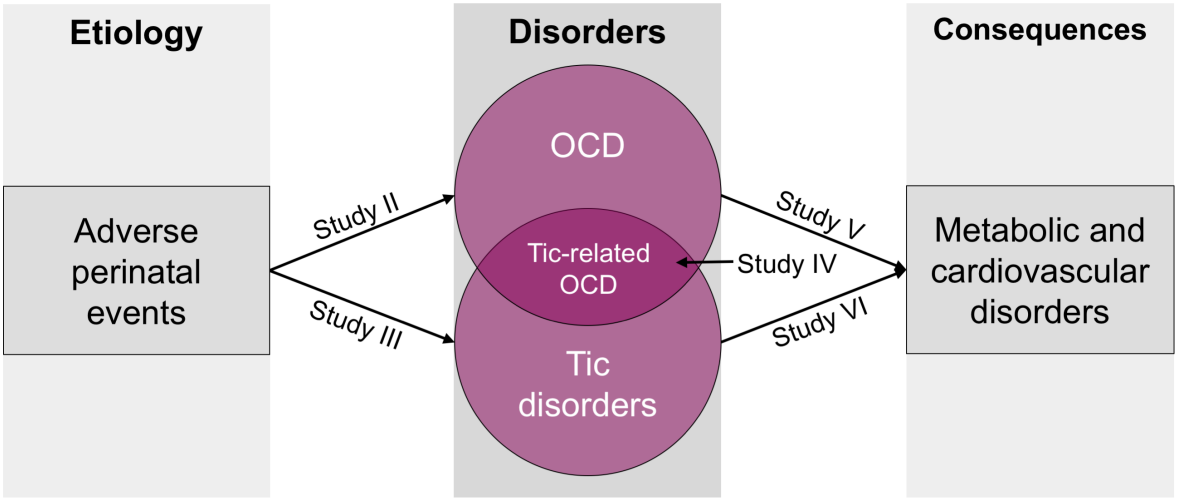

Figure 1. Overview of the topics examined in studies II-VI

4 METHODS

4.1 ETHICAL APPROVAL

No ethical approval was required for study I (systematic review). Studies II-VI were approved by the Regional Ethical Review Board in Stockholm (reference number 2013/862-31/5). These studies were register-based and no individuals were identifiable at any time, therefore the requirement for informed consent was waived.

4.2 STUDY DESIGNS

This thesis contains one systematic review and five observational studies. The observational studies are register-based with prospectively collected data from several Swedish National Registers. As such, the cohort design is generally the best suited for the data, including as many individuals as possible and taking advantage of the long-term follow up for different outcome variables.

Potential measured confounders that could be associated with both exposure and outcome were adjusted for. However, there may still be other, unmeasured factors that better explain the associations. A useful method to control for some unmeasured confounders is to compare full siblings within the same family with each other. By doing so, several familial factors, such as shared environmental factors (e.g., socioeconomic status, parental education), and about 50% of the genetic liability, are held constant in the analyses. If, for example, socioeconomic status is associated with both the exposure (e.g., having OCD) and the outcome (e.g., metabolic and cardiovascular disorders), comparing siblings from the same family would effectively control for this confounder. For this reason, studies II, III, V, and VI all employed full sibling comparisons to control for unmeasured confounders shared between siblings.

4.2.1 Systematic review in study I

Study I is a systematic review of environmental risk factors for OCD, following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. The PRISMA statement consists of a 27 item checklist and a four-phase flow chart intended to help authors improve the reporting of systematic reviews and meta-analyses.[91] The items in the checklist cover all sections of the review (i.e., title, abstract, introduction, methods, results, discussion, and funding) and include recommendations aimed at promoting transparency and complete reporting of the included studies.

Studies included in the systematic review were chosen in the basis of a series of inclusion and exclusion criteria. Papers were included if they reported data on OCD as the primary outcome, used standardized diagnostic criteria to define OCD diagnosis, reported on potential environmental risk factors, and included a control group, a comparison to general population

data, or a well-characterized clinical cohort without control group. On the other hand, studies that did not include OCD-specific data, did not provide information on the assessment procedure, and those on obsessive-compulsive personality disorder and case reports or small case series were excluded.

4.2.2 Birth cohorts in studies II & III – perinatal risk factors

By means of a birth cohort design, studies II and III examined the association between adverse perinatal events and having OCD and tic disorders, respectively. For study II, we identified from the Medical Birth Register all individuals born in Sweden between January 1, 1973 and December 31, 1996, and for study III, those born between January 1, 1973, and December 31, 2007. The reason behind the difference in time periods was motivated by the differences in the course of the disorders and wanting to give the individuals included in the respective cohorts enough time to develop the disorders. Everyone included in the cohort was followed from birth until the first date of a recorded diagnosis of OCD (study II) or tic disorder (study III), death, emigration, or end of follow-up, whichever came first.

4.2.3 Birth cohort and sub-cohorts of relatives in study VI – family clustering of tic-related OCD

Study IV examined the risk of OCD in relatives of individuals with tic-related OCD and in relatives of individuals with non-tic-related OCD, compared to relatives of unaffected individuals. Tic-related OCD was defined as having a lifetime diagnosis of OCD and a lifetime diagnosis of any tic disorder registered in the National Patient Register (NPR). We identified all individuals born in Sweden between January 1, 1967 and December 31, 2007 from the Total Population Register. Thus, the oldest individuals included were 6 years old in 1973, when the coverage of psychiatric disorders in the NPR was good, and the youngest were 6 years old at end of follow-up on December 31, 2013. This age was selected as inspection of the data in the NPR indicated that an OCD diagnosis before age 6 was very rare. From this birth cohort, we used information on parentage from the Multi-Generation Register to create sub-cohorts consisting of all twins (combining both monozygotic and dizygotic), full siblings, maternal and paternal half siblings, and cousins. In each sub-cohort, we then followed everyone from birth until the first date of a recorded OCD diagnosis, emigration, death, or the end of follow-up (December 31, 2013), whichever came first. Individuals who died or emigrated before 6 years of age and individuals with conflicting migration dates were excluded from the study population.

4.2.4 Total population cohorts in studies V and VI – metabolic and cardiovascular disorders

Study V examined the association between having OCD and developing metabolic and cardiovascular disorders. Study VI examined the association between having tic disorders and metabolic and cardiovascular disorders. As metabolic and cardiovascular disorders are generally developed later in life, the birth cohort design would not have provided enough follow-up time to capture all outcomes. For this reason, a total population cohort design was applied instead, including everyone *living* in Sweden anytime between 1973 and 2013.

For study V, people who emigrated or died before age 6 were excluded; as described in study IV above, this was based on recorded diagnoses of OCD before age 6 being very rare. Additionally, in study V, individuals with organic brain disorder, psychotic disorder, bipolar disorder, pervasive developmental disorder, Tourette syndrome, and chronic tic disorders were also excluded from the cohort since these disorders are commonly medicated with antipsychotics, which in turn have been associated with metabolic complications.[87] Study VI used a less restrictive cohort, without restrictions for birth years (since tic disorders tend to start early in life) or psychiatric comorbidity.

All individuals were followed from their 6th birthday (study V), the date of birth (study VI), or January 1, 1973 (both studies), until the date of a diagnosis of a metabolic or cardiovascular disorder, emigration, death, or end of follow-up on December 31, 2013, when no more information was available from the Swedish National Registers.

4.3 DATA SOURCES

4.3.1 Structured literature search (study I)

For study I, we performed a structured literature search in three medical databases, namely PubMed, Embase, and Scopus, using keywords and Medical Subject Heading (MeSH) terms. The search terms covered both general risk factors and *a priori* defined specific areas that, based on the literature, were suspected likely candidates, including perinatal events (e.g., birth complications, birth weight, gestational age, parental and family factors, season of birth), reproductive cycle events (including menarche, pregnancy, postpartum, and menopause), parental rearing styles, stressful life events (e.g., childhood trauma, amount of life events, traumatic life events), socioeconomic status, infections, traumatic brain injury, substance abuse, vitamin deficiency, famine, immigration, adoption, and urbanization. The search included all papers published from inception until October 6, 2015. Reference lists were also examined for relevant papers to supplement the search.

4.3.2 The Swedish national registers and the personal identification numbers

Data for studies II-VI were obtained by linking information from Swedish national registers through the unique personal identification numbers (PIN) assigned to all Swedish citizens at birth or immigration.[92] The linkage was performed by the National Board of Health and Welfare where the PINs were replaced by randomly assigned sequential numbers before the data was delivered. Each of the relevant registers will be briefly described here.

4.3.3 The Total Population Register

The Total Population Register contains demographic information (e.g., sex, birth date, family relationships, migration) on all Swedish inhabitants since 1968. The Total Population Register is also used to construct the Migration Register and the Multi-Generation Register.

The Migration Register contains information about emigration since 1961 and immigration since 1969 from and to Sweden.[93] The Multi-Generation Register connects every person born in Sweden since 1932, and ever registered as living in Sweden from 1961, with their parents, both biological and adoptive. This allows for identifying relatives of different genetic relatedness, such as siblings. The register contains information on 100% of mothers and 98% of fathers of individuals born after 1961.[94]

4.3.4 The National Patient Register

The NPR covers all primary medical diagnoses and up to eight additional diagnoses given from inpatient hospital admissions since 1969, with diagnoses based on the International Classification of Diseases (ICD), eighth (ICD-8; 1969–1986), ninth (ICD-9; 1987–1996), and tenth (ICD-10; 1997–2013) revisions. All counties in Sweden started recording psychiatric care from 1973 and from 2001 outpatient specialist care is also included.[95]

4.3.5 The Medical Birth Register

The Swedish Medical Birth Register includes data on more than 99% of all pregnancies and deliveries in Sweden since 1973. The register is constructed based on information from Medical Birth Reports, which are summarized medical records on a standard form prepared by secretaries at obstetric clinics. From 1982, an updated form is used, concentrating on antenatal care of the mother, the delivery record, and the record for the pediatric examination of the newborn. At the same time, the contents of the register were expanded and for some categories, check boxes were introduced instead of medical codes.[96]

4.3.6 Other registers

The Prescribed Drug Register contains data on all dispensed prescriptions of medication to the whole population of Sweden since July 1, 2005. The information includes type of medication classified according to the Anatomical Therapeutic Chemical (ATC) classification system, date of the prescription, and dosage. It does not include information on indication for treatment.[97] The Cause of Death Register includes dates and causes of more than 99% of all deaths of Swedish residents, both in Sweden and abroad, since 1961.[98]

4.4 MEASUREMENTS

4.4.1 Systematic review (study I)

For each one of the eligible studies to be included in the systematic review, a number of variables were extracted, including sample size, nature of the sample (e.g., clinical sample, population cohort), study design (e.g., case-control, cross-sectional), diagnostic procedures, outcome measures, and relevant results.

4.4.2 OCD and tic disorder diagnoses in the observational studies

For all register-based studies contained in this thesis (studies II-VI), OCD and/or tic disorders constituted either the exposure or the outcome variable. The NPR was used to identify all individuals with either disorder (or both) by their diagnostic codes using the ICD-8, ICD-9, and ICD-10 classificatory systems (**Table 1**).

Table 1. ICD codes for obsessive-compulsive disorder and tic disorders

Disorder	ICD-8 codes	ICD-9 codes	ICD-10 codes
Obsessive-compulsive disorder	300.3	300D	F42
Tourette syndrome and tic disorders	306.2	307C	F950: Transient tic disorder F951: Chronic motor or vocal tic disorder F952: Tourette syndrome F958: Other tic disorders F959: Unspecified tic disorder

The quality of the results of these studies relies completely on the validity of the variables in the registers. To that end, it is imperative that validation studies are performed. The diagnostic codes for OCD and tic disorders in the NPR have, prior to the studies in this thesis, been

validated.[99] The validation process was performed by chart review. Complete medical records of 100 randomly selected OCD cases and 100 randomly selected tic disorder cases (based on ICD-8, ICD-9, and ICD-10 definitions) were requested from three different Swedish counties (Stockholm, Södermanland, and Gotland). For every other case with a tic disorder, a control with a registered epilepsy diagnosis was also randomly selected, and for every other case with OCD, a control with major depression was selected. Two blinded psychiatrists independently performed the chart review of the complete medical records of all cases and controls.

The positive predictive value (PPV; correctly diagnosed cases divided by the sum of true positives and false positives) of OCD was 0.71-0.72, with a Cohen's κ inter-rater reliability of 0.98. Similar results have been produced by a Danish study of 100 children with early-onset OCD, finding a PPV of 0.85.[100] However, Rück et al.[99] found unacceptably high rates of false positives in OCD diagnosed with ICD-8 and ICD-9 codes. It was recommended that mainly ICD-10 codes were used in OCD research using the Swedish NPR.

Based on the recommendations by Rück et al.,[99] OCD was defined as a registered ICD-10 diagnosis in study II. In studies IV and V, ICD-8 and ICD-9 codes for OCD were also included to maximize the OCD cohort size and statistical power, but sensitivity analyses including ICD-10 codes only were performed.

For tic disorder codes, the validity was excellent, with a PPV of 0.92 and Cohen's κ of 1. This corresponds well with a Finish chart review performed on the medical records of 88 children diagnosed with Tourette, finding a validity of 95%.[101] However, when Rück et al.[99] contrasted different forms of tic disorders against each other, there was less consistency, clinicians seemingly using the codes for Tourette syndrome and of chronic tic disorder interchangeably. For this reason, studies from our research group cannot separate Tourette syndrome from chronic tic disorder, a distinction that has equally been questioned in the literature.[102] Rück et al.[99] proposed an algorithm to ensure that only chronic tic disorders were used in research, and was aimed at excluding individuals with transient tic disorders and ascertain whether individuals with other tic disorders or unspecified tic disorder indeed were chronic or not.

The algorithm for tic disorders suggested by Rück et al.[99] was employed in studies III and VI. In study IV, any registered tic disorder diagnosis was used in accordance with the description of the tic-related specifier to OCD in DSM-5, which does not specify that tics need to be chronic.[1]

4.4.3 Perinatal risk factors (studies II & III)

In studies II and III, the associations between several adverse perinatal events and OCD or tic disorders were examined. As described above, the NPR was used to identify OCD and tic disorders cases (outcomes). The Medical Birth Register was used to identify adverse perinatal events (exposures). The perinatal events in focus were maternal smoking during pregnancy,

labor presentation, obstetric delivery, gestational age, birth weight, birth weight in relation to gestational age, Apgar score at 5 minutes, and head circumference.

Maternal smoking during pregnancy

When the Medical Birth Reports were updated in 1982, maternal smoking during pregnancy was introduced as a variable. Therefore, this variable was examined only in individuals born from 1982 onwards, thereby reducing the size of the birth cohorts in both studies for this category. The information on maternal smoking is collected at the first antenatal care visit and is a categorical variable with three levels: no daily smoking, 1 to 9 cigarettes per day, and more than 10 cigarettes per day.

Labor presentation

Labor presentation was divided into three categories: normal presentation, breech presentation, and other malpresentation (e.g., face or brow presentations, transverse lie). The proportion of unknown labor presentations has varied greatly over time in the Medical Birth Register. However, the number of various non-normal presentations has remained fairly stable, suggesting that the majority of unknown presentations were likely normal presentations.[96] To avoid introducing bias by making assumptions, unknown presentations were handled as missing values.

Obstetric delivery

Delivery method is recorded in the Medical Birth Report as spontaneous vaginal, forceps, vacuum extraction, or cesarean section.[96] To increase power, delivery by forceps or vacuum extraction were collapsed into a single variable: assisted (instrumental) vaginal delivery. At inspection of the database, it was noted that these three categories were not mutually exclusive in the Medical Birth Register, and they were therefore hierarchically ordered. If there was a record of cesarean section, that was prioritized, if not, assisted delivery was prioritized, and otherwise recorded vaginal delivery was used. Where no information was recorded and method of delivery was unknown, the value of the variable was set to missing (despite the fact that, as with labor presentation, most missing values were likely unassisted vaginal deliveries).

Gestational age

In the Medical Birth Register, pregnancy duration is estimated combining the date of the last menstrual period, the estimated date of delivery, the corrected estimated date of delivery based on second-trimester ultrasound, and information on pregnancy duration from the pediatric

record.[96] In study II, examining the association between gestational age and OCD, gestational age was divided into four categories: very preterm birth (<32 weeks), preterm birth (32-36 weeks), term birth (37-41 weeks), and postterm birth (≥42 weeks). It was additionally analyzed as a continuous variable, including both linear and quadratic terms, distributed as every week. Because tic disorders are less common disorders than OCD, the analyses of gestational age needed to be adjusted in study III. Instead of four categories, three were used: preterm birth (<37 weeks), term birth (37-41 weeks, reference category), and postterm birth (≥42 weeks). Since the continuous representation of gestational age served the purpose of further exploring the validity of a potential dose-response pattern, it served no purpose to conduct this additional analysis in study III, since no dose-response pattern could be extracted from only three categories.

Birth weight

Birth weight was analyzed both as a categorical variable and as a continuous, linear and quadratic, variable in both studies II and III. Study II employed six categories, consisting of "very low birth weight" (≤1500 g), "low birth weight" (1501-2500 g), 2501-3500 g, "normal birth weight" (3501-4500 g, reference category), and "high birth weight" (>4500 g). Due to the lower number of tic disorders cases, the "very low birth weight" category needed to be excluded in study III. Similar to gestational age, the continuous representation of birth weight served the purpose of further examining a potential dose-response pattern. Birth weight is greatly associated with gestational age. Therefore, to ensure that a potential association between birth weight and either OCD (study II) or tic disorders (study III) was due to an association between gestational age and either disorders, all analyses of birth weight were further adjusted by gestational age as a continuous variable, both linear and quadratic.

Birth weight in relation to gestational age

The Medical Birth Register includes two binary variables for small for gestational age and large for gestational age. The definition of these variables is two standard deviations below or above the mean weight for that gestational week, respectively, based on the Scandinavian fetal growth curve, adjusted for sex.[103] The association between these two variables and OCD (study II) and tic disorders (study III) was analyzed as an addition to gestational age and birth weight.

Apgar score at 5 minutes

The Apgar score is a convenient tool to determine the general health of newborn infants, generally stated at 1 minute, 5 minutes, and 10 minutes after birth. It is comprised by five indicators, rated 0 to 2, chosen because they can be easily determined without interfering with the care of the infant.[104] The indicators and scores are listed in **Table 2** below.

Table 2. List of Apgar items and scores

Indicator	Score 0	Score 1	Score 2
Appearance / complexion	Blue or pale all over	Blue at extremities, body pink	No cyanosis, body and extremities pink
Pulse rate	Absent	<100	>100
Grimace / reflex irritability	No response to stimulation	Grimace / feeble cry when stimulated	Cry or pull away when stimulated
Activity	None	Some flexion	Flexed arms and legs that resist extension
Respiration / respiratory effort	Absent	Weak, irregular, gasping	Strong, lusty cry

For each time interval, there is an increasing proportion of missing values for Apgar scores in the Medical Birth Register. The higher the total score at the preceding rating, the higher proportion of missing values for the succeeding one, suggesting that the majority of missing values are due to normal scores.[96] Apgar at 5 minutes was chosen for studies II and III to capture deteriorating health status after birth, while at the same time not losing too many cases to missing values. It was not assumed that missing values were normal, but remained missing in the analyses. The scores were divided into three categories in study II, in accordance with neonatal practice: normal (score of ≥7), distress (4-6), or near death (≤3).[105] Due to lower power, only two categories were used in study III: normal (score of ≥7) or abnormal (<7).

Head circumference

Head circumference is recorded in centimeters in the Medical Birth Register. Based on categories established according to the World Health Organization standards,[106] this information was converted into a categorical variable with three levels. For birth at every gestational week, small head circumference was defined as a head circumference below the 10th percentile whereas large head circumference above the 90th percentile.

4.4.4 Tic-related OCD (study IV)

Study IV examined the risk of OCD in relatives of individuals with OCD with versus without comorbid tics, compared to relatives of unaffected individuals. The NPR was used to identify all individuals with a lifetime diagnosis of OCD. Among them, everyone with a lifetime diagnosis of a tic disorder, in addition to OCD, was identified. A lifetime OCD diagnosis, with

or without a tic disorder diagnosis, constituted the exposures, and the first date of a recorded OCD diagnosis in the relative, independent of a tic diagnosis, constituted the outcome.

4.4.5 Metabolic and cardiovascular outcomes (studies V & VI)

Study V examined the association between OCD and metabolic and cardiovascular disorders, and study VI the association between tic disorders and metabolic and cardiovascular disorders. The metabolic syndrome refers to a cluster of risk factors associated with cardiovascular disease and type 2 diabetes mellitus. The cluster includes abdominal obesity, increased triglyceride levels, reduced high-density lipoprotein cholesterol levels, high blood pressure, and hyperglycemia.[107] The metabolic syndrome does not have a dedicated ICD code. Instead, medical conditions associated with the criteria for metabolic syndrome were used as proxies. Type 2 diabetes mellitus and cardiovascular diseases were additionally included because of their strong association with the metabolic syndrome. Obesity, hypertension, type 2 diabetes mellitus, and cardiovascular diseases were identified through their ICD codes in the NPR. To additionally capture those only diagnosed and followed up in primary care, individuals with specific medications prescribed for dyslipidemia, hypertension, and type 2 diabetes mellitus were identified in the Prescribed Drug Register (**Table 3**). Since the medications to treat cardiovascular diseases and hypertension generally overlap, and could therefore not be meaningfully separated from each other, these disorders were combined under the term circulatory system diseases, following the ICD nomenclature for the group including these conditions. Individuals with recorded diagnoses of both type 2 diabetes mellitus and type 1 diabetes mellitus were excluded, to avoid confounding from an etiologically distinct condition. In individuals with both a registered ICD diagnosis and a corresponding registered drug prescription, the earliest of date was used as censoring date in the survival analysis.

Table 3. Correspondence between the harmonized definition of the metabolic syndrome[107] and the selected metabolic and cardiovascular disorders and drug prescriptions for such disorders used as proxy in the current study

Criteria for clinical diagnosis of the metabolic syndrome[107]		Metabolic and cardiovascular disorders from the Swedish National Patient Register	Drug prescriptions for metabolic and cardiovascular disorders from the Swedish Prescribed Drug Register
Measure	**Categorical cut points**		
Elevated waist circumference [it is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available]	Population- and country-specific definitions	Obesity [*ICD-8* code 277; *ICD-9* codes 278.0/.1; *ICD-10* code E66]	–
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥150 mg/dL (1.7 mmol/L)	–	Lipid modifying agents, plain [ATC code C10A]
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in males	–	Lipid modifying agents, plain [ATC code C10A]
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg	Hypertension [*ICD-8* codes 400-404; *ICD-9* codes 401-405; *ICD-10* codes I10-15]	Antihypertensives [ATC code C02] (In study VI clonidine (ATC code C02AC01) and guanfacine (ATC code C02AC02) were excluded due to these drugs being prescribed for tic disorders) Diuretics [ATC code C03] Beta blocking agents [ATC code C07] Calcium channel blockers [ATC code C08] Agents acting on the renin-angiotensin system [ATC code C09]
Elevated fasting glucose [most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria] (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL	Type 2 diabetes mellitus [*ICD-10* code E11], but not type 1 diabetes mellitus [*ICD-10* code E10]	Blood glucose lowering drugs, excluding insulins [ATC code A10B], but not Insulins and analogues [ATC code A10A]
–	–	Ischemic heart diseases [*ICD-8* codes 410-414; *ICD-9* codes 411-414; *ICD-10* codes I20-25] Arrhythmia [*ICD-8* codes 427-429; *ICD-9* codes 426-429; *ICD-10* codes I44-49] Cerebrovascular diseases and transient ischemic attack [*ICD-8* codes 430-438; *ICD-9* codes 430-437; *ICD-10* codes I60-66 and G45] Arteriosclerosis [*ICD-8* codes 440-444; *ICD-9* codes 440-444; *ICD-10* codes I70-74]	Cardiac therapy [ATC code C01] Antihypertensives [ATC code C02] Diuretics [ATC code C03] Peripheral vasodilators [ATC code C04] Vasoprotectives [ATC code C05] Beta blocking agents [ATC code C07] Calcium channel blockers [ATC code C08] Agents acting on the renin-angiotensin system [ATC code C09]

Abbreviations: AHA/NHLBI American Heart Association/National Heart, Lung, and Blood Institute; ATC Anatomical Therapeutic Chemical Classification System; HDL-C High-Density Lipoprotein Cholesterol; ICD International Classification of Diseases; IDF International Diabetes Federation.

Prolonged use of psychiatric medication has been linked to the risk for metabolic syndrome.[87] Therefore, we explored the impact of psychiatric medication on the risk for metabolic and cardiovascular disorders in OCD and tic disorder patients. The information on the use of medication was retrieved from the Prescribed Drug Register, which is limited to July 2005 through December 2013. For OCD, the impact of the antidepressant medication family SRIs, with or without additional antipsychotic medication, was examined, and for chronic tic disorders, antipsychotic medication.

4.4.6 Covariates

In all observational studies, there are factors that are suspected to be associated both with the exposure and the outcome, thereby confounding potential associations between them. For example, in studies II and III, it could be that the age of the mother at the time of birth of the offspring might increase the risk of preterm birth and, independently, the risk of OCD or tic disorders. In order to examine as much of the true associations as possible, potential confounders were adjusted for in all observational studies.

In studies II and III, we adjusted for the following potential confounders: birth year, sex of the infant, parity, and the age of the mother and the age of the father at childbirth. Information on all these variables was collected from the Medical Birth Register, except for paternal age at childbirth, which was calculated from the date of birth of the father (collected from the Multi-Generation Register) and date of birth of the infant (collected from the Medical Birth Register). In studies IV-VI, birth year and sex were adjusted for; information that was retrieved from the Total Population Register.

4.5 STATISTICAL METHODS

4.5.1 Quality assessment in study I

In study I, the systematic review could unfortunately not be complemented with a meta-analysis. The data from the studies included proved too heterogeneous or insufficient to conduct comparisons. Therefore, only a qualitative synthesis of the studies was conducted, by which characteristics of the samples (e.g., size, selection) and methods (e.g., design, measures) were weighted with the reported results.

4.5.2 General statistical methods in studies II-VI

In studies II-VI, survival analyses were performed to take advantage of the detailed information on timing of different events. Survival analyses examine the time it takes for events to occur, often comparing the survival times depending on one or more predictors. Everyone not having the event contributes to the analysis as comparisons until they are "lost to follow-up" (e.g.,

migration, death, or end of study period), when there is no more information about them. All of the observational studies in this thesis employed Cox proportional hazards regression as the main survival analysis method, to estimate hazard ratios (HR) and 95% confidence intervals (CI) of the associations between exposure and outcome. HR can essentially be interpreted as multiplication of likelihood, where a HR of 2 would be twice as likely, 1.25 would be 25% increased likelihood, 1 would be no difference in likelihood, and 0.75 would be a 25% *decrease* in likelihood. Studies II, III, V, and VI applied the same basic quasi-experimental approaches to strengthen the observed associations by combining study designs aimed at excluding alternative explanations. The designs included:

- Main analysis (with varying adjustments and/or stratifications)
- Sibling comparison (to control for shared family confounders)
- Analyses excluding individuals with comorbid psychiatric disorders (one [or one cluster] at a time, to rule out that associations were explained by the presence of comorbid disorders)

4.5.3 Statistical methods in studies II and III – perinatal risk factors

Cox regression was used to estimate HRs and corresponding 95% CI for the association between adverse perinatal events and OCD (study II) or tic disorders (study II). In order to ascertain that the perinatal events and OCD or tic disorders were not both explained by other measured and available factors, so-called confounders, the analysis was run three times: first without any adjustments, second adjusting for sex and birth year, and third adjusting for parity and age of mother and father at birth of the offspring in addition to sex and birth year.

To exclude alternative explanations of the associations, we compared full siblings within the same family with each other, using stratified Cox regression, thereby controlling for confounders shared between full siblings, such as 50% of the genetic liability and shared environmental factors like socioeconomic status. These analyses were also adjusted for all measured confounders.

To examine whether other psychiatric disorders mediated (or confounded) the association between adverse perinatal events and having OCD or tic disorders, the adjusted Cox regression model was run while excluding all individuals with comorbid psychiatric disorders, one [or one cluster] at a time.

4.5.4 Statistical methods in study IV – family clustering of tic-related OCD

In study VI, we used Cox regression to estimate HR, and corresponding 95% CI, for the risk of OCD in relatives of individuals with tic-related OCD *vs.* in relatives of individuals with non-tic-related OCD, compared to unaffected individuals. This was applied to each sub-cohort, namely twins (of any zygosity), full siblings, maternal half siblings, paternal half siblings, and

cousins. Birth year and sex were adjusted for in both the exposing and the outcome individuals. Because the hypothesis was that the presence of OCD (with or without tics) was a proxy for familial factors, lifetime presence was used as exposure. This also meant that the effect was analyzed in both directions between a pair of relatives, both potentially exposing each other, instead of favoring time-varying exposure where only the first to have a registered diagnosis would serve as the exposing individual. Including all possible combinations of pairs and directions of effects between them meant that each individual could occur multiple times in the analyses. See **Table 4** for an example of a family of three full siblings. Cox regression assumes independence between observations. However, data within family or individual clusters tend to be positively correlated. If this non-independence of clustered data is not addressed, standard errors (which are the bases for confidence intervals and statistical significance testing) would be underestimated. To correct standard errors to account for the non-independence of clustered data, robust standard errors were used, which provided more stringent definitions of statistical significance.

Table 4. Example of combinations of associations examined in a family with three siblings

Exposure individual		Outcome individual
Sibling 1	→	Sibling 2
Sibling 1	→	Sibling 3
Sibling 2	→	Sibling 1
Sibling 2	→	Sibling 3
Sibling 3	→	Sibling 1
Sibling 3	→	Sibling 2

To further investigate the associations, we conducted a series of sensitivity analyses. Tic-related OCD has been associated with early onset.[21,25] In previous studies, early onset OCD, in turn, has been associated with increased risk of other family members also having OCD.[19,20] It might, therefore, be that the early onset of OCD in tic-related OCD is the driving force behind it being associated with increased risk of other family members having OCD. To check this hypothesis, we matched 5 randomly selected non-tic-related OCD cases to every tic-related OCD case by date of first registered OCD diagnosis (± 1 year), excluded all other non-tic-related OCD cases, and ran the Cox regression model again on these sub-groups. Furthermore, because tic disorders are highly heritable neuropsychiatric disorders, it might be that its comorbidity with OCD was behind the increasing the risk of OCD in relatives. This would suggest that OCD in combination with another heritable neuropsychiatric disorder would also

result in an increased likelihood of family members having OCD. To investigate this, we ran analyses where we compared OCD cases with comorbid ADHD or autism spectrum disorders (ASD) to OCD cases without ADHD or ASD.

4.5.5 Statistical methods in studies V and VI – metabolic and cardiovascular disorders

Cox regression was used to estimate HRs and corresponding 95% CI for the association between OCD (study V) or tic disorders (study VI) and metabolic and cardiovascular disorders. The main analysis in both studies was the association with *any* of the *a priori* defined metabolic and cardiovascular disorders, followed by analyses for each separate metabolic or cardiovascular disorder. All models were adjusted for sex and birth year. In addition to adjusting for sex, the analyses were also stratified by sex, to identify potential difference in risk depending on this variable. As above, sibling comparisons were employed to rule out alternative explanations.

Other comorbid psychiatric disorders (or clusters of them) were excluded one at a time and the Cox regression run again, to ascertain that associations were not explained in full by or completely dependent on the presence of other disorders.

Since the cohorts were based on everyone living in Sweden in 1973 or later, there was a proportion of the cohort with unknown events before 1973. For this reason, the main Cox regression model was run on subgroups of the cohorts, consisting of everyone with complete follow-up from age 6 in study IV and from birth in study V. Additionally, in study IV, the main analysis was run including only OCD defined by ICD-10 codes, since validity for the ICD-8 and ICD-9 codes is poor.[99]

To examine whether associations between OCD or chronic tic disorders and metabolic and cardiovascular disorders were better explained by the use of long-term medication, we conducted exploratory analyses to examine the risk of metabolic and cardiovascular disorders in OCD or chronic tic disorders, depending on the use of psychotropic medication. We used cumulative time-varying exposure to determine duration of medication, and divided the duration into categories. In study IV, both duration and dosage were divided into categories (in ≤1 year, 1-3 years, >3 years, and small doses or occasional use, moderate doses, and high doses, respectively), creating nine categories compared to the tenth category of 'no SRI medication'. These categories were further stratified into with or without additional antipsychotic medication. Since tic disorders are less common than OCD, the small sample of chronic tic cases was prohibitive of the same categorization. Instead, only duration was used and categorized as ≤1 year and >1 year, compared to no antipsychotic medication.

5 RESULTS

5.1 SYSTEMATIC REVIEW OF ENVIRONMENTAL RISK FACTORS FOR OCD (STUDY I)

Study I systematically summarized the results from all previously published papers on a broad range of environmental risk factors for OCD. The initial search from the three selected databases identified a list of 9,950 potentially relevant papers. Of these, 3,415 proved to be duplicates and were removed. The remaining papers were first screened on title and abstract, before full text assessments were performed. Ultimately, 128 papers were included in the qualitative synthesis, 12 of which were identified from reference lists. The heterogeneity and the insufficiency of the data collected from the included papers unfortunately precluded conducting a meta-analysis. Instead, a qualitative synthesis of the studies was performed.

The findings indicated that birth complications in general, and specific complications, such as low birth weight, delivery by forceps, and protracted labor, had been previously linked to OCD. The results for other birth and family related factors (such as season of birth, family size, and birth order) appeared to be either conflicting or not supported.

On the other hand, reproductive cycle events (e.g., menarche, pregnancy, and postpartum) appeared to increase risk for OCD and for exacerbated obsessive-compulsive symptoms in women. However, there have also been reports of ameliorated obsessive-compulsive symptoms during pregnancy and postpartum.

Several studies reported that patients with OCD associate the onset of the disorder with stressful or traumatic life events. Associations were found between OCD and stressful life events in general, increased amount of life events, and traumatic life events (with or without post-traumatic stress disorder) in both adulthood and childhood, including sexual abuse, physical abuse, and verbal or emotional abuse. However, some studies examining stressful or traumatic life events did not find any association. Nonetheless, hypothetically, individuals with OCD may be more prone to recall negative events and connect them to their OCD onset.

The most extensively researched association between OCD and infections has been that with autoimmune dysfunction caused by the group-A beta-hemolytic streptococcal infections (GABHS), leading to the clinical presentation known as Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS).[108] The clinical characteristics of PANDAS differ from classic OCD in that it has a sudden onset in prepubertal age, a relapsing-remitting course, temporal association with GABHS, and neurological abnormalities. However, only a few of the studies trying to find associations between OCD and GABHS actually found positive associations.

Additionally, parental rearing styles, socioeconomic status, brain injury, substance use disorders, and vitamin deficiency have been researched to a varying extent. Studies have reported either no associations or too conflicting results to draw any firm conclusions from.

The majority of the papers included in the systematic review suffered from important methodological limitations, including small clinic-based samples and retrospectively collected data.

5.2 PERINATAL RISK FACTORS (STUDIES II & III)

Study II used a cohort consisting of 2,421,284 individuals, of which 17,305 had a recorded OCD diagnosis in the NPR. From this cohort, 743,885 families with at least two full siblings were identified for the full sibling comparison. In study III, 3,026,861 individuals were included, of which 5,597 had a record of a tic disorder diagnosis in the NPR. For the full sibling comparison, 947,942 families with at least two siblings were identified. This difference in sample size was a consequence of only including individuals born in 1996 or earlier in study II and in 2007 or earlier in study III, the reason being the earlier onset of tic disorders and wanting all individuals to have sufficient time to have a diagnosis registered.

An overall pattern emerged whereby adverse perinatal events were associated with increased risk of both OCD and tic disorders. For OCD, those not better explained by shared family factors included mothers smoking 10 or more cigarettes per day during pregnancy, breech presentation, cesarean section, low birth weight, preterm birth, large for gestational age, and Apgar distress scores. For tic disorders, especially impaired fetal growth, as represented both by low birth weight and small for gestational age, was robust when shared family factors were taken into account. Additionally, the risk estimates for breech presentation, cesarean section, and preterm birth remained when shared family factors were accounted for. A summary of the most important results from the fully adjusted models in both disorders is presented in **Table 5**.

The continuous representations showed that the lower the birth weight, the higher the risk of OCD and tic disorders, and the shorter the gestational age, the higher the risk of OCD, lending additional support to the dose-response nature of the associations observed in the categorical analyses of birth weight and gestational age.

Additionally, we found that perinatal complications cumulatively contribute to the risk of both OCD and tic disorders, in that the greater the number of adverse perinatal events, the higher the risk for the disorders (illustrated in **Figure 2**)

Table 5. Adverse perinatal events and risk of OCD (study II) or tic disorders (III). All the results remained in the subsequent sibling comparison analysis unless otherwise specified

Perinatal event	Risk of OCD in the offspring (study II)	Risk of tic disorders in the offspring (study III)
Maternal smoking during pregnancy	1-9 cigarettes/day was associated with a 6% increased risk[1]	1-9 cigarettes/day was associated with a 40% increased risk[1]
	≥10 cigarettes/day was associated with a 20% increased risk	≥10 cigarettes/day was associated with a 88% increased risk[1]
Labor presentation	Breech presentation was associated with a 26% increased risk	Breech presentation was associated with a 17% increased risk[2]
Obstetric delivery	Cesarean section was associated with a 9% increased risk	Cesarean section was associated with a 22% increased risk[1]
	Assisted vaginal delivery was associated with a 12% increased risk[2]	-
Gestational age	Very preterm birth was associated with a 61% increased risk[2]	N/A[3]
	Preterm birth was associated with a 20% increased risk	Preterm birth was associated with a 25% increased risk[2]
Birth weight	Low birth weight was associated with a 10% increased risk	Low birth weight was associated with a 26% increased risk[2]
	High birth weight was associated with a 17% increased risk[2]	-
Small for gestational age	10% increased risk[2]	49% increased risk
Large for gestational age	20% increased risk	-
Apgar score at 5 minutes	Distress scores were associated with a 28% increased risk	-
	Near death scores were associated with a 40% increased risk[2]	-
Small head circumference	7% increased risk[1]	31% increased risk[1]

[1] The results did not remain in the sibling comparison
[2] The results did not remain statistically significant in the sibling comparison, but the estimates remained approximately the same
[3] This level of the variable was not included in study III

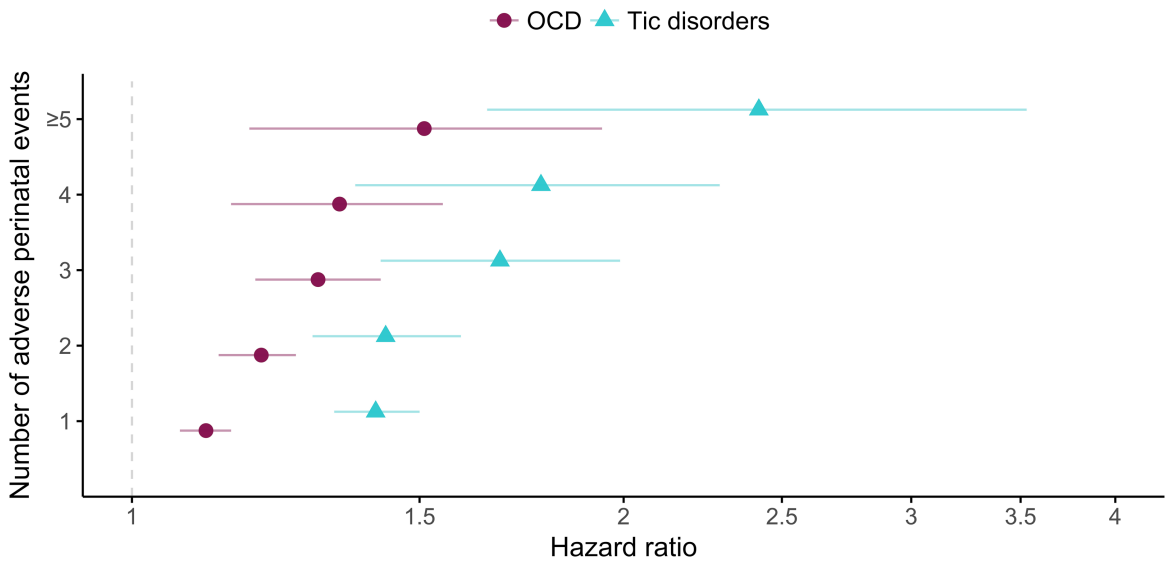

Figure 2. Association between number of adverse perinatal events and OCD or tic disorders, expressed as hazard ratios and 95% confidence intervals

In general, excluding individuals with comorbid psychiatric disorders one (or one cluster) at a time from the analysis attenuated some estimates and reduced precision, but did not indicate that the presence of these disorders explained the associations between the adverse perinatal events and OCD or tic disorders.

5.3 FAMILY CLUSTERING OF TIC-RELATED OCD (STUDY IV)

A total of 4,085,367 individuals were included in the birth cohort for study VI. Of these 1,257 had tic-related OCD and 20,975 had non-tic-related OCD. Tic-related OCD was defined as the combination of both a lifetime OCD diagnosis and a lifetime tic disorder diagnosis.

The estimated risk of OCD in relatives of individuals with OCD increased proportionally to the degree of genetic relatedness in both groups, compared to relatives of individuals without OCD, indicating that OCD is a familial disorder, regardless of tic disorder status. However, the estimates were higher across most types of relatives of individuals with tic-related OCD (**Figure 3)**. Furthermore, twins, full siblings, and maternal half siblings of individuals with tic-related OCD were more than twice as likely to have OCD, compared to the same relatives of non-tic-related OCD.

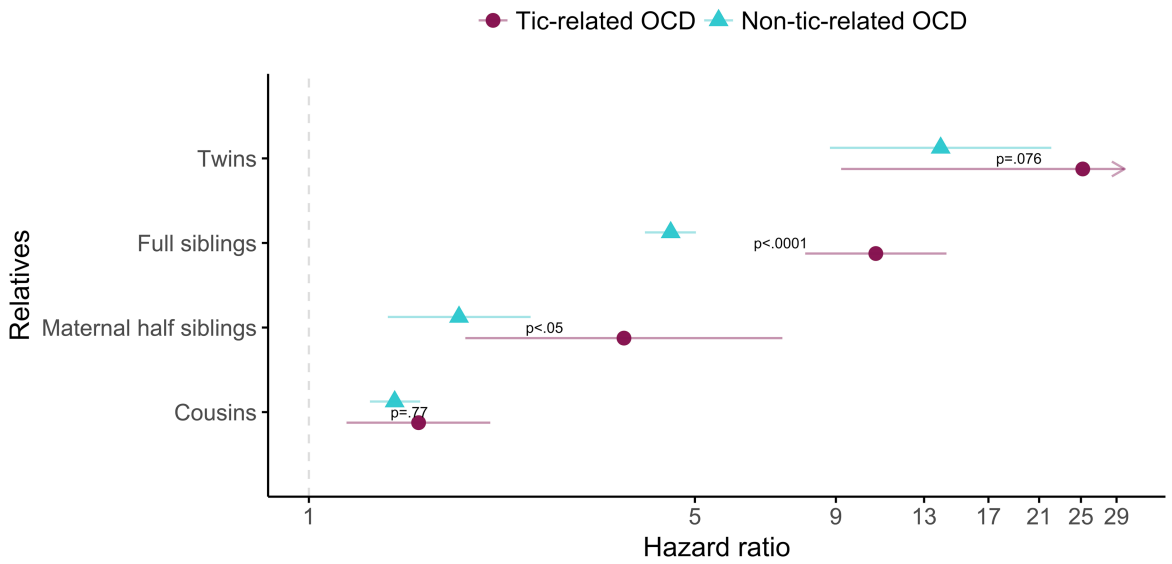

Figure 3. Hazard ratios (95% CIs) of OCD in relatives of individuals with OCD, stratified by tic disorder status, compared to unaffected population. P-values for hazard ratios between OCD groups

Matching the OCD cases by age at first diagnosis did not significantly change the results from the main model, with consistently higher estimates for relatives of individuals with tic-related OCD.

The same pattern of increased risk of OCD in relatives of individuals with tic-related OCD was not observed when, instead of tic disorders, co-occurring ADHD or ASD was used.

5.4 METABOLIC AND CARDIOVASCULAR DISORDERS (STUDIES V & VI)

The total population cohort for study V included 12,497,002 individuals, of which 25,415 had a recorded OCD diagnosis. Furthermore, 2,583,209 families with at least two full siblings were identified from the complete cohort for sibling comparisons. For study VI, the total population cohort consisted of 14,045,026 individuals, of which 7,804 had a recorded tic disorder. From these 14 million people, 2,675,482 families with at least two siblings were identified for sibling comparisons. The difference in sample sizes was due to stricter exclusion criteria in study V, consisting of excluding individuals dying or emigrating before age 6 (because having an OCD diagnosis before then is unlikely) and individuals with psychiatric disorders that are known to be medicated with antipsychotic medication (i.e., organic brain disorder, psychotic disorder, bipolar disorder, pervasive developmental disorder, Tourette syndrome, chronic tic disorders), which in turn has been associated with metabolic syndrome.[87]

Both tic disorders and OCD were associated with an increased risk of metabolic and cardiovascular disorders in general, and specifically with an increased risk of obesity, type 2 diabetes mellitus, and circulatory system diseases. In general, the risks were much larger for tic disorders than for OCD. For example, the risk of having any metabolic or cardiovascular disorder was increased by 45% in individuals with OCD, compared to unaffected individuals, whereas the same risk in individuals with tic disorders was increased by 99%.

When we adjusted for unmeasured familial confounding in the sibling comparison models, we found that the risk of metabolic and cardiovascular disorders in individuals with OCD remained virtually the same. By contrast, for tic disorders, the risk was considerably reduced in the sibling comparison (from 99% increased risk to 37% for any metabolic and cardiovascular disorder). The main results from the fully adjusted models are summarized in **Table 6**.

Table 6. Risk of metabolic and cardiovascular disorders in individuals with OCD (study V) or tic disorders (study VI). All the results remained in the subsequent sibling comparison analysis unless otherwise specified

Metabolic and cardiovascular disorders	Individuals with OCD (study V)	Individuals with tic disorders (study VI)
Risk of any complication	45% increased risk	99% increased risk
Risk of obesity	63% increased risk	176% increased risk
Risk of dyslipidemia	No association in main model, but a 22% increased risk in the sibling comparison	-
Risk of type 2 diabetes mellitus	22% increased risk	67% increased risk[1]
Risk of circulatory system diseases	44% increased risk	76% increased risk

[1] The estimate was reduced and did not remain statistically significant in the sibling comparison

When individuals with different psychiatric disorders were excluded from the analysis, the results remained largely unchanged in both studies. The exception was when individuals with ADHD were removed from the analysis of tic disorders and metabolic and cardiovascular disorders; the estimate was reduced, but remained statistically significant.

The exploratory analyses of the effects of medication on the risk of metabolic and cardiovascular disorders showed similar results in both studies. In OCD patients, the risk of metabolic and cardiovascular disorders was significantly reduced the longer the duration and the higher the dose of SRI medication, compared to OCD patients without SRI medication, independently of additional antipsychotic medication. In tic disorder patients, being on antipsychotic medication for more than one year significantly reduced the risk of metabolic and cardiovascular disorders, compared to tic disorder patients without antipsychotic medication.

6 DISCUSSION

6.1 SYSTEMATIC REVIEW OF ENVIRONMENTAL RISK FACTORS FOR OCD (STUDY I)

This was the first systematic review conducted to summarize the extensive and varied literature on potential environmental risk factors for OCD. The review identified several promising areas, particularly perinatal complications, reproductive cycle events in women, and stressful or traumatic life events. However, most of the studies included were based on small clinical samples and/or retrospective data. Additionally, there has been a substantial heterogeneity and inconsistency in the definitions and measurements of the risk factors, prohibiting direct comparisons between studies. Therefore, none of these areas have provided enough high quality results about true associations for any confident conclusions to be drawn. Conversely, it follows from the methodological limitations of the included studies that none of the other potential risk factors covered in this review can be ruled out either.

Since the publication of the systematic review in 2016, further studies have investigated the role of environmental risk factors in the etiology of OCD. For example, a recent meta-analysis concluded that toxoplasmosis could indeed be a risk factor for the development of OCD[109] and systemic autoimmune diseases were associated with an 85% increased risk of OCD in a Taiwanese population-based study.[110] Increased maternal age was associated with a 30% increased risk of OCD in a Finnish population.[111] Patients with OCD from an outpatient clinic exhibited significantly higher scores of childhood adversities, both compared with healthy controls and unaffected first degree relatives, especially in emotional abuse and emotional neglect.[112] A longitudinal twin study reported that stressful life events predicted the development of obsessive-compulsive symptoms.[113] Lastly, a study of 51 adult survivors of the Kosovo war found a prevalence of 35% for OCD,[114] which is considerably higher than 2% that would be expected in the general population.[7] While important and adding to the accumulation of results pointing at the potential involvement of stressful life events, maternal age, and infections in the development of OCD, these new studies suffer from the same limitations as those included in the systematic review.

In light of the methodological limitations that have dominated the research field, the systematic review also proposed a road-map for future studies on the role of environmental risk factors in the development of psychiatric disorders in general, and of OCD in particular (illustrated in **Figure 4**). This road-map emphasized the importance of using quasi-experimental study designs based on prospectively collected data at the population level. Measured potential confounders, decided *a priori*, should be adjusted for and potentially confounding or mediating effects of comorbid psychiatric conditions should be investigated. A combination of study designs should be applied to synergize the results and exclude alternative explanations of the associations. For example, the family-based study design, including full sibling comparisons, is a convenient method to control for confounding factors that are shared at the family level, including some genetic factors and unmeasured shared environment. The most robust of the family-based designs is the discordant monozygotic twin design, which controls for 100% of

the genes and shared environmental factors, including age- and sex-related factors and shared prenatal factors. Finally, any robust conclusions cannot be expected to be produced from a single study or a single population. It is therefore of critical importance that each finding is independently replicated in other populations.

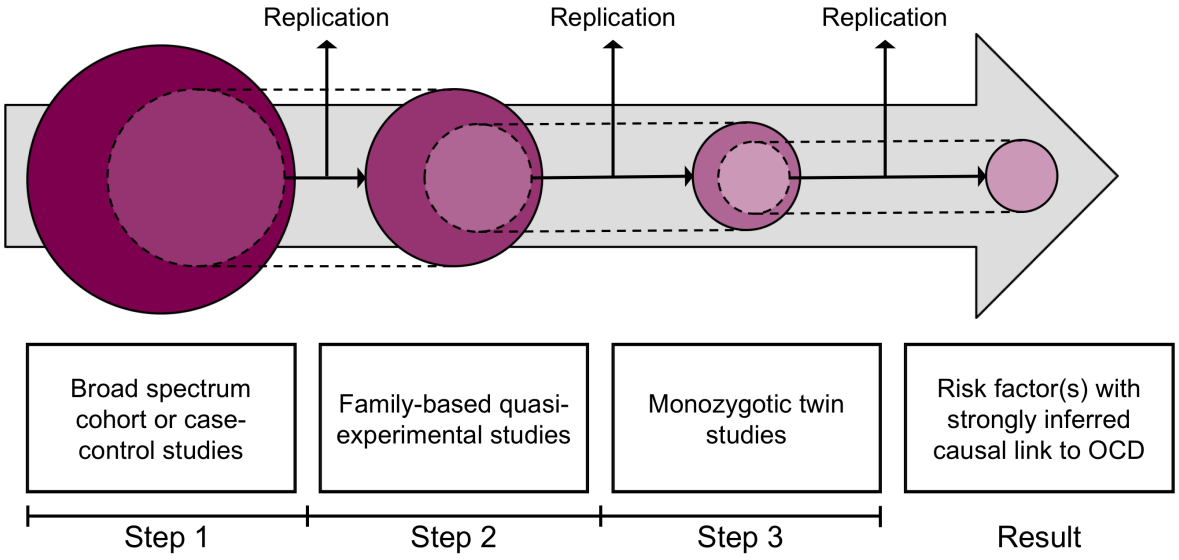

Figure 4. Possible roadmap towards the identification of environmental risk factors in the causal pathway to OCD

This was the first systematic review conducted to synthesize the literature of environmental risk factors for OCD. While no environmental risk factors could be confidently established, the study identified the methodological limitations permeating the field and proposed research strategies to overcome them.

6.2 PERINATAL RISK FACTORS (STUDIES II & III)

With up to 40 years of follow-up, studies II and III found that several adverse perinatal events were associated with increased risk for both OCD and tic disorders. In the fully adjusted models, both disorders were associated with maternal smoking during pregnancy, breech presentation, caesarean section, preterm birth, low birth weight, small for gestational age, and small head circumference. OCD was additionally associated with assisted vaginal delivery and distress and near death Apgar scores at 5 minutes. Dose-response associations between birth weight and both OCD and tic disorders and between preterm birth and OCD further supported the associations. The magnitude of the associations was similar across disorders, but estimates were less precise in tic disorders, due to the lower power. In parallel, knowledge on the genetic basis of both disorders will continue to improve and it may be possible to understand how genetic and environmental risk factors interact or correlate to increase the risk to both disorders.

The results are in line with previous research on both OCD[115-121] and tic disorders.[122-128] However, these previous studies were methodologically limited by often small, clinically-based samples and retrospectively collected data. Additionally, these studies did not control for family confounders, something study II and III addressed in full sibling comparisons. The associations between most adverse perinatal events and OCD remained significant in the sibling comparison, except for small head circumference, for which the association disappeared, and assisted vaginal delivery and small for gestational age, where the estimates remained approximately the same, but were statistically non-significant. Conversely, in tic disorders, only the associations between tic disorders and small for gestational age and birth weight of 2501-3500g remained in the sibling comparison. The estimates of the other associations remained approximately the same, but lost statistical significance, likely due to the lower power in the sibling comparison. The two exceptions were maternal smoking during pregnancy and small head circumference, where the associations disappeared in the sibling comparison.

These results are in line with previous research where higher risk of psychotic or bipolar disorders, ASD, and ADHD has previously been associated with preterm birth,[129] low birth weight,[130,131] and birth complications.[132,133] Previous quasi-experimental studies have provided results showing that the associations between maternal smoking during pregnancy and various psychiatric disorders and other adverse outcomes are better explained by familial confounding,[134,135] in line with our findings on tic disorders. It is therefore of particular interest that the association between mothers smoking more than 10 cigarettes per day during pregnancy and OCD in the offspring remained significant in the full sibling comparison. It is thus clear that, while adverse perinatal events are not specific risk factors for OCD and tic disorders and they seem to increase the vulnerability or susceptibility for many psychiatric disorders, the exception being maternal smoking during pregnancy which as this point has only been associated with increased risk of OCD independent of familial confounding. A specific limitation of the variable for maternal smoking during pregnancy in the Medical Birth Register is that it is self-reported at the first antenatal care visit, therefore more objective measurements are needed to confirm these findings. High levels of cotinine (which is metabolized in the liver from nicotine) in blood samples of mothers during pregnancy have recently been associated with increased risks of ADHD and schizophrenia in offspring.[136,137] Thus, in order to confirm maternal smoking during pregnancy as a risk factor for OCD, cotinine levels in mothers should be examined, preferably supplementing the design with a sibling comparison analysis.

A biological pathway between adverse perinatal events and OCD and tic disorders has not been established. Adverse fetal environments or insults (e.g., hypoxia-ischemia, white matter injury, reduced blood flow, malnutrition, differences in development of the serotonergic system) have been observed to affect brain development.[138-140] Similarly, the fetal programming hypothesis posits that the adaptation to the fetal environment may lead to adverse effects in life.[141,142] It also has been shown that variations in fetal growth are associated with brain development well into childhood and adolescence.[140,143] In recent years, the gut microbiota has been linked to brain function and behavior, including neuropsychiatric disorders.[144] Contact with the maternal

vaginal and intestinal flora at delivery has been suggested to be important for the development of the infant's gut flora.[145] Delivery by cesarean section may thus impair the development of the microbiota and consequently represent a pathway to the development of psychiatric disorders. This would also imply that elective cesarean section would represent an increased risk equal to that of emergency cesarean sections, a theory recently supported in a meta-analysis finding that elective and emergency cesarean sections were associated with virtually identical risks of ADHD and ASD.[146]

These studies contribute new knowledge about the etiology of OCD and tic disorders. Future studies are needed to replicate these findings in other populations. There are also many more adverse perinatal events not covered in these studies, such as prolonged labor and maternal infections that need to be examined. Cesarean section should be studied in more detail to get a better understanding of whether elective cesarean section represents less of a risk for subsequent psychiatric disorders than emergency cesarean sections, or whether the procedure itself (e.g., by means of being unexposed to the gut microbiome) represents an increased risk. Additionally, dose-response associations were observed for the total number of adverse perinatal events in both OCD and tic disorders, whereby the greater the number of events, the greater the risk. This cumulative effect suggests that in the future it may be feasible, once a fuller picture of environmental risk factors emerges, to calculate an 'environmental risk score' for OCD and tic disorders, similar to what has recently been attempted for psychotic disorders.[147]

Taken together, the results suggest that reducing adverse perinatal events could also reduce the risk or even prevent the development of OCD and tic disorders. Amongst all perinatal factors identified, the most plausible targets for prevention work are maternal smoking during pregnancy and, potentially, the use of unnecessary (i.e., elective) cesarean sections.

6.3 FAMILY CLUSTERING OF TIC-RELATED OCD (STUDY IV)

The heterogeneity of OCD may be obstructing progress of identifying etiological factors and treatment success. By identifying more homogeneous subtypes, or even extract unique disorders, future etiological studies, including gene-searching efforts, may be informed and treatment approaches may be more individually refined. The proposed subtype of OCD that has gained the most support is tic-related OCD.

Replicating previous findings, OCD was found to be a familial disorder, with risk increasing in parallel with genetic relatedness.[18,22,38,40] Furthermore, as predicted, the risk of OCD in relatives was highest in individuals with tic-related OCD, compared to the risk of OCD in relatives of individuals with non-tic-related OCD.

Using age at first OCD diagnosis as a proxy for age of onset, our data confirmed previous reports that tic-related OCD is associated with earlier onset.[21,25,26] Early onset OCD has also been linked to increased familiality.[19,20] Therefore, in order to rule out that the increased risk

of OCD in relatives of individuals with tic-related OCD was better explained by the early onset, we matched the patients in the tic-related and the non-tic-related OCD groups closely by age at first diagnosis. The results remained virtually the same, with the risks being higher in the tic-related OCD group than the non-tic-related OCD group.

Another explanation of the increased familiality of tic-related OCD, compared to non-tic-related OCD, could be that tic disorders are highly heritable by themselves.[17,72,148] If that was the case, the combination of OCD and another highly heritable disorder would present with the same pattern of increased risks. To that end, we ran the main analysis twice, first exchanging tic disorders for ADHD and then for ASD. While there was a small, but significant, increase in risk of OCD in full siblings of individuals with OCD and ADHD, compared to full siblings of individuals with OCD but without ADHD, no other significant differences in risks were observed in either ADHD or ASD. These results indicate that the increased familiality of tic-related OCD is not entirely explained by the comorbidity with another highly heritable neuropsychiatric disorder, but is specific to OCD with tic disorders.

What remains unclear is the nature of tic-related OCD, whether it is quantitatively or qualitatively different from OCD (or tic disorders). This cannot be determined from observational register data. An approach to investigate this would instead be by means of genetic research. However, that would require DNA data from considerable sample sizes of both tic-related OCD and non-tic-related OCD. Gene studies have already yielded some results of interest in the combination of OCD and tic disorders. No individual genes have been linked to either disorder but there is evidence that OCD and tic disorders are genetically correlated disorders. [70] At the same time, genome-wide analyses have shown that OCD and tic disorders have at least some genetic components that are distinct from each other, and that the underlying genetic architecture of OCD may be different depending on the presence of tic disorders.[71] Fortunately, the samples of genotyped individuals with OCD are growing steadily worldwide and further progress is to be expected in the not-too-distant future.

Altogether, this is the first study to provide evidence for a tic-related OCD subtype at the population level, confirming the validity of the DSM-5 tic-related OCD specifier, while at the same time confirming previous suggestions that tic-related OCD is a more familial subtype of OCD. Identifying homogeneous subgroups of OCD may also prove essential for ongoing gene-searching efforts.

6.4 METABOLIC AND CARDIOVASCULAR DISORDERS (STUDIES V & VI)

With a follow-up time of more than 40 years and nationwide population cohorts consisting of almost 12.5 million individuals in study V and 14 million individuals million individuals in study VI, we found that both OCD and tic disorders were associated with increased risks for metabolic and cardiovascular disorders. OCD was associated with a 45% increased risk and tic disorders were associated with twice the risk of any metabolic and cardiovascular disorder, and both disorders were more specifically associated with increased risks for obesity, type 2

diabetes mellitus, and circulatory system diseases. The risks were consistently higher in individuals with tic disorders, compared to individuals with OCD (non-overlapping confidence intervals). Whereas the risks remained the same for OCD in the sibling comparison, the risk for tic disorders dropped considerably, indicating either that there are genetic or environmental factors affecting both the likelihood of tic disorders and metabolic and cardiovascular disorders or that siblings of individuals with tics still have undiagnosed tic disorders, or another neuropsychiatric disorder associated with metabolic and cardiovascular disorders.

Excluding individuals with other psychiatric disorders, one disorder (or one cluster) at a time, did not alter the main results considerably; the exception being a reduced, but still significant, effect when excluding individuals with ADHD from the tic disorder analysis. However, in that analysis, 47% of all tic disorders patients were excluded, and it is thus questionable to what extent the remaining 53% are representative of tic disorder patients. Only one naturalistic study had previously examined metabolic syndrome and OCD,[82] finding a higher prevalence than could be expected by chance of metabolic syndrome in the 104 OCD patients. More extensive research has been conducted finding increased risks of metabolic syndrome in individuals with other psychiatric disorders, such as schizophrenia,[78] bipolar disorder,[77] and major depression.[149]

The association between tic disorders and metabolic and cardiovascular disorders has previously only been reported as adverse effects of psychiatric medication, especially antipsychotics.[83-86] The association between psychiatric medication, both antipsychotics and antidepressants, and metabolic syndrome has also been reported in other psychiatric conditions, such as schizophrenia and depression.[87,150-153] These reported associations prompted conducting exploratory analyses to investigate whether the increased risks for metabolic and cardiovascular disorders in individuals with OCD and tic disorders were mainly due to long-term medication. Evidence-based treatment includes SRI medication for OCD[88] and antipsychotic medication for tic disorders.[89,90] Therefore, we conducted exploratory analyses investigating the association between metabolic and cardiovascular disorders and SRI use, with or without antipsychotics, in OCD and antipsychotics use in tic disorders. Contrary to previous reports on use of psychiatric medication in other disorders, we found *negative* associations between the use of medication and risk of metabolic and cardiovascular disorders. A similar, negative association has previously been observed between the use of antipsychotic and antidepressant medication and the risk of mortality in patients with schizophrenia.[154] From observational data, however, conclusions cannot be drawn about whether these decreased risks were due to the medication itself, whether the patients taking medications for OCD and tic disorders are inherently different from those not on medication, or whether the regular contact with health care professionals provides a better control of their general health and promotes healthier lifestyles.

The biological mechanisms behind the observed associations between OCD or tic disorders and metabolic and cardiovascular disorders have so far not been detailed. However, the results of the sibling comparison analyses excluded shared family factors, including genetic and

environmental factors, as the explanation of the associations. Furthermore, the exploratory analyses revealed that long-term medication with SRIs or antipsychotics, did not increase the risk of metabolic and cardiovascular disorder further, but, on the contrary, suggested to decrease the risk. Taken together, this indicates that the observed increase in risk might largely be a functional consequence of the disorders themselves. OCD and tic disorders are highly debilitating disorders affecting daily functioning. This, in turn, may influence lifestyle choices to include smoking, poor diet, and sedentarism, which has been associated with metabolic and cardiovascular disorders.[155] This does not, however, preclude other explanations of the underlying mechanisms, including shared vulnerability for both OCD or tic disorders and metabolic and cardiovascular disorders. For example, in a correspondence letter to study VI, another mechanism was suggested involving impaired dopaminergic transmission. Kuhn et al.[156] noted that tic disorders have been linked to dopaminergic dysfunction and that this in turn has been associated with food intake and consequently the homeostatic processes and metabolism. Epidemiological studies, such as ours, can only offer limited mechanistic explanations but our results generate a number of interesting testable hypotheses.

The results of studies V and VI have important clinical implications for the management of individuals with OCD and tic disorders. In addition to treating the psychiatric disorders, emphasis needs to be put on additional lifestyle interventions and carefully monitoring the physical health of individuals with OCD and tic disorders with long-term follow-up in order to prevent serious health problems and premature death. Future studies should continue mapping the long-term health consequences of these disorders as well as replicating these results in other populations. The mechanisms behind the increased risk of metabolic and cardiovascular disorders in OCD and tic disorders also need further investigating, including the potential role of dopaminergic transmission. Family studies could also elucidate the nature of the association by exploring the risk of metabolic and cardiovascular disorders in unaffected relatives of individuals with either OCD or tic disorders.

Taken together, while OCD and tic disorders are impairing in their own right, these patients are also at an increased risk of adverse long-term health consequences that, so far, have been neglected in clinical practice. Measures need to be taken to regularly monitor the physical health of these patient groups, and ensure they stay on evidence-based treatment. Furthermore, impact of adding lifestyle interventions aimed at reducing cardiovascular risk to the regular management of these patients should be evaluated in clinical trials.

6.5 METHODOLOGICAL CONSIDERATIONS

6.5.1 Register-based research

Register-based research provides unique opportunities to study phenomena that would otherwise have been impossible or too costly to study. Using population-based registers provides nearly complete coverage of the entire population, minimizing selection bias and offering the opportunity to study rare exposures and outcomes. The data has, generally, been

collected prospectively and independently of the research question, which virtually eliminates recall bias and limits bias introduced by the influence of the diagnostic process. The data is also longitudinal, making it possible to study long-term effects and taking time at risk into account.

There are, however, numerous limitations to consider. Since the data is pre-recorded and collected for other purposes than research, important information may be unavailable. That limits both what can be studied and how. For example, for our research purposes, severity scores of OCD and tic disorders would have been very informative and would have opened up the possibility of additional approaches and more detailed analyses but only the presence or absence of the diagnoses is available in the NPR. Additionally, some of the data, such as maternal smoking during pregnancy in the Medical Birth Register, is still self-reported and could thus be subject of information bias.

While being limited to the variables in the registers, these variables may additionally have been subject to change over time or by coding practices between departments or institutions. For example, the medical birth reports, on which the Medical Birth Register is based, has gone through changes, most notably in 1982, changing the definition of some variables (e.g., elective and emergency cesarean section) and introducing others (e.g., maternal smoking during pregnancy). The changing definitions of cesarean section in the Medical Birth Register precluded us from looking at elective and emergency cesarean sections independently in studies II and III, which would have been informative of the potential mechanisms behind the increased risks for OCD and tic disorders. The later introduction of maternal smoking during pregnancy shortened the follow-up time for that specific variable and thereby reducing power in studies II and III.

There may also be a lack of information in the registers. Most notably, the first registered date of diagnosis may not represent a very accurate approximation of date of onset. In fact, individuals with OCD have been shown to delay treatment for a mean of 7 years from onset.[157] This limits what conclusions can be drawn from the timing of the first recorded diagnosis, and also what research questions can be addressed. For example, considering studying reproductive cycle events in women, a first registered OCD diagnosis during postpartum may not represent postpartum onset, but help-seeking behavior for existing problems that have been present for several years. For this reason, and also due to the natural course of these disorders, which generally are chronic in nature, we have preferred using diagnoses of OCD and tic disorders as lifetime diagnoses in our studies.

Missing data is another important limitation in register-based research and it is often not clear what missingness means, and whether the data is systematically missing or missing at random. For some variables in the Medical Birth Register, there is a considerable amount of missing data. For example, in studies II and III, a quarter of the birth cohort had missing values on labor presentation. As suggested by the National Board of Health and Welfare,[96] most of these missing data could be assumed to be normal vaginal births. For scientific research, this assumption cannot be relied on, leaving two potential courses of action: imputing probable values based on the variable's association to other available variables, or to let them remain

missing and thereby not be included in the analyses. While imputation is a valid method for values missing at random, it is not appropriate for values missing not at random,[158] which cannot be assumed here. Furthermore, it is not advisable to impute values when such a large proportion of values are missing. With 25% of missing values for some of the variables which could not be assumed to be missing at random, imputation was not an option. Instead, we performed analyses only on the data available to us. Missing data or misclassification of exposure independent of the association under study should not bias any results. If there is a true association between the exposure and outcome, and there is false negative misclassification of either, then the observed results would be underestimated. In our studies, missing data and misclassification would thus most likely mean that the true associations are even stronger than reported.

6.5.2 OCD and tic disorders in the National Patient Register

Up until December 31, 2013, there were, in total, 37,868 individuals in the NPR with a registered OCD diagnosis, and 6,457 individuals with tic disorders, defined using the algorithm proposed by Rück et al.[99]

Rück et al.[99] confirmed that the validity of the OCD codes in ICD-10 and of the tic disorder codes in ICD-8, ICD-9, and ICD-10 is good. On the other hand, there were unacceptably high rates of false positives of OCD diagnoses in ICD-8 and ICD-9 codes, leading the authors to recommend that only ICD-10 codes should be used for OCD analyses. In Studies IV and V, it was still decided to use ICD-8 and ICD-9 codes to identify cases in order to maximize statistical power and follow-up time. It should, however, be noted that only a small fraction of all OCD cases have received the diagnosis in ICD-8 or ICD-9 only without also having a recorded ICD-10 diagnosis at a later date. For example, in Study VI, 22,232 OCD cases were identified, and of these, only 349 (1.57%) had the diagnosis recorded only in ICD-8 or ICD-9. Running sensitivity analyses using only ICD-10 did not alter the results significantly in either study.

Furthermore, the NPR does not cover the totality of OCD and tic disorder cases in Sweden. Many individuals with OCD or tic disorders do not seek help, only inpatient admissions were included in the NPR before 2001 and the coverage is therefore incomplete before then, and individuals diagnosed by general practitioners and non-specialists are not included. In fact, a study comparing primary care and specialist or in-patient care showed that a majority of OCD patients only appeared in primary care.[159] Even though the characteristics of patients in our registers resemble patients recruited in specialist clinics globally and the prevalence of the disorders corresponds to register-based studies from other countries,[73,74,160] it might be that our cases represent the more severe end of OCD and tic disorders and might not then generalize to individuals with milder symptoms. While we are then fairly certain that our cases were true cases, it is to be expected that there were a considerable number of false negative cases for both OCD and tic disorders. However, this misclassification likely attenuated the effects, suggesting that our results, if anything, are on the conservative side.

6.5.3 The natural experiment

Studies II, III, V, and VI applied natural experiments, or quasi-experimental study designs, in order to further control for unmeasured confounding and exclude alternative explanations. Natural experiments signify studies of events where there is a naturally occurring contrast between being exposed or unexposed.[161]

Randomized controlled experiments are generally regarded as the gold standard of research designs, offering the best possibility to make strong inferences about causality when its assumptions are met.[162] However, there are many research questions for which randomized experiments are neither feasible nor ethical. This is definitely true for research on risk factors and long-term health consequences, where it would not be possible or ethically appropriate to expose a random selection of individuals to, for example, a caesarean section or smoking during pregnancy, to observe the outcome. Instead, researchers have to rely on correlations in observational data of naturally occurring events. However, statistically significant correlations in observational studies do not necessarily mean that there is a causal effect between exposure and outcome.[161] The correlation can instead have alternative explanations, such as genetic mediation, selection bias, reverse causation, misidentification of risk factor, or a confounding variable.[163] Still, the literature is full of correlational studies indirectly implying a causal link.

In order to reduce the number of alternative explanations and strengthen a potential causal inference from observed correlations, several different quasi-experimental study designs have been devised. The difference between a traditional experiment and a quasi-experiment is that the latter lack random assignment.[161] Quasi-experiments are methods designed to control for genetic and environmental confounding in other ways than by randomization. Individually, these designs do not control for all potential confounders, but when different quasi-experimental designs with different strengths and limitations support the same conclusion, causal inference is greatly strengthened.[164] Often, the most feasible quasi-experimental designs include family-based designs. By comparing differentially exposed relatives (such as full siblings, twins, or cousins) some of the genetic factors and a big proportion of unmeasured environmental factors are controlled for.[164] Specifically, by comparing monozygotic twins, 100% of the genetic factors are controlled for, whereas full sibling comparisons control for 50% and half sibling comparisons control for 25%.[134] Full sibling control designs thus inherently control for many unmeasured confounders that are stable within the family but may vary between families, such as socioeconomic factors, parental mental health history, and region of residence, in addition to genetic factors.

There are also some limitations that should be taken into account when using sibling designs. Sibling designs do not control for potential carry-over effects, where the exposure or outcome of one sibling affects the exposure or outcome in another sibling.[165] In studies II and III, this was partially addressed by adjusting for parity, since, for example, a previous cesarean section is an indication of another cesarean section in subsequent deliveries.

Sibling comparisons have lower statistical power than population-based estimates,[166] resulting in broader confidence intervals, and the results need to be interpreted with this in mind. Only focusing on whether statistical significance remains may result in discarding accurate findings due to low statistical power.[167-169] Instead, comparing the magnitude of the estimates to determine whether the sibling comparison confirms the population-based results is preferable. Because only the discordant siblings are informative in sibling controls, the results are sensitive to random measurement errors of the exposure and will attenuate the effects of the observed association.[170] A recent paper demonstrated that sibling control designs control for confounders, but may attenuate the effect of the association by also controlling for mediators shared between siblings.[171] Additionally, sibling controls introduce selection bias in that discordant siblings are more likely to be discordant for confounders as well and may result in spurious associations.[170]

Individual quasi-experimental study designs, while being powerful tools to come closer to causal inference, thus also have their own limitations to take into account and do not control for all possible confounders. It is therefore essential to combine different designs and to *a priori* identify possible measured confounders to adjust for.

6.5.4 Multiple testing problem

None of the studies included in this thesis corrected for multiple testing. The argument for taking multiple testing into account is that if we keep testing different associations long enough, eventually something will turn out to be statistically significant. One way to counter this is to introduce more stringent levels of statistical significance. The Bonferroni method stipulates to multiply the desired significance level by number of performed tests.[172]

On the other hand, the Bonferroni method assumes the general null hypothesis, that all null hypotheses are true at the same time and applies only if the two groups are identical on all variables. Receiving a Bonferroni-corrected significant result would then signify that at least one of the variables is truly significantly different, but would not actually indicate which one. Furthermore, interpretation of results would be dependent on how many other tests were performed, which could easily lead to dismissing true findings.[173] Most importantly, the Bonferroni method requires that tests be independent,[172] which does not apply to the exposures or outcomes in studies II, III, IV, and VI of this thesis.

A preferable course of action, which we chose to take in this thesis was to base the research hypotheses on previous research, describe the methods in great detail, discuss the interpretations and their plausibility, and to promote replication studies in other populations.

6.6 ETHICAL CONSIDERATIONS

The ethical dilemma of epidemiological, register-based research on psychiatric disorders is that sensitive personal data is processed, which constitutes an infringement on the integrity of the individuals unless there is informed consent. On the one hand, the Law on Ethical Vetting (LOE)[174] requires informed consent from all the participants (LOE 16-17§). On the other hand, there is no feasible way to collect informed consent from millions of people and there are no other methods by which to address pertinent research questions involving etiology and long-term health consequences. However, there are exceptions to the requirement of informed consent, such as if the research can be regarded as being of public interest. (LOE 20-22§).

Research conducted in Sweden that involves individual human beings is regulated by the Ethical Review Act (2003:460) and requires approval from an ethical vetting process. The vetting process takes into account human rights and fundamental liberties, that the welfare of the individual is of greater concern than societal or scientific values, and that potential gain of knowledge outweighs potential risks of physical injury, mental injury, or violation of integrity that the study participants are exposed to. Furthermore, the Personal Information Act (PUL)[175] 9§ requires that only the bare minimum of information is acquired, that this information has to be necessary for the study, and that it is used only for the defined purpose of the project. It is therefore of importance to determine exactly what information is needed for the project *a priori.*

Mental health data is considered sensitive personal data (PUL 18§), and therefore ethical vetting was required for studies II-VI in this PhD project. The studies in this PhD project were conducted in close collaboration with the department of Medical Epidemiology and Biostatistics and were thereby covered by their obtained ethical approval for studies investigating the associations between risk factors and the risk for psychiatric disorders as well as the underlying mechanisms (DNR 2013/862-31/5).

The data for this project have been acquired from registers at central authorities and national registers in Sweden. Before the data is obtained for this project, the personal identification numbers were replaced by unique ID numbers and the key is only held at the National Board of Health and Welfare for future updates. Still, with the great amount and detail of information available in the registers, it would be theoretically possible to identify individuals through the combination of key data. However, protecting the privacy and integrity of the participants and not misuse any information discovered should be of highest priority. Furthermore, all results should always be presented in an aggregated form so that identification of individual participants is not possible. When studying very rare events, the combinations of which may result in frequencies of very few affected people, these should not be reported as to avoid undeliberate identification. The data is handled and stored in a secure way to minimize the risk of data misuse.

The etiology and consequences of OCD and tic disorders have so far been neglected in research. The gap in knowledge about these disorders may obscure identifying early detection and the

development of improved intervention strategies. Meanwhile, these disorders are associated with great impairment and disability of the patients as well as societal costs. The studies in this thesis address research questions that may be of value to the individual patients as well as to further research. It is our firm position that the potential benefits of this research, greatly outweigh the marginal risks to the individuals included in these studies.

7 CONCLUSIONS

While numerous potential environmental risk factors for OCD and tic disorders have been previously studied, methodological limitations have precluded any firm conclusions. The literature has, however, provided insight into what areas could be of importance, including birth complications, reproductive cycle events, stressful life events, and infections. These broad risk factors need to be examined in well-controlled studies, ideally at the population level, using prospective longitudinal data, standardized measures and genetically informative designs.

Our empirical studies indicated that a number of adverse perinatal events were associated with higher risks of OCD and tic disorders, independently of shared familial confounders and measured covariates. These perinatal events included breech presentation, cesarean section, preterm birth, and low birth weight. Specific for OCD, maternal smoking during pregnancy was associated with an increased risk, whereas the same association for tic disorders disappeared in the sibling comparison. The number of adverse perinatal events exhibited associations in a cumulative manner, in that the greater the number of events, the greater the risk for OCD and tic disorders. This cumulative effect provides some hope that, in the future, it may be possible to derive environmental risk scores for these disorders. Future studies should also examine additional environmental risk factors for the disorders, as well as replicating these results in other populations, not least to determine whether maternal smoking during pregnancy, ideally objectively confirmed via cotinine levels in utero, might be a specific risk factor for OCD. Combined with parallel advances in genetics research, these results will further contribute to the understanding of the etiology of OCD and tic disorders, and also identify potential areas for prevention and intervention.

Relatives of individuals with tic-related OCD are at a higher risk of developing OCD themselves than relatives of individuals with non-tic-related OCD. These results support the validity of the DSM-5 tic-related OCD specifier. Identifying homogeneous subgroups of OCD may inform treatment selection, earlier detection, and future studies of OCD etiology, including gene-searching efforts. These gene-searching efforts would also serve to uncover the nature of the tic-related OCD subtype. Further investigating whether these patients require different treatment approaches than non-tic-related OCD patients would be advisable, as prior studies have been inconclusive.

OCD and tic disorders are associated with increased risks of metabolic and cardiovascular disorders. The risks in individuals with tic disorders were substantially higher than those in individuals with OCD. However, the risks in the tic disorders study were reduced to about same levels in the sibling comparisons, indicating that environmental or genetic components may partially influence both the tic disorders and the metabolic and cardiovascular disorders, or that the siblings of individuals with tic disorders may have undiagnosed tic disorders or other neuropsychiatric disorders that are associated with metabolic and cardiovascular disorders. Further family studies could help establish if OCD and tic disorders co-aggregate in families of individuals with metabolic and cardiovascular disorders. Future studies should continue examining other detrimental long-term health consequences. From a clinical perspective, the

results of our studies emphasize the importance of monitoring the long-term physical health of individuals with OCD and tic disorders. These results further suggest that lifestyle interventions may be fruitful alongside other standard evidence based treatments to reduce the risk of premature mortality in these patients.

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