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RISK FACTORS OF TOURETTE SYNDROME

A Nationwide Register Study

Susanna Leivonen

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To my family

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SUSANNA LEIVONEN: Risk factors of Tourette syndrome – A nationwide register study
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ABSTRACT

Tourette syndrome (TS) is a neurodevelopmental disorder characterised by both motor and vocal tics. The syndrome's etiology of the syndrome is not fully understood, although it is known that it has a hereditary component. This study aimed to examine prenatal, perinatal and parental risk factors for TS. Another aim was to validate TS diagnoses in the Finnish Hospital Discharge Register (FHDR).

The study identified all children born between 1991-2010 diagnosed with TS or other tic disorders in the FHDR before 2010. The study was based on nested case-control design, and each case was matched to four controls identified from the Finnish Population Register Center (FPRC). Data were collected from FHDR, Finnish Medical Birth Register (FMBR) and FPRC. Conditional logistic regression analyses were used to used to examine the association between the exposures and TS.

Prenatal maternal smoking was associated with TS when comorbid with Attention deficit/hyperactivity disorder (ADHD). Nulliparity was associated with TS, and increasing parity was associated with decreasing risk for TS/CT (Chronic Tic Disorder). The birth weight of 4000-4499g was associated with a decreased risk for TS. Any maternal and paternal psychiatric diagnoses were associated with an increased risk for TS. However, the association between maternal psychiatric disorders, and TS/CT was stronger than the association between paternal psychiatric disorders and TS/CT, and all maternal-specific diagnostic categories were associated with TS/CT. The validity of the register-based diagnoses in the FHDR was good.

This study identified risk factors associated with TS including nulliparity, parental psychiatric disorders and prenatal maternal smoking when TS is comorbid with ADHD. Further research is needed to elucidate the mechanism of the found associations.

KEYWORDS: Tourette syndrome, tic disorder, risk factor, prenatal maternal smoking, parity, parental psychiatruc disorders

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Lastenpsykiatrian oppiaine
SUSANNA LEIVONEN: Touretten oireyhtymän riskitekijät – kansallinen rekisteritutkimus
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TIIVISTELMÄ

Touretten oireyhtymä on lapsuusiässä alkava kehityksellinen neuropsykiatrinen häiriö, jonka ydinoireita ovat sekä motoriset että äänelliset nykimisoireet eli tic-oireet. Touretten oireyhtymän syntyyn vaikuttavat perintötekijät, mutta etiologia ei ole vielä tarkasti tiedossa, ja myös ympäristötekijöiden on arvioitu vaikuttavan häiriön puhkeamiseen. Tämän tutkimuksen tavoitteena oli tutkia äidin raskauden aikaisen tupakoinnin, synnytykseen liittyvien riskitekijöiden sekä vanhempien psyykkisen sairastavuuden yhteyttä Touretten oireyhtymään. Lisäksi tutkimuksessa arvioitiin Touretten oireyhtymän diagnoosin paikkansapitävyyttä Hoitoilmoitus-rekisterissä.

Tutkimusaineisto koostui 1991-2010 syntyneistä henkilöistä, jotka olivat saaneet Touretten oireyhtymä tai krooninen tic-häiriö diagnoosin. Jokaiselle tapaukselle poimittiin neljä verrokkia, jotka oli kaltaistettu sukupuolen, iän ja asuin paikan mukaan. Tiedot kerättiin Hoitoilmoitusrekisteristä, Syntymärekisteristä sekä Väestörekisteristä. Logistisen regressioanalyysin avulla on tutkittu yhteyttä altistuksen ja Touretten oireyhtymän välillä.

Äidin raskauden aikainen tupakointi oli yhteydessä Touretten oireyhtymään silloin, kun lapsella/nuorella oli myös ADHD. Raskauteen ja synnytykseen liittyvistä tekijöistä synnyttymättömyys oli yhteydessä Touretten oireyhtymään. Syntymäpaino 4000g–4499g oli yhteydessä matalampaan Touretten oireyhtymän riskiin. Sekä äidin että isän psykiatrinen diagnoosi oli yhteydessä Touretten oireyhtymään/krooniseen tic-häiriöön, mutta yhteys äidin psykiatrisen sairastavuuden ja Touretten oireyhtymän /kroonisen tic-häiriön välillä oli voimakkaampi. Kaikki diagnostiset kategoriat äitien osalta olivat yhteydessä Touretten oireyhtymään/ krooniseen tic-häiriöön. Hoitoilmoitusrekisteriin kirjatut Touretten oireyhtymä diagnoosit olivat luotettavia.

Tämä tutkimus tunnisti Touretten oireyhtymään liittyviä riskitekijöitä. Lisää tutkimustietoa tarvitaan, jotta voidaan arvioida mihin havaitut yhteydet perustuvat.

AVAINSANAT: Touretten oireyhtymä, tic-häiriö, riskitekijä, raskauden aikainen tupakointi, pariteetti, vanhemman psykiatrinen sairaus

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Abbreviations

ADHD	Attention deficit/hyperactivity disorder
APA	American Psychiatric Association
ASD	Autism spectrum disorder
CI	Confidence interval
CT	Chronic tic disorder
DSM	Diagnostic and Statistical Manual for Mental Disorders
FHDR	Finnish Hospital Discharge Register
FPRC	Finnish Population Register Centre
FMBR	Finnish Medical Birth Register
ICD	International classification of disease
NICU	Neonatal intensive care unit
OCB	Obsessive compulsive behavior
OCD	Obsessive compulsive disorder
OR	Odds ratio
SES	Socioeconomic status
SGA	Small for gestational age
SD	Standard deviation
THL	The Finnish Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos)
TS	Tourette syndrome
WHO	World Health Organization
YGTSS	Yale Global Tic Severity Scale

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Leivonen S, Voutilainen A, Hinkka-Yli-Salomäki S, Timonen-Soivio L, Chudal R, Gissler M, Sourander A. A nationwide register study of the characteristics, incidence and validity of diagnosed Tourette syndrome and other tic disorders. *Acta Pædiatrica*, 2014; 103: 984-90.

II Leivonen S, Chudal R, Joelsson P, Ekblad M, Suominen A, Brown AS, Gissler M, Voutilainen A, Sourander A. Prenatal maternal smoking and Tourette syndrome: A nationwide register study. *Child Psychiatry and Human Development*, 2016; 47: 75-82.

III Leivonen S, Voutilainen A, Chudal R, Suominen A, Gissler M, Sourander A. Obstetric and Neonatal Adversities, Parity, and Tourette Syndrome. *The Journal of Pediatrics*, 2016; 171: 213-9.

IV Leivonen S, Scharf JM, Mathews CA, Chudal R, Gyllenberg D, Sucksdorff D, Suominen A, Voutilainen A, Brown AS, Sourander A. Parental Psychopathology and Tourette Syndrome/Chronic Tic Disorder in Offspring: A Nationwide Case-Control Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 2017; 56: 297-303.

1 Introduction

Dr. Gilles de la Tourette published a paper in 1885, “Etude sur une affection nerveuse caracterisee par de l’incoordination motrice accompagnee d’echolalie et de copralalie” (Study of a neurologic condition characterized by motor incoordination accompanied by echolalia and coprolalia), that described a disorder characterised by incoordination in the form of abrupt and rapid muscle jerks that can be accompanied by articulated or inarticulated sounds (Goetz & Klawans, 1982). Several of Dr. Gilles de la Tourette’s original observations have been confirmed by research during the following 140 years: The condition starts in childhood or during adolescence at the latest, is more prevalent in males and the condition’s severity varies. The motor symptoms often occur first, and they are often first present in the face or upper extremities. Dr. Gilles de la Tourette stated also that the disorder is hereditary. This has been confirmed in both twin studies and population-based studies (Goetz &Klawans, 1982; Knight et al., 2012; Leckman et al., 2014, Price et al., 1985, Mataix-Cols et al., 2015, Johnson et al., 2023). Environmental influences are likely to contribute to the development of TS in addition to its genetic basis (Mataix-Cols et al., 2015; Hoekstra et al., 2013). However, the detailed etiology of the disorder that bears Dr. Gilles de la Tourette´s name remains unclear. The disorder is referred to as Tourette syndrome (TS) in this thesis.

Brain development is a genetically determined, epigenetically programmed and environmentally influenced process that begins early and occurs most rapidly during the prenatal period. Neuronal proliferation, migration, synaptogenesis, myelination and apoptosis, all major events in brain development, start early on in the prenatal period (Tau & Peterson, 2010). The early developmental period is vulnerable, and prenatal and perinatal adversities may have long-term effects on an individual’s development and health. The prenatal environment has also been associated with many psychiatric/neurodevelopmental disorders (Hanson & Gluckman, 2014, Räikkönen et al., 2012).

The pioneering study on pre- and perinatal risk factors for tic disorders was published in 1956 (Pasamanick & Kawi, 1956). Existing studies on the prenatal, perinatal and contributing to the development of TS have been limited (Chao et al., 2014) despite the increasing number of studies examining TS (Black et al., 2014)

during the next 60 years. A systematic review published in 2014 identified 22 studies that are mainly derived from clinical and/or small samples, resulting in inconsistent findings (Chao et al., 2014). The role of pre-and perinatal incidents in the development of TS has remained unclear.

Dr. Gilles de la Tourette also noted the family history of his patients. He described it as follows: "Five of our 9 patients had significant past medical histories: one whose mother´s mental state became peculiar during pregnancy, one whose mother was insane, one whose mother was very nervous and whose grandparents had migraines, one whose grandparents had chorea, whose father was very nervous and whose sister had similar tics, and finally, one patient whose father had a non-painful tic of the face and whose aunt was insane" (Goetz & Klawans, 1982). Parental mental health during the prenatal, perinatal or postnatal period may have an effect on a child´s health and development. Several mechanisms have been suggested as being involved, from genetics and epigenetics to parenting (Stein et al., 2014). Familial aggregation of tic disorders, obsessive compulsive disorder (OCD) and ADHD has been shown repeatedly (O´Rourke et al., 2011, Mathews et al., 2011, Debes et al., 2010, Pauls et al., 1986, Pauls et al., 1991 Hirschtritt et al., 2015), but less is known about the associations between other psychiatric disorders and TS.

TS affects 0.5-0.8 % of all children, and the prevalence of other tic disorders is higher (Scharf et al., 2015, Knight et al., 2012). TS impairs the quality of life and is associated with academic underachievement and increased mortality (Evans et al., 2016, Perez-Vigil et al., 2018 Fernandez and Mataix-Cols., 2020). Identifying risk groups for this disorder may lead to earlier detection of this still underrecognised and underdiagnosed disorder. Given that the etiology of the disorder involves interplay between multiple genetic and non-genetic risk factors, teasing out each factor is essential for understanding the origin of this complex disorder.

This thesis aimed to examine prenatal, perinatal and parental risk factors for Tourette syndrome in a nationwide sample. Additionally, the characteristics of the children and adolescents diagnosed with tic disorders in specialised health care in Finland were described and the validity of Tourette syndrome diagnoses in a clinical sample was studied.

2 Review of the Literature

2.1 Definitions of tics and tic disorders

Tics are defined as involuntary, rapid, recurrent, non-rhythmic motor movements or vocal productions that are of sudden onset and serve no apparent purpose (WHO 1992). Motor tics are contractions in muscles or muscle groups. Common motor tics are eye-blinking, nose twitching and face grimaces and shoulder jerks (Cath et al., 2011; Leckman et al., 2014). The vocal tics are the sounds that are produced when the air flows through the vocal cords. Common vocal tics are throat clearing, grunts, high-pitched sounds and sniffing (Cath et al., 2011; Leckman et al., 2014). Both motor and vocal tics can be simple or complex. The simple tics are restricted to one muscle or muscle group as in the examples above, whereas complex tics may have a more repetitive or compulsive nature and involve sequences of movements. The vocal tics are complex if they are elaborated into words with semantic content. Complex vocal tics include also coprolalia, echolalia and palilalia. Sensory and cognitive tics have also been described in addition to motor and vocal tics. The sensory tics are described as sensory phenomena, either in a ticing muscle or elsewhere, occurring prior to the tic. The execution of a tic may be experienced as a relief after the sensory phenomenon. The cognitive tics have been described as thoughts that are repetitive and a response stimulus. However, unlike obsessions, cognitive tics are not driven by anxiety (Cath et al., 2011; Leckman et al., 2014).

The International Classification of Diseases (ICD) defines tic disorders as syndromes in which a tic is the predominant manifestation. The 10th revision of the ICD (ICD-10), which has been used in Finland since 1995, shows five diagnostic codes for tic disorders: transient tic disorder (F95.0), chronic tic disorder (F95.1), combined motor and vocal tic disorder (F95.2), which is referred in this thesis as Tourette syndrome (TS), other tic disorders (F95.8) and tic disorder unspecified (F95.9). Transient tic disorder persists no longer than 12 months. Either motor or vocal tics exist and persist longer than 12 months in chronic tic disorder. There are multiple motor and one or more vocal tics in Tourette syndrome, although these need not have occurred concurrently (WHO, 1992).

ICD-9 was used in Finland from 1987 to 1995 before ICD-10 and provided diagnostic codes for tic disorder unspecified (3072A), transient tic disorder (3072B),

chronic tic disorder (3072C) and Tourette syndrome (3072D) (Lääkintöhallitus, 1988). ICD-8, used from 1969 to 1986, provided a code 306.20 for tic (Lääkintöhallitus 1969).

ICD-10 Classification of Mental and Behavioral Disorders Diagnostic Criteria for research includes more specific criteria for tic disorders (WHO 1993). Table 1 presents the criteria. The National Institute of Health and Welfare (THL) in Finland provided an ICD classification, including psychiatric disorders, in 1997 that was updated in 2012 (Psykiatrian luokituskäsikirja, 2012). The diagnostic criteria for tic disorders in this are similar to the ICD-10 Classification of Mental and Behavioral Disorders Diagnostic Criteria for research, presented in Table 1 (WHO 1993).

The diagnostic criteria for tic disorders have been rather similar in another widely used diagnostic manual, the Diagnostic and Statistical Manual of Mental Disorders (DSM). The criteria in the DSM-IV-TR included a demand for a no tic-free period of more than 3 consecutive months, which was removed in DSM 5 (APA, 1994). Table 1 presents the current criteria for provisional tic disorder, chronic tic disorder and Tourette´s disorder according to DSM 5 (APA, 2013).

ICD-11, which is not used in Finland yet, lists Tourette syndrome (8A05.00), Chronic motor tic disorder (8A05.01), Chronic phonic tic disorder (8A05.03), transient motor tics (8A05.0Y), other specified primary tics or tic disorders (8A05.0Y), and primary tics or tic disorders, unspecified (8A05.0Z). There are also secondary tics (8A05.1), other specified tic disorders and tic disorders unspecified (8A05.Z). Diagnosis of TS in ICD-11 includes one or more motor and one or more vocal tics of multiple motor tics and one or more vocal tics (World Health Organization, 2023).

Table 1. Diagnostic criteria for tic disorders according to ICD-10 and DSM 5 (modified from WHO (1993), Psykiatrian luokituskäsikirja (2012) and APA (2013)).

TIC DISORDER	ICD-10[1,2]	DSM 5
Transient tic disorder/ Provisional tic disorder	A. Single or multiple motor or vocal tic(s) or both, that occur many times a day, most days over a period of at least four weeks	Single or multiple motor and/or vocal tics are present.
	B. Duration of twelve months or less.	The tics have been present less than one year since the first tic onset.
	C. No history of Tourette syndrome, and not due to physical conditions or side effect of medications.	The onset before the age of 18 years.
	D. Onset before age 18 years.	The disturbance is not attributable to the physiological effects of a substance (e.g. cocaine) or other medical condition (e.g., Huntington´s Disease, post-viral encephalitis).
		Criteria have never been met for Tourette´s disorder or persistent (chronic) motor or vocal tic disorder.
Chronic tic disorder	A. Motor or vocal tics, but not both, that occur many times per day, most days over a period of at least twelve months.	Single or multiple motor or vocal tics, but not both, have been present at some time during the illness.
	B. No period of remission during that year lasting longer than two months.	The tics may wax and wane in frequency but have persisted for more than one year since first tic onset.
	C. No history of Tourette syndrome, and not due to physical conditions or side effects of medication.	The onset before the age of 18 years.
	D. Onset before age 18 years.	The disturbance is not attributable to the physiological effects of a substance (e.g. cocaine) or other medical condition (e.g., Huntington´s Disease, post-viral encephalitis).
		Criteria have never been met for Tourette´s disorder.

TIC DISORDER	ICD-10[1,2]	DSM 5
Tourette syndrome/ Tourette´s disorder	A. Multiple motor and one or more vocal tics that have been present at some time during the disorder but not necessarily concurrently.	Both multiple motor and one or more vocal tics have been present at some time during the illness although not necessarily concurrently.
	B. The frequency of tics must be many times a day, nearly every day for more than one year, with no period of remission during that year lasting longer than two months.	The tics may wax and wane in frequency but have persisted for more than one year since first tic onset.
	C. Onset before age of 18.	The onset before the age of 18 years.
		The disturbance is not attributable to the physiological effects of a substance (e.g. cocaine) or other medical condition (e.g., Huntington´s Disease, post-viral encephalitis).

[1]The ICD-10 Classification of Mental and Behavioral Disorders Diagnostic Criteria for research, [2] Psykiatrian luokituskäsikirja, 2012.

2.2 Epidemiology of tic disorders

2.2.1 Prevalence

The earliest prevalence estimates indicated that TS was a rare disorder with a prevalence of 5/10000 (Robertson, 2008a). Subsequent studies have shown that tic disorders and TS are not as rare as previously thought (Roberson, 2008a, Knight et al, 2012, Scharf et al, 2015). A meta-analysis by Knight et al. (2012) reported a prevalence of 3.0% (95% CI 1.6-5.6) for transient tic disorders and 1.6% (95% CI 0.9-2.8) for chronic tic disorders. The prevalence of TS, based on 13 studies utilizing school-based clinical assessment, was 0.8% (95% CI 0.4-1.5) (Knight et al., 2012). The prevalence was 1.1% (95% CI 0.4-1.5%) for boys and 0.3 (95% CI 0.1-1.2%) for girls (Knight et al., 2012). The most recently published meta-analyses examined the prevalence of TS in 21 population-based studies and reported a prevalence estimate of 0.5% TS (Scharf et al., 2015, Jafari F et al., 2022). A study comparing the time trend of registered TS diagnoses and other neurodevelopmental disorder diagnoses in different countries reported a prevalence of 1031/1 079 796 for TS in Finland (Atladottir et al., 2015).

The meta-analysis did not find geographical variability in the TS prevalence in Europe, North America, the Middle East and Far East (Scharf et al., 2015). A few studies suggest that TS may be less common in sub-Saharan black Africans or African-Americans in North America (Robertson, 2008a, Robertson 2008b). It has been hypothesised that the lower prevalence in sub-Saharan Africa could be due to other medical priorities, lack of awareness or ethnic, genetic or epigenetic differences or also chance, and more studies are needed to confirm this possible geographical variation (Robertson 2008b).

The knowledge is low on the prevalence of tic disorders in adult populations. A meta-analysis of two studies resulted in a prevalence estimate of 0.05% (95% CI 0.03-0.08) for TS in 16–17-year-olds (Knight et al., 2012). A recent meta-analysis of three studies reported the prevalence of 118 cases of TS per million adults (95% CI: 19-751 cases per million adults) (Levine JLS et al., 2019).

2.2.2 Incidence

A Danish population-based study utilizing Danish nationwide registers showed a cumulative incidence of 6.6 per 10 000 (95% CI 5.2-8.0) by the age of 13 for a birth cohort born in 1990-1991 (Atladottir et al., 2007).

A Norwegian study comprising all children born in Norway from 2002-2010 showed that 0,43% of children were diagnosed with TS by age 12 (0,71% boys and

0,15% girls). The same study reported that 0,16% of the children were diagnosed with chronic motor or vocal tic disorder, and of these, 16% were also diagnosed with TS (Suren et al.,2019). Like Finland, Denmark and Norway are northern European countries. There are no previous incidence studies of TS in Finland.

2.2.3 Comorbidities

TS co-occurs often with other neurodevelopmental or psychiatric disorders (Freeman et al., 2000; Hirchtritt et al., 2015; Scharf et al., 2012). Attention Deficit/Hyperactivity Disorder (ADHD) and Obsessive Compulsive Disorder (OCD) have been the most commonly reported comorbidities, although the frequencies vary, presumably due to a variety of study methods and study populations (Freeman et al., 2000; Hirchtritt et al., 2015; Scharf et al., 2012, Khalifa and von Knorring, 2005). An international consortium collecting clinically derived data from 3500 TS-affected individuals in 22 countries in Europe, South America, Australia, North America, Asia and Africa reported that 64% of males and 44% of females were diagnosed with ADHD and approximately 30% of all had OCD (Freeman et al., 2000). A study comprising 1374 participants recruited from a TS specialty clinic and a Tourette syndrome association showed that approximately 85% of the participants met the criteria for a comorbid psychiatric disorder, and 58% had more than one disorder (Hirschtritt el al. 2015). Approximately half of the TS affected individuals had co-occurring ADHD or OCD (Hirschtritt et al., 2015). Mood disorders, anxiety disorders and disruptive behaviour disorders were also present in approximately 30% of TS-affected individuals (Hirschtritt et al., 2015). Other co-occurring psychiatric/neurodevelopmental problems are conduct disorder, learning disorder, sleeping problems, anger control problems and pervasive developmental disorders (Freeman et al., 2000, Hirschtritt et al., 2015).

Population-based studies have also resulted in varying frequencies of comorbidities. A Swedish population-based study derived from a school population reported that approximately 90% of the children with TS had at least one psychiatric comorbidity, and ADHD was found in 68% of the children. Pervasive developmental disorder, depressive disorder, and developmental coordination disorder were found in 20% and OCD in 16% of the children (Khalifa et al., 2006). The study's sample size was small (n=25) (Khalifa & von Knorring, 2006). Another population-based study, derived from Avon Longitudinal Study of Parents and Children, reported that ADHD and OCD were present in approximately 18% and 20% of the children with TS, respectively (Scharf et al., 2012). The percentage of children in that study with TS and without OCD or ADHD was 69% (Scharf et al., 2012). This study was based on questionnaires addressed to mothers and included 50 children with TS (Scharf et al., 2012).

A Norwegian register-based study comprising 1814 children with TS showed that 70% of TS-diagnosed children were diagnosed with other psychiatric and neurological diagnoses. Half of these children were also diagnosed with ADHD and 11% with Autism Spectrum Disorder (ASD). OCD was diagnosed in 7%, anxiety disorders in 7% and behavioural disorders in 6%. Language disorder was diagnosed in 9% and learning difficulties in 6% of the children diagnosed with TS (Suren et al., 2019).

2.3 The clinical course of Tourette syndrome

The mean age of onset is around the age 4-6 years and the symptoms start typically between age 3 and 8 (Cath et al., 2011, Leckman et al., 2014, Johnson KA et al., 2023). Over 90 % of the individuals experience the onset of tics by the age of 10 years (Freeman et al., 2000).

The natural course of tics waxes and wanes. Tics typically occur in bouts, and symptom frequencies vary over a day, weeks and months (Leckman et al., 2014, Johnson KA et al., 2023). The motor tics generally appear first, and simple tics occur before complex tics (Leckman et al., 2014, Cath et al., 2011). The most common tics are the eye-tics that occur among 95% of all individuals with TS (Martino et al., 2012). The motor tics evolve in a rostro-caudal direction after the onset of eye and other facial tics (Leckman et al., 2014). The vocal tics typically onset 1-2 years after the onset of the motor tics (Leckman et al., 2014, Cath et al., 2011). Less than five percent <of whom?> are reported to develop vocal tics first (Cath et al., 2011). The worst tic severity is typically experienced between the ages 10 and 12 (Leckman et al., 2014). The awareness of premonitory urges also increases around age 10 (Cath et al., 2011). The cognitive tics are reported to affect adolescents and adults. The clinical course of TS is favourable for most of the affected individuals over the long term. Over half of the individuals have no tics or minimal tics during young adulthood, about one quarter has mild tics and around one fifth has moderate or worse tic severity (Leckman et al., 2014). Co-occurring symptoms and disorders often cause more impairment than tics in TS (Leckman et al., 2014).

2.4 Diagnosing tic disorders

Diagnosis of tic disorder is based on clinical assessment. Multi-informant data collection including, e.g., history, observation and video, are preferable in the diagnostic process and evaluating the symptom severity due to the condition's waxing and waning nature (Cath et al., 2011, Johnson et al., 2023, Szejko et al., 2021). Symptom onset, duration, severity, disturbance, family history, occurrence in different situations and possible premonitory urges are important data to be

collected. The Yale Global Tic Severity Scale (YGTSS) is the most-used tool for evaluating tics and tic severity (Leckman et al., 2014, Martino et al., 2017, Szejko et al., 2021). The Materials and Methods section, page 48, presents a detailed description of the YGTSS. Further examinations with, e.g., MRI or EEG, are unnecessary if the clinical presentation is typical for tic disorder (Szejko et al., 2021). It is also important to assess the possible comorbid conditions.

The potential differential diagnoses for tics include obsessive compulsive behavior (OCB)/obsessive compulsive disorder (OCD), motor stereotypies, epileptic seizures (absence), dystonia, facialis spasm, chorea, myoclonus and synkinesis and psychogenic movements and functional tic-like behaviours (Cath et al., 2011; Cohen et al., 2013; Johnson et al., 2023, Szejko et al., 2021). Tics may be suppressible, and the experience that tics are partly voluntary may help to differentiate them from other movements (Cath et al., 2011). OCB/OCD is more likely to be ritualised, goal-directed and mostly related to anxiety when tics are compared with obsessive compulsive behavior. The motor stereotypies typically occur at a younger age (<2 years), are more rhythmic, their pattern is more identical and predictable, and the stereotypies may be suppressed by external distractions (Cath et al., 2011).

Tic disorders are diagnosed in Finland according to ICD-10 criteria from 1996 onwards and according to ICD-9 and ICD-8 prior to that. No national guidelines for diagnosing tic disorders exist.

2.5 Etiology of Tourette syndrome

Several studies have supported Gilles de la Tourette´s statement that the illness is hereditary. A twin study by Price et al. (1985) from the United States included 30 probable monozygotic and 13 probable dizygotic twin pairs and showed that concordance rates for any tics were 77% and 23% for monozygotic and dizygotic twin pairs, respectively. The respective figures for TS were 53% and 8%, which suggest a genetic basis for the disorder (Price et al., 1985). Another twin study that included 16 monozygotic twin pairs reported that 94% were concordant for tic disorders and 56% were concordant for TS (Hyde et al., 1992).

Two nationwide, register-based studies have examined the familial clustering of TS and Chronic tic disorder (CT) (Browne et al., 2015; Mataix-Cols et al., 2015). The Danish study identified 5596 individuals with diagnosed chronic tic disorder (TS or CT). The offsprings' risk of being diagnosed with TS/CT was approximately 60 times more likely in the individuals whose parents were diagnosed with TS/CT compared with the offspring of a parent without a TS/CT diagnosis (Browne et al., 2015). The Swedish study identified 4826 individuals diagnosed with TS/CT and compared the risk of tic disorders in their relatives to risk of tic disorders in relatives of controls. The odds ratio to have TS/CT for first-degree relatives of probands with

TS was 19 with 95% CI 15-24 compared with matched controls. The odds ratio for second-degree relatives was 5 with 95% CI 3-7. Additionally, the heritability of the tic disorders estimated by using tetrachoric correlations was 0.77 (Mataix-Cols et al., 2015).

Studies have consistently suggested that the TS etiology is highly heritable; however, the genetic architecture of this disorder is unclear. There are studies reporting potentially important findings for isolated cases of TS (e.g., mutation in L-histidine carboxylase gene), but there are no replicated findings that would increase the risk of TS for larger populations with TS (Pauls et al., 2014). It seems that the TS etiology is multifactorial including both polygenic and non-genetic factors (Davis et al., 2013; Mataix-Cols et al., 2015 Lin W.D. et al., 2022).

Non-genetic environmental factors, in addition to genetic factors, are indicated to be involved in development of TS (Hoekstra et al., 2013, Chao et al., 2014). A systematic review published in 2014 identified 22 studies examining prenatal and perinatal risk factors for the onset of Tourette syndrome, the severity of the symptoms or presence or severity of the comorbidities (Chao et al., 2014). The review concluded that the studies examining the association between pre- and perinatal factors and TS are few and have some major methodological limitations including clinic-based rather than epidemiologically based samples and retrospective data collection. The outcomes also varied significantly. Prenatal maternal smoking and low birth weight were associated most consistently.

The etiology of TS has not been studied in Finland.

2.5.1 Prenatal maternal smoking

In Finland, 15% of the pregnant women used to smoke (Ekblad et al., 2014); luckily, the prevalence has decreased during recent years (Perinatal statistics – parturients, deliveries and newborns, 2019). Smoking is associated with young age, lower socioeconomic status (SES) and marital status as single women are more likely to smoke than married women (Ekblad et al., 2014). Prenatal maternal smoking has been associated with several adverse effects in children (Gould et al., 2020).

There are 10 studies examining the relationship between prenatal maternal smoking and tic disorders. Table 2 lists those studies. Four of the studies are based on population-based samples (Mathews et al., 2014, Cubo et al., 2015, Browne et al., 2016, Brander et al., 2017).

The first prospective population-based study examining the association between prenatal maternal smoking and TS was derived from the Avon Longitudinal Study for Parents and Children (ALSPAC). This study found no association between prenatal maternal smoking and TS or TS/CT (Mathews et al., 2014). The second population-based study is a retrospective case-control study derived from a Spanish

school population. That study found an association between maternal smoking during pregnancy and tic disorders in general. The frequency of maternal smoking was high in both cases (40%) and in the controls (25%) (Cubo et al. 2015).

There are also two recently published, large register-based studies examining the association between maternal smoking during pregnancy and TS/CT. A Danish study showed an association between heavy maternal smoking (≥10 cigarettes/day) and TS/CT. No significant association between light smoking and TS/CT was detected. Furthermore, prenatal maternal smoking (both heavy and light) was associated with TS/CT with comorbid psychiatric disorder, and heavy maternal smoking was associated with TS/CT with ADHD (Browne et al., 2016). A Swedish birth cohort study found an association between maternal smoking and TS/CT in a dose-responsive manner, but the association was attenuated when the cases with comorbid ADHD were excluded. No association was detected in the sibling comparison model either (Brander et al., 2018).

The rest of the studies are based on clinically derived samples (Motlagh et al., 2010, Bos-Veneman et al., 2010a, Bos-Veneman et al., 2010b, Pringshem et al., 2009, Mathews et al., 2006 and Santangelo et al., 1994). Table 2 describes the study designs, outcomes and results of these studies.

Table 2. Studies examining the association between prenatal maternal smoking and tic disorders.

AUTHOR, YEAR, COUNTRY	DESIGN	DATA SOURCE; DIAGNOSTIC CRITERIA.	OUTCOME	COVARIATES	SAMPLE SIZE; STUDIED TIC DISORDERS	AGE RANGE	RESULTS
POPULATION-BASED STUDIES							
Brander et al., 2018 Sweden	Prospective, population/ registered-based cohort	Medical Birth Register, Multigeneration register, Swedish National Patient Register, Migration Register, Cause of Death Register ICD-8, ICD-9, ICD-10	TS/CT	Year of birth, maternal age, paternal age, sex, parity	All singletons born in Sweden 1973-2003 followed until 2013. In the cohort of 3026861 individuals, 5597 were diagnosed with TS/CT.	10-40	Maternal smoking of 1-9 cigarettes was associated with TS/CT in the adjusted model HR=1.40 (95% CI: 1.29–1.52) and ≥10 cigarettes HR=1.88 (95% CI: 1.71–2.06). The association attenuated in the sibling comparison model: HR 0.72 (95% CI 0.54–0.96) for 1-9 cigarettes and HR 0.79 (95% CI 0.55–1.15)
Browne et al., 2016 Denmark	Prospective population-based cohort study	Data on smoking: Interviews of mothers on 17th and 32nd weeks of gestation. Diagnoses from Danish Psychiatric Central Registers and Danish National Hospital Register, ICD-10	TS/CT, TS/CT spectrum including all tic disorders.	Sex, parity, birth year, maternal age, maternal psychiatric history, alcohol consumption, smoking hashish, coffee intake, partner´s smoking, gestational age and birth weight	Cohort included 89 189 births, 667 children with TS/CT spectrum disorders including 531 children with TS/CT	Median duration of the follow-up 13 years.	Heavy smoking (≥10 cigarettes/day) was associated with TS/CT (aHR 1.7, 95% CI 1.2-2.4). No significant association between light smoking and TS/CT. Heavy maternal smoking was associated with TS/CT with comorbid ADHD (aHR 1.9,95% CI 1.1-3.3). No significant association between light smoking and TS/CT and comorbid ADHD. Both light smoking and heavy smoking increased the risk for TS/CT with any psychiatric comorbidity (aHR 1.8, 95%CI 1.2-2.8 and aHR 2.5 95%CI 1.3-4.8)

Mathews et al., 2014, the UK	Prospective, population-based cohort.	Maternal questionnaires supplemented by medical records DSM IV-TR	TS, TS/CT	Maternal age, parity, more/less than adequate weight gain during pregnancy, alcohol use during pregnancy, cannabis use during pregnancy, SES*.	Cohort comprised 6090 children, 50 with TS and 72 with CT.	13-14	No association between prenatal maternal smoking and TS or TS/CT.
Cubo et al., 2014 Spain	Retrospective, population-based nested case-control study.	First screening and the ascertainment of tic disorder by neurologist. DSM-IV-TR	Tic disorders	Family history of tics, comorbid neuropsychiatric disorders.	Cohort of 1858, 64 children with tics, 89 without tics were included in the analyses.	6-16	Prenatal tobacco exposure was associated with tic disorders (OR 3.1 95%CI 1.2-7.6).
			CLINICAL STUDIES				
Abdulkadir et al., 2016, the US, Europe, South Korea	Case-control, retrospective	Questionnaires and interviews. Data on exposure: self-report or parent on child report DSM-IV-TR	Tic severity, OCD and OCD severity, ADHD and ADHD severity	SES	586 cases with a chronic tic disorder; and 527 unaffected family members as controls; mean age= 43.9, SD = 13.2 years; range = 2–83 years, 47.6% males)	mean age = 23.6, SD = 17 years, range = 3–79 years, 66.7% males	No differences between cases and controls regarding maternal smoking *P*=0.89.
Motlagh et al., 2010, the US	Case-control Retrospective	Questionnaires and interviews DSM-IV	TS, TS+ADHD, ADHD	Gender	Cases: TS n=45 TS+ADHD n=60 ADHD n= 52 Controls: n=65	7-18	Maternal smoking >10 cigarettes per day was not associated with TS (OR 4.6, 95%CI 0.5-46.6) or TS+ADHD (OR 8.5, 95% CI 0.97-75.2).

Bos-Veneman et al., 2010, the Netherlands	Cross-sectional Retrospective.	Questionnaire completed by parents. DSM-IV-TR	Tic severity, ADHD severity	Family history of mental disorder or tics	TS 62, chronic motor tic disorder 12, chronic vocal tic disorder 1	6-18	Hyperactivity-impulsivity score was higher in children exposed to prenatal maternal smoking compared and had a family history of mental disorder compared with the ones without family history of mental disorders.
Bos-Veneman et al., 2010, the Netherlands	Cross-sectional, retrospective.	Interviews (YGTSS, CYBOCS, CSBQ, RCADS). Questionnaires on pre- and perinatal factors.	Tic severity and comorbid symptoms of OCD, ASD, depression, anxiety.	Gender, age.	TS 96, chronic motor tic disorder 12, chronic vocal tic disorder 2.	6-18	Maternal smoking during pregnancy was associated with more severe depression and autistic symptoms. (Higher MDD RCADS, CSBQ orientation)
Pringshem et al., 2009, Canada	Retrospective case-control study.	Retrospective. Information booklet completed by the parents. DSM-IV-TR.	TS+ADHD	Low birth weight, premature birth, breathing problem, maternal, alcohol use, gender, family history of ADHD.	Cases: TS +ADHD n= 181 Controls: TS only n=172	5-17	Maternal smoking during pregnancy was associated (OR 2.4, 95% CI 1.2-4.8) with combination of TS+ADHD in comparison with TS only.
Mathews et al., 2006, Costa-Rica, the US	A cross-sectional, retrospective study.	Clinical interview of the cases and the parents. DSM-IV	Tic severity (YGTSS), comorbid OCD, ADHD and self-injurious behavior.	Sex, group, age at the interview, referral source, family history	180	3-59	Maternal smoking was associated with 4-point increase in total tic severity and 3-point increase in phonic tic severity ($p<0.001$ for both). No association was found between maternal smoking and motor tic severity.
Santangelo et al., 1994, the US	Retrospective	Interview of the mothers.	OCD in TS subjects. Gender differences in TS subjects		92	7-62	Yes. Comorbid OCD was associated in utero exposure to coffee, cigarettes and alcohol (TS+OCD 73% of 15 proband were exposed compared with TS-OCD 35% of 34 probands)

*socioeconomic status

2.5.2 Maternal, obstetric and neonatal factors

2.5.2.1 Maternal factors: parity and blood pressure

Pregnancy not only alters female physiology during the pregnancy, but it also may have long term consequences (Clifton et al., 2012). For example, obesity or excess weight gain, altered vascular endothelial function, perturbed metabolic function or altered autoimmune function have been reported post- pregnancy (Clifton et al., 2012). Parity has been associated with neurodevelopmental disorders such as autism, and schizophrenia in Finnish studies (Cheslack-Postava et al., 2014, Haukka J., 2004). However, the mechanisms underlying these associations are unclear.

2.5.2.2 Obstetric factors

Approximately 16-17% of births in Finland are caesarean sections, of which 5% are emergency caesarean sections. Induction of labour is conducted in approximately 31% of the labours. The percentage of inductions has been increasing during the last 20 years as the percentage of caesarean sections has been quite similar (THL, 2019).

Induction of labour can be conducted when the risks of continuing the pregnancy are greater than the risks of induction. Induction can be related to maternal or foetal factors. The most common indications leading to induction are post-term pregnancy, premature rupture of membranes, preeclampsia, maternal hypertension, maternal chronic illness, blood type immunization, foetal growth restriction, diabetes, gestational heptoses, and oligohydramnios (Kruit et al., 2016). Induction targets vaginal labour by cervical ripening and/or stimulation of uterine contractions. Induction of labour increases the risk for caesarean section (Kruit et al., 2016). Induction of labour has been associated with increased odds for autism or pervasive developmental disorder in large population-based studies in the United States and in Finland (Gregory et al., 2013, Polo-Kantola et al., 2014). It was hypothesised that, e.g., exogenous oxytocin used in induction/augmentation could explain the detected association. However, a recently published study based on register data that also included siblings found no increased risk for autism after induction of labour when the exposure discordant siblings were included in the analyses (Oberg et al. 2016).

2.5.2.3 Neonatal factors

Neonatal factors such as prematurity, low birth weight, foetal growth restriction and low Apgar scores have been associated with an adverse neurodevelopment (Miller et al., 2016) and some childhood onset neurodevelopmental disorders (Sucksdorff et al., 2015).

The World Health Organization defines preterm as babies born alive before 37 weeks of pregnancy are completed. Subcategories are extremely preterm < 28 weeks, very preterm 28 to <32 weeks and moderate to late preterm 32 to <37 weeks. The proportion of babies born preterm in Finland has decreased a little in recent years, being 5.9% in 2021 (THL, 2021).

Prematurity is associated with both structural and functional changes in the brain (Salmaso et al., 2014). The global injury has been explained by chronic hypoxia caused by immature lung development (Salmaso et al., 2014). Prematurity is associated with adverse neurodevelopmental outcomes. A meta-analysis of 14 studies examining academic achievements, 12 studies examining executive functions and 9 studies examining behavioural problems, published between 1998 and 2008, concluded that deficits in attention problems, poor executive functions and internalising behaviour are associated with prematurity (Aarnoundse-Moens et al., 2009). Several studies have showed an association between prematurity and ADHD (Franz A.P. et al., 2018). A Finnish study also demonstrated an increasing risk for ADHD by every declining week of gestation (Sucksdorff et al., 2015).

Low birth weight is defined as a weight of less than 2500g irrespective of gestational age. Subcategories include very low birth weight <1500g and extremely low birth weight < 1000g. In 2021, 4,2% of newborns in Finland weighing less than 2500g and 0.7 % had very low birth weight (THL, 2021). A mean weight of a Finnish baby boy in 2021 was 3562g; the respective figure for a baby girl was 3448g (THL, 2021).

Small for gestational age (SGA) refers to weight and length below 2 standard deviations for gestational age (ICD-10). SGA refers both to babies that are naturally small and healthy and to babies that are small due to foetal growth restriction. Foetal growth restriction describes a condition when a baby has not reached its growth potential. Foetal growth restriction is associated with neurodevelopmental deficits (Miller et al., 2016). There are also studies showing an association between foetal growth restriction/low birth weight and ADHD and autism (Sucksdorff et al., 2015, Class et al., 2014). The mechanisms are yet unclear (Class et al., 2014). Several other factors are also associated for a baby to be SGA including maternal or paternal short stature, low weight, ethnicity, nulliparity, smoking, mother being SGA and maternal medical conditions, e.g., hypertension (McCowan & Horgan, 2009).

The Apgar score was developed by Dr. Virginia Apgar over 60 years ago (Finster & Wood, 2005). It was intended to predict survival during the neonatal period, and it has remained valid through the decades for that purpose (Casey et al., 2001). Table 3 shows the five items included in the Apgar scores. The items are evaluated at 1 and 5 minutes after birth. (American Academy of Pediatrics Committee on Fetus and Newborn; American College of Obstetricians and Gynecologists Committee on Obstetric Practice, 2015). Dr. Apgar suggested categorisations of low 0-3,

intermediate 4-6 and normal 7-10. However, few neonates score 0-3; thus, 0-6 is often combined in studies to indicate a low Apgar score (Ehrenstein V, 2009). An Apgar score is influenced by several factors including maternal sedation, congenital malformations, gestational age, trauma and inter-observer variability (American Academy of Pediatrics Committee on Fetus and Newborn; American College of Obstetricians and Gynecologists Committee on Obstetric practice, 2015); thus, an asphyxia diagnosis cannot be given based only on Apgar. For population level, low Apgar scores (1min and 5min) are associated with increased neurological morbidity (Leinonen et al., 2018).

Table 3. Apgar score (adapted from AAP, 2015)

SIGN	**SCORE**		
	0	1	2
Color	Blue or pale	Acrosyanotic	Completely pink
Heart rate	Absent	< 100beats/min	>100 beats/min
Respirations	Absent	Weak, cry, hypoventilation	Good, strong cry
Muscle tone	Limp	Some flexion	Active motion
Reflex irritability	No response	Grimace	Cry or active withdrawal

2.5.2.4 Neonatal treatment

Monitoring and treatment at the neonatal intensive care unit (NICU) may reflect several different factors related to neonate birth complications. Monitoring and/or treatment at the NICU have been associated with childhood autism and pervasive developmental disorder (Polo-Kantola et al., 2014).

2.5.2.5 Maternal, obstetric and neonatal factors and TS

Table 4 lists the majority of the studies examining the associations between obstetric factors, neonatal factors and TS or tic disorders. There are four population-based studies altogether (Mathews et al., 2014, Cubo et al., 2015 Khalifa et al., Brander et al., 2017), of which two were prospective (Mathews et al., 2014, Brander et al., 2017). One study examined all tic disorders (Cubo et al., 2015) and one examined pre- and perinatal optimality score and no specific factors (Khalifa and von Knorring, 2005). A prospective population-based study reported that being second or later born vs. first born was associated with decreased odds for TS/CT. Maternal alcohol and cannabis use and inadequate weight gain were also associated with TS/CT. No association was found between birth weight, preterm labour or maternal hypertensive disorder and TS/CT (Mathews et al., 2014). A retrospective case-control study

derived from a Spanish school population found that caesarean section was associated with tics. There were no differences in that study between children with and without tics regarding exposure to gestational age, birth weight, Apgar score, and prematurity (Cubo et al., 2015).

A Swedish birth cohort study reported that impaired foetal growth, preterm birth, breech presentation and caesarean section were associated with higher risk for TS/CT in that study (Brander et al., 2017).

The rest of the studies were derived from clinical populations most of them including < 200 participants (Pasamaniac and Kawi, 1956; Leckman et al., 1987; Burd et al., 1999; Motlagh et al., 2010, Bos-Veneman et al., 2010; Pringshem et al., 2009, Mathews et al., 2006, Abdulkadir et al., 2016). The first study examining perinatal risk factors for tic disorders was conducted in the 1950s. Pasamanick and Kawi examined the birth records of 51 “tiquers” and 51 controls. A proportion of at least one pregnancy complication were 33.3% and 17.6% among cases and controls, respectively, but the results were not statistically (Pasamanick and Kawi, 1956). Table 4 describes the studies.

Table 4. Studies examining the associations between obstetric and neonatal factors and tic disorders.

AUTHOR/ YEAR/ COUNTRY	DESIGN	DATA SOURCE; DIAGNOSTIC CRITERIA.	OUTCOME	COVARIATES	SAMPLE SIZE; STUDIED DISORDERS	AGE RANGE	RESULTS
POPULATION-BASED STUDIES							
Brander et al., 2017, Sweden	Cohort, prospective	Medical Birth Register, Multigeneration register, Swedish National Patient Register, Migration Register, Cause of Death Register ICD-8, ICD-9, ICD-10	TS/CT	Year of birth, maternal age, paternal age, sex, parity.	All singletons born in Sweden 1973-2003 were followed until 2013. In the cohort of 3026861 individuals, 5597 were diagnosed with TS/CT.	10-40	Birth weight ≤2500g and 2501-3500g were associated with TS/CT (HR=1.26, 95% CI 1.06–1.51, HR=1.12, 95% CI: 1.06–1.19, respectively). In the sibling comparison model, birth weight ≤2500g was not associated with TS/CT (HR=1.20 (95% CI: 0.80–1.80). Birth weight 2501–3500 g remained associated with TS/CT (HR=1.23 95% CI: 1.07–1.41). SGA was associated with TS/CT in both the adjusted model and the sibling comparison model (HR=1.49, 95% CI: 1.30–1.70 and HR=1.46, 95% CI: 1.06–2.01, respectively).
Mathews et al., 2014, the UK	Cohort, prospective	Maternal questionnaires supplemented by medical records DSM IV-TR	TS, TS/CT	Maternal age, maternal smoking, more/less than adequate weight gain during pregnancy, alcohol use during pregnancy, cannabis use during pregnancy, SES.	Cohort included 6090 children, 50 with TS and 72 with CT.	13-14	Parity second or later born vs. first born was associated with decreased odds for TS/CT (OR 0.7, 95% CI 0.5-0.97). Hypertensive disorders, Apgar score at 5 min, preterm birth were not associated with TS/CT.

Khalifa et al., Sweden	Case control	Preliminary screening by questionnaires, followed by interview and clinical assessment. Medical records. DSM-IV	TS, CT		Total population 4479, 25 with TS and 58 with chronic tic disorder, 25 children with transient tics, 25 controls with same age, sex and school as children with TS.	7-15	Mothers of children with TS were 2 times more likely to have had complications during pregnancy. (non-optimality score 61 for TS and 31 for controls).
Cubo et al., 2015, Spain	A nested case-control study, population based	First screening and the ascertainment of tic disorder by neurologist. Birth certificates and questionnaires. DSM-IV-TR	Tic disorders	Family history of tics, comorbid neuropsychiatric disorders, body mass index.	Cohort 1858. 64 with tics, 89 without tics were included in the analyses.	6-16	Cesarean section was associated with tic disorders (OR 5.8, 95% CI 1.6-20.9). No differences in frequencies of prenatal alcohol exposure, gestational age, vaginal delivery presentation, perinatal hypoxia, Apgar score, birth weight/length, prematurity, other significant co-existent medical conditions between children with and without tic disorders. Neonatal respiratory distress syndrome and prenatal infection were not associated with CT.
CLINICAL STUDIES							
Abdulkadir et al., 2016 the US, Europe, South Korea	Case control	Questionnaires and interviews. Data on exposure: self-report or parent on child report DSM-IV-TR		SES*	586 cases recruited from Tic genetics study. 527 unaffected family members as controls		More cases than controls were exposed to at least one pregnancy complication, and premature birth. Morning sickness requiring medical attention were associated with CT. The total number of pre- and perinatal complications was higher in cases.

Motlagh et al., 2010, the US	Case control, retrospective.	Questionnaires and interviews. DSM-IV	TS, TS+ADHD, ADHD	Gender	Cases: TS n=45 TS+ADHD n=60 ADHD n= 52 Controls: n=65	7-18	No statistically significant differences were found between the groups regarding birth weight, prematurity or delivery complications.
Bos-Veneman et al., 2010, the Netherlands	Cross-sectional, retrospective.	Interviews regarding tic severity. Questionnaires regarding pre- and perinatal information.	Current and worst ever tic severity.		TS 62, chronic motor tic disorder 12, chronic vocal tic disorder 1		Tic severity score was higher in the ones exposed to pregnancy or delivery complications compared with the ones who were unexposed.
Bos-Veneman et al., 2010, the Netherlands	Cross-sectional, retrospective	Interviews on tic severity and severity of comorbid disorders. Questionnaires	Tic severity, severity of OCD, ASD, depression and anxiety symptoms.	Gender and age.	TS 96, chronic motor tic disorder 12, chronic vocal tic disorder 2.		Patients with pregnancy complications had lower CYBOCS ratings.
Pringshem et al., 2009, Canada	A nested case-control. Retrospective.	Information booklet completed by the parents. DSM-IV-TR.	TS+ADHD	Maternal smoking, maternal alcohol use, gender, family history of ADHD	Cases: TS +ADHD n= 181 Controls: TS n=172	5-17	Birth weight <2500g (OR2.7, 95% CI 1.03-7.29) and prematurity < 37 weeks (OR 2.9, 95%CI 1.1-7.8) were associated with TS+ADHD compared with TS only. No significant differences between the cases and controls regarding maternal hypertension, operative delivery, SGA**.
Mathews et al., 2006, Costa-Rica, the US	Retrospective.	Clinical interview of the cases and the parents. The YGTSS. DSM-IV	Tic severity, comorbid OCD, ADHD and self-injurious behavior	Sex, group, age at the interview, referral source, family history	180	3-59	Birth weight, perinatal distress or prenatal problems were not associated with tic severity or comorbid OCD. Birth weight and number of prenatal problems were associated with increased risk of comorbid ADHD (OR 0.7, 95%CI 0.5-0.9 and (OR 3.0, 95% CI 1.3-6.9).

Burd, 1999					Cases 53, controls 265		
Leckman et al., 1990, the US	Retrospective.	Interview of the mother and YGTSS.	Current tic severity		31		Maternal stress and vomiting during pregnancy were associated with tic severity.
Leckman et al., 1987, the US					6 pairs of monozygotic twins discordant for TS.		The affected twin´s birth weight was lower than the unaffected twins' (p= 0.006).
Pasamanick and Kawi, 1956, the US	Retrospective	Examination of birth records			51 children with tic and 51 controls matched by race, sex, SES and maternal age.		Among mothers to children with tics, 33.3% had at least one complication compared with 17.6% of mothers of children without tics (OR 2.3, 95% CI 0.9-5.9) p=0.07.

*Socioeconomic status **small for gestational age

2.5.3 Parental psychiatric disorders

Psychiatric disorders are common (Kessler et al., 2009) and contribute to an individual's disability (Rehm J. & Shield K.D., 2019). Psychiatric disorders impact both the individual with the disorder and the family (Schultze et al., 2005). Perinatal maternal psychiatric disorders have been associated with adverse outcomes in offspring, including emotional, behavioural and cognitive development (Stein et al., 2014). It was also shown that paternal psychiatric disorders can be associated with offspring adverse outcomes (Stein et al., 2014). The mechanisms behind the associations between parental psychiatric disorders and a child's development are complex and include several possible pathways. Prenatally occurring direct biological effects are specific to mothers because genetic or postnatally occurring events may reflect both maternal and paternal influences. Possible factors explaining the association are 1) shared genetic factors, 2) epigenetic modification, 3) foetal programming, 4) maternal programming, 5) chronic exposure, 6) interparent conflict, 7) parenting (Stein et al., 2014). The associations may also be moderated by some factors (e.g., socioeconomic status and sex). Parental psychiatric disorders have been associated with childhood onset neurodevelopmental disorders including autism and ADHD (Jokiranta et al., 2013, Joelsson et al., 2017).

Several studies have examined familial aggregation of OCD, ADHD and tic disorders (Hirsctritt et al., 2015, O'Rourke et al., 2011, Mathews and Grados, 2011, Debes et al., 2010). Familial aggregation of tic disorders and OCD was shown in nationwide register studies (Browne et al., 2015, Mataix-Cols et al., 2015). Fewer studies have examined the associations between non-OCD and non-ADHD parental psychiatric diagnoses and TS. Table 6 lists studies examining the associations between parental psychiatric disorders (other than OCD, ADHD and tic disorders) and TS or rates of psychiatric disorders in relatives of TS probands compared with relatives of controls.

There are two population-based studies. A prospective population-based study comprising 122 children with TS/CT showed an association between self-reported maternal anxiety and prenatal depression and TS/CT (Ben-Shlomo et al., 2015). Another population-based study comprising 25 children with TS suggested that first-degree relatives of the cases with TS had more psychiatric diagnoses, mostly tic disorders, ADHD, OCD, and depression compared with relatives of controls (Khalifa and von Knorring, 2005).

A pioneering clinical study published in the UK in the 60s showed that 31% of the children with tics had a parent with a psychiatric illness compared with the 9% of children attending the dental clinic. The majority was mothers having an affective disorder ($p<0.02$) (Corbett et al., 1969). A family study of 130 TS probands reported that affective disorders and any behavioural disorders were more common among the relatives of TS probands compared with relatives of the controls. The study

included first, second and third degree relatives (Comings and Comings, 1990). No differences were found when only first-degree relatives were included. Another family study reported that generalised anxiety disorder, major depressive disorder, panic disorder and phobia were elevated among first degree relatives of TS probands. Further analyses in this genetically focused study found no significant differences when the relatives with TS, CT or OCD were excluded and probands depression was taken into account (Pauls et al., 1994).

A recently published clinical study comprising 1364 TS-affected persons and their 1142 first degree relatives found genetic correlations between mood and anxiety disorders and TS; these relationships were mediated by the presence of co-occurring OCD and/or ADHD (Hirschtritt et al., 2015).

Table 5. Studies examining the relationship between parental non-OCD and non-ADHD psychiatric and TS.

AUTHOR, PUBLICATION YEAR, COUNTRY	STUDY DESIGN	DATA SOURCE, DIAGNOSTIC CRITERIA	OUTCOME	COVARIATES	SAMPLE SIZE	AGE RANGE	RESULTS
POPULATION-BASED STUDIES							
Ben-Shlomo et al., 2015, UK	Prospective, population based	Maternal questionnaires supplemented by medical records DSM IV-TR	TS/CT	SES, in addition the final analyses are included.	Cohort included 6090 children, 50 with TS and 72 with CT.	13-14	Self-reported chronic maternal anxiety and prenatal maternal depression were associated with TS/CT (OR 2.2, 95% CI 1.2-3.8 and OR 1.9 95%Ci 1.0-3.2).
Khalifa et al.	Population based, retrospective	Preliminary screening by questionnaires, followed by interview and clinical assessment. DSM-IV	TS	No.	Total population 4479, 25 with TS and 58 with chronic tic disorder. 25 children without tics and 25 children with transient tics with same sex, age and school were chosen as controls.	7-15	80% of the 1st degree relatives of children with TS reported some psychiatric illness compared with 20% of the control children (p<0.001). The most common ones were tic disorders, ADHD, OCD and depression.
CLINICAL STUDIES							
Hirsctritt et al., 2015, the US		DSM-IV-TR			1142 TS affected individuals		
Comings et al., 1990, the US		Questionnaires and interviews of the parents of the probands. DSM-II-R			130 TS probands with 1851 relatives and 25 controls with 541 relatives. Probands were from City of Hope Tourette Syndrome program and the controls were recruited from the		Among the relatives of TS patients, 30.6% had some behavior disorder (ADHD, learning disorder, alcoholism, drug abuse, obesity) compared with 6.1% among relatives of the controls (p<.0001). 5.2% of the TS probands' relatives had

					families attending the genetic clinics for prenatal diagnosis due to maternal age >35.		affective disorder compared with 0.8% of control relatives ($p<0.0005$). No differences between the rates of affective disorders were noted when only first-degree relatives were examined.
Pauls et al., 1994, the US	Case control	DSM-III	Interview		338 biological first-degree relatives of 85 probands, 92 relatives of 27 unaffected controls, 21 non-biological relatives of 6 adopted TS probands. Probands were primarily selected from members of TSA. Controls were volunteers.		Frequencies of generalised anxiety disorder, major depressive disorder, panic disorder and phobia were elevated among first-degree relatives of TS probands ($p<0.05$). The results remained significant only for major depressive disorders when the relatives without TS, CT and OCD were excluded. When the probands were divided into groups with and without MDD, there was no significant difference rate of MDD in relatives in a group where TS probands did not have MDD.
Cooper et al., 2003, the UK		DSM-III-R	Interview of one or both parents.			7-16	

2.6 Tic disorders in Finnish health-care system in brief

The Finnish health-care system was based on a municipal health-care system during the study period, but wellbeing services counties are responsible for the health-care services since 2023. However, primary health care is provided by health centres and includes maternity clinics, child health clinics and school health care. Primary health care in Finland is free of charge for children and adolescents.

Nearly all children in Finland visit child health clinics several times during the first year and yearly up to age seven when the controls at school health care begin. Public health nurses and physicians collaborate in the child health clinics to follow a child's health, growth, and development. The child is referred to specialised health care if a child is suspected to have growth or development deviations or diseases that need further evaluation. Children with simple tics that do not necessarily need treatment may be followed in the child health clinics.

Specialised health care is provided by university and central hospital clinics. Access to specialised health care requires a referral from a physician, e.g., from primary healthcare or private clinics.

Children with complex neurodevelopmental disorders (e.g., suspected TS that needs treatment) are mostly referred to a child psychiatrist or occasionally to child neurologist depending on possible co-occurring symptoms and local traditions. Some of the children may receive treatment in private clinics. Health professionals are obliged to provide the data from the visits, e.g., diagnoses to population-based registers, including data on health-care service use. Data of the children diagnosed in specialised health care is registered to the Finnish Hospital Discharge Register (FHDR). The FHDR include personal identity code, date of admission and discharge and primary diagnosis at discharge, together with three possible subsidiary diagnoses. The Methods and materials section, page 52, provides a detailed description of the FHDR.

2.7 Nationwide registers as data source for epidemiological studies

Nordic countries have a long tradition of collecting administrative population data, including health-care related data (Erlangsen and Fedyszyn, 2015; Sund, 2012). An increasing number of studies have used nationwide registers as data source for epidemiological studies of both somatic and psychiatric disorders. Studies have provided information on health services, e.g., prevalence and incidence, outcome and etiology of psychiatric disorders (Munk-Jorgenssen and Østergaard, 2011). Linking data between several nationwide registers on an individual level is possible by using personal identity codes. The strengths of this approach are that the studies

are representative for nationwide populations, longitudinal follow up from prenatal period to death, loss to follow-up is minimal, sample sizes are large and it is possible to take several covariates into account (Erlangsen and Fedyszyn, 2015).

The limitations of using register-based data are that degree of hospitalisation or referrals to specialised healthcare affect the representativeness, and the validity of the register-based diagnoses may vary. The time of the disease onset also cannot be determined based on register-based diagnoses (Erlangsen and Fedeszyn, 2015, Munk-Jorgenssen and Østergaard, 2011).

2.8 Validity of the diagnoses in the Finnish Hospital Discharge Register

Several studies, including 10 studies focusing on psychiatric disorders, have examined the validity of the diagnoses in the FHDR in comparison to external data (Sund, 2012). Psychotic disorders have been the most frequently examined. The largest study examining the validity of schizophrenia diagnoses showed that 80-82% of diagnoses were correct when the latest diagnosis or the diagnoses given 1982 were included (Pihlajamaa et al., 2008). The validity of the diagnoses in the FHDR is in line with the validity of the Swedish National Inpatient Register (Sund 2012, Ludvigsson et al., 2011).

The validity of two childhood onset neurodevelopmental disorders' diagnoses has been studied in the FHDR. The validity of an autism diagnosis has been examined in a study that used Autism Diagnostic Interview-Revised to interview the caregivers of the children diagnosed with autism. The results showed that 77/80 (96%) of the children having an autism spectrum diagnosis in the FHDR fulfilled the diagnostic criteria (Lampi et al., 2010). The validity of ADHD diagnoses in the FHDR was examined in a study that was based on telephone interviews of the parents based on the ADHD section of the Development and Well-Being Assessment (DAWBA). The results showed that 61 of the included 68 children (88%) met the full diagnostic criteria for ADHD according to DSM-IV criteria (Joelsson et al., 2015).

No previous validation study of tic disorder diagnoses in the Finnish Hospital Discharge Register exists. Rück et al. have examined the validity of the tic disorder diagnoses in the Swedish National Patient Register by chart review. The positive predictive value, defined as the number of the correctly diagnosed cases divided by the sum of true and false positives, was 97% in ICD-10 (Rück et al., 2015). The same study also examined the charts of 43 individuals diagnosed with epilepsy or depression; no false negative cases of tic disorders were detected (Rück et al., 2015).

2.9 Gaps in the existing literature

A growing body of evidence exists indicating that prenatal, perinatal and parental factors are associated with neurodevelopmental disorders, but there is a gap in the literature on the relationship between these factors and TS. The most studies on the topic when this study started were clinical studies with small sample sizes and varying outcomes, resulting in inconsistent results. There were no studies examining the association between prenatal, perinatal or parental factors and TS in Finland. No nationwide, register-based studies were published that examined prenatal maternal smoking, obstetric or neonatal factors and parental psychiatric disorders as risk factors for TS. Utilizing nationwide registers as an information source provides strengths to the study design. However, the validity of the register-based diagnoses is an essential ground for the register-based studies. No previous study has examined the validity of TS diagnoses in the FHDR.

3 Aims

The specific aims in this thesis were:

1. To describe the characteristics and incidence of the diagnosed TS and other tic disorders in the Finnish Hospital Discharge Register (FHDR) and additionally to validate TS diagnoses in the FHDR.
2. To determine the relationship between prenatal maternal smoking and Tourette syndrome (TS) with and without comorbid hyperkinetic disorder.
3. To examine the associations between parity, neonatal and obstetric factors and TS.
4. To examine the associations between parental psychiatric diagnoses and TS/CT (Chronic tic disorder).

4 Materials and Methods

4.1 Overview of the study design

This thesis consists of four original publications (studies I-IV). Study I is a description of the characteristics of the children and adolescents diagnosed with tic disorders and the validity of the Tourette diagnoses given at the hospital clinics in Finland. Study I is based on both register data obtained from the Finnish Hospital Discharge Register (FHDR) and clinically derived data from five Finnish hospitals. Studies II-IV, examining the risk factors for TS and TS/CT, are based on a population-based, nested case-control design. The data for studies II-IV were obtained from two national registers maintained by the National Institute of Health and Welfare and Central Population Register.

4.2 Characteristics of diagnosed Tourette syndrome and other tic disorders

The source population of the study consisted of all children born in Finland from 1 January, 1991, to 31 December, 2010 (n=1 199 112). All children recorded to have a tic disorder diagnosis in the FHDR were identified. A description of the FHDR is available on page 52. The children with both a tic disorder diagnosis and severe or profound mental retardation (F72, F73 in ICD-10 or 3181, 3182 in ICD-9) were excluded (n=6). The diagnoses were based on ICD-10 from 1996 and onwards, and on ICD-9 from 1991 to 1995. Table 6 presents the diagnostic codes for chronic tic disorder (CT), TS, and other tic disorder and examined comorbid diagnoses in ICD-10 and ICD-9. The last diagnosis was used if the child was recorded to have more than one tic disorder diagnoses. The follow-up time ended on 31 December, 2010. Altogether 3003 children with tic disorders were identified, of whom 767 were diagnosed with TS, 390 with chronic tic disorder and 1846 with other tic disorders.

Table 6. ICD-10 and ICD-9 codes for tic disorders and the comorbid diagnoses included in the study.

TIC DISORDER	ICD-10	ICD-9
Tourette syndrome	F95.2	3072D
Chronic tic disorder	F95.1	3072C
Other tic disorders	F95.0, F95.8, F95.9	3072B, 3072A
COMORBID DIAGNOSES	**ICD-10**	**ICD-9**
Hyperkinetic disorders	F90.0, F90.1, F90.8, F90.9	3140A, 3140B
Obsessive-compulsive disorder	F42.0, F42.1, F42.2, F42.8, F42.9	3003A
Autism spectrum disorder	F84.0, F84.1, F84.5, F84.8, F.84.9	2990AB, 2998AB, 2999AB
Conduct disorder	F91.0, F91.1, F91.2, F91.3, F91.8, F91.9	3138A, 3120A

4.3 Validation study (study Ib)

The data were collected from five university/central hospitals from different regions in Finland: Helsinki University Hospital, Turku University Hospital, Jyväskylä Central Hospital, Mikkeli Central Hospital and Rovaniemi Central Hospital. Children born in 1997 and onwards who were recorded to be diagnosed with TS and visited hospital during 2010-2011 were identified in the hospital's data system. Altogether 88 children were identified, of whom 58 were in Helsinki, 7 in Turku, 12 in Jyväskylä, 10 in Mikkeli and 1 in Rovaniemi.

The validation study had two parts: a chart review and a telephone interview. The chart review comprised 88 identified participants. The guardians of 55 participants were interviewed by telephone: 34 from Helsinki University Hospital, 5 from Turku University Hospital, 5 from Jyväskylä Central Hospital, and 9 from Mikkeli Central Hospital.

4.3.1 Chart review

Pediatric, child psychiatric and child neurological charts of the participants were collected and reviewed. The review was conducted by doctoral candidate Susanna Leivonen, who was resident in pediatric neurology. The process was supervised by pediatric neurologist Arja Voutilainen and child psychiatrist Andre Sourander. The review included evaluating if the child or adolescent was recorded to have tics, did the described symptoms fit the characteristics of tics and were both motor and vocal tics described in the charts. Data on the duration of the symptoms or possible pauses in the symptoms could not be collected due to variability in recording the symptoms and their clinical course.

4.3.2 Interview study

The interview study was conducted by interviewing the participants' guardians by telephone. The interview was based on the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a semi-structured instrument that combines information about the tics from the previous week based on reports from the child and parent and with clinical observations. The interview consists of a comprehensive list of both motor and vocal tics and includes the tic severity rating and the impairment rating. The tic severity scores are reviewed for number, frequency, intensity, complexity and interference of tics on 0-5 scale for each. The severity is reviewed separately for motor and phonic tics. The maximum number of points on the severity scale is 50, consisting of 0-25 points for both motor and vocal tics. The impairment score also ranges from 0 to 50, and a total maximum score of the YGTSS is 100 (Leckman et al., 1989). The YGTSS is one of the most widely used checklists on pediatric tics and tic severity (Cath et al., 2011, Johnson K. et al., 2023). The YGTSS has been translated into Finnish by Dr Leppämäki by permission from Dr Leckman, one of the original developers of the YGTSS. The Finnish translation was back translated into English to control the translation's accuracy. This study's main purpose was to evaluate if the child or adolescent had had symptoms that fit the characteristics of motor and vocal tics. The following questions were added to the interview, in addition to questions based on the YGTSS: 1) Have the tic symptoms been absent more than 2 months since they started? 2) How many years did it take after the symptoms started to get the diagnosis? 3) Did you feel that getting the diagnosis was beneficial? It was also asked whether the child or adolescent was treated with medication for tics.

4.4 Overview and the design of the register-baser risk factor studies (studies II-IV)

Figure 1 shows the overall design of the studies II-IV. Figure 2 shows the number of the cases included in studies II, III and IV separately. Studies II-IV were based on a nested case-control design. The source population included all children born in Finland between 1 January, 1991 and 31 December, 2010 (n=1 199 112).

The cases in studies II and III were defined as children and adolescents diagnosed with TS before 31 December, 2010, excluding the children with severe or profound mental retardation. The cases were identified from the FHDR with a total number of 767 identified cases. The cases born from twin (n=24) or triple (n=1) pregnancies were excluded for the analyses because twin/triple pregnancies are associated with several risks that may cause confounding. Each case was matched to four randomly selected controls on sex, date of birth (±30 days) and place of birth. The controls were identified from the Finnish Population Register Centre (FPRC). The controls were defined as children or adolescents without any registered tic disorder or without

severe or profound mental retardation. Furthermore, the controls who emigrated from Finland before the case was diagnosed (n=9), died before the case was diagnosed (n=12), were born from multiple pregnancy (n=87) or whose case was born from multiple pregnancy (n=98) were excluded.

The children and adolescents in study IV diagnosed with CT were also included. The cases were the children and adolescent diagnosed with TS or CT during the same time period as in studies II and III. The exclusion criteria for the cases and controls were similar to the criteria in study II and III. Altogether 1120 cases and 4299 controls were included in the study.

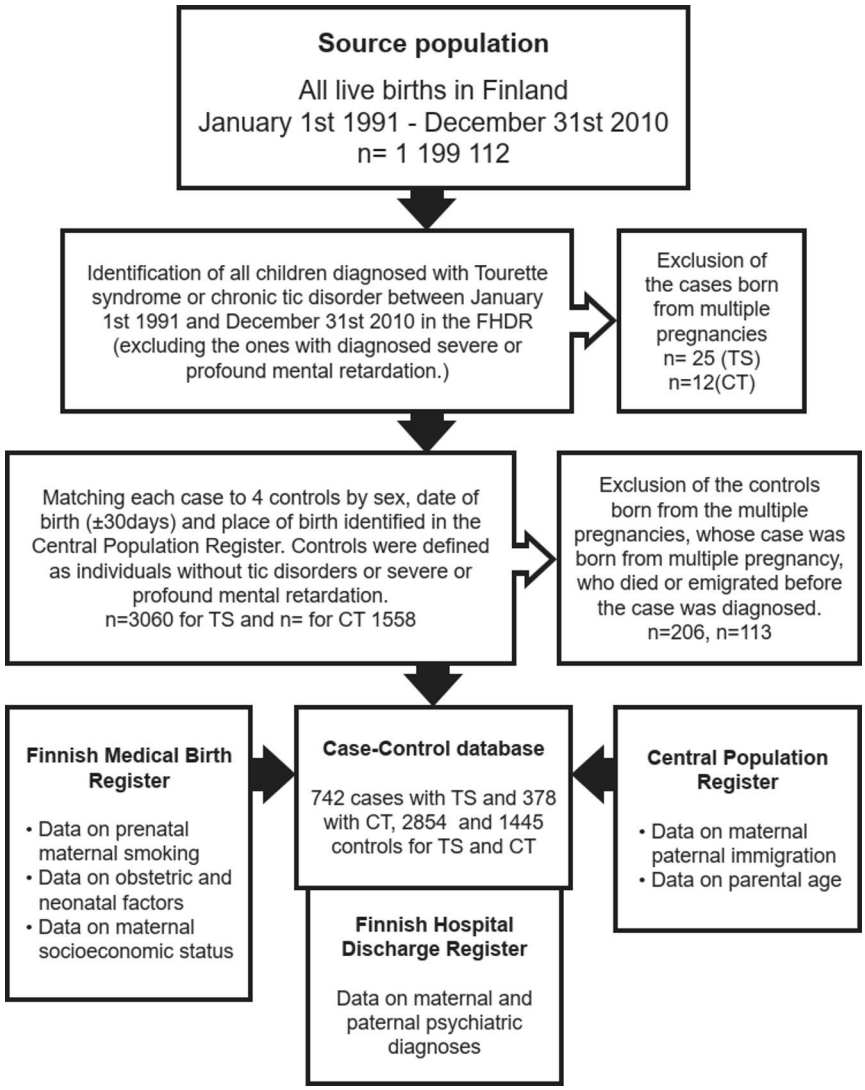

Figure 1. Flowchart of the study design in studies II-IV.

4.4.1 Data sources and linkage procedure

Studies II-IV are based on linking data from three Finnish nationwide registers: Finnish Hospital Discharge Register, Finnish Medical Birth Register and Finnish Population Register Centre. Table 7 presents a summary of the registers. Data linkage from the registers is achieved by using the personal identity codes, which have been used in Finland since the 1960s. This is a unique code for each individual consisting of date of birth, sex, individual number and a control number or alphabet. Personal identity codes are permanent throughout an individual's life with few exceptions, for example, if a person's sex changes or it is needed to protect the person, or the personal identity code has been misused by some other person.

Table 7. Registers used as data source in the thesis.

	FINNISH HOSPITAL DISCHARGE REGISTER	FINNISH MEDICAL BIRTH REGISTER	POPULATION INFORMATION SYSTEM
Year of origin	1969	1987	1969
Maintainer	National Institute of Health and Welfare	National Institute of Health and Welfare	Ministry of Finances
Purpose	To collect data on the health-care system and its customers for statistics, research and planning.	To collect data to develop and organise maternal care, deliveries and newborn care. To collect data for statistics and research.	To facilitate, execute and secure the information management and functions of society and the rights and responsibilities of the members of society.
Data content used in this study	Personal identity codes, diagnoses given in specialised health care, 1991-1997, in inpatient care and 1998-2010 from both in- and outpatient care. Diagnoses of parental psychiatric disorders.	Personal identity codes of mother and child, maternal socioeconomic status, previous pregnancies and deliveries, maternal smoking during pregnancy, maternal hypertension during pregnancy, birthplace, gestational age, birth type, multiple pregnancies, birth weight, Apgar score, monitoring after birth.	Personal identity code, parent´s personal identity numbers, municipality and home country of the birth, time of death, mother tongue.
Sources of data	Providers of health-care services.	Maternity hospitals, population register centre and Cause of Death register at Statistics Finland.	Data are received from authorities, e.g., hospitals, Finnish Immigration service or from individual citizens.

4.4.1.1 The Finnish Hospital Discharge register

The Finnish Hospital Discharge Register (FHDR) has covered all hospitals in Finland since 1967, and computerised data are available from 1969. The FHDR covers inpatient care in somatic and psychiatric hospitals, as well as inpatient wards of local health-care centres, military wards, prison hospitals, and private hospitals. The Hospital Discharge Register was changed to the Care Register for Health Care in 1994. This thesis uses the name Finnish Hospital Discharge Register (FHDR). The FHDR has also covered outpatient care in public hospitals since 1998. Data on outpatient visits in primary health care have been collected since 2011.The data are based on care notifications submitted by the health-care units. The collected data include the personal identity code, date of admission and discharge and primary diagnosis at discharge, together with three possible subsidiary diagnoses. Diagnostic information in the register is based on clinical diagnoses set by the attending physician and the international classification of diseases. All medical diagnoses are registered in the FHDR by health-care personnel. The FHDR's validity is described on page 43.

4.4.1.2 The Finnish Medical Birth Register

The Finnish Medical Birth Register (FMBR) includes data on mother, pregnancy, delivery and newborn. Data are collected for all born alive and still births when the gestational age is at least 22 weeks or weight 500 grams. Prenatal data collected in maternity care are delivered to the maternity hospital where a standardised form is completed by an attending midwife or physician. According to The Finnish Institute for Health and Welfare (THL), 99.7% of pregnant women in Finland visit a maternity clinic. Coverage of births in the FMBR is considered to be complete. The consistency of data in the FMBR was 98.5% when studied by comparing women’s reproductive histories in several pregnancies (Gissler and Shelley, 2002).

4.4.1.3 The Population Information System

The population centre register and local register officers control the data in the Finnish Population Information System, which is a computerised national register. It records data on Finnish citizens and foreign citizens residing permanently in Finland.

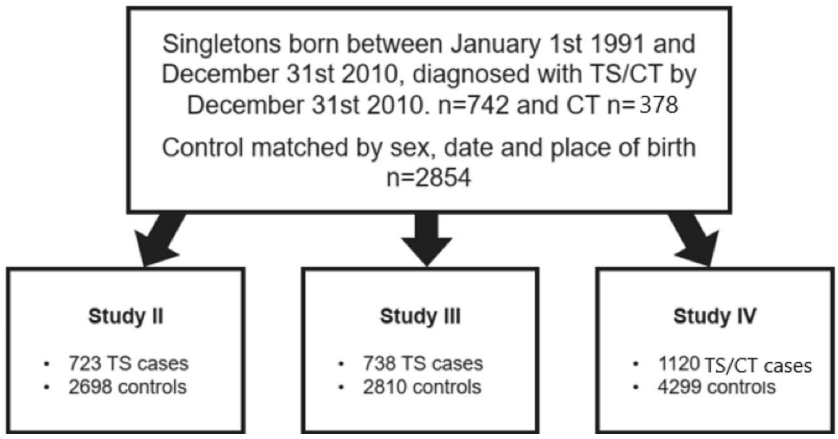

Figure 2. Numbers of cases and controls in studies II-IV*.

4.5 Prenatal maternal smoking and TS

The data on maternal smoking during pregnancy are derived from the Finnish Medical Birth Register (FMBR). Data were collected at maternity clinics during obstetric visits. The data on smoking during pregnancy were divided into three categories: no smoking, smoking during the first trimester only, and smoking throughout the pregnancy.

The cases diagnosed with TS in this study were also stratified by comorbid hyperkinetic disorder (ICD-10 codes F90.0, F90.1, F90.8, F90.9 and ICD-9 codes 314X).

4.6 Maternal, obstetric and neonatal factors and TS (study III)

The data on all factors examined in this study were derived from the FMBR. Maternal high blood pressure requiring hospitalisation was examined as a binary variable: yes, no (reference). Parity was divided into three categories: 0, 1-2 (reference) and ≥3.

Obstetric factors were categorised as birth presentation: vaginal cephalic, breech and other; birth type: vaginal cephalic (reference), vacuum extractor or forceps, vaginal breech, planned cesarean, other cesarean including urgent and emergency cesarean; induced labor: yes, no (reference).

The neonatal factors were categorised as 1) birth weight: <1500, 1500-2499, 2500-3999 (reference), 4000-4499, and ≥4500g; 2) gestational age: <32, 32-37, 38-41 (reference) and ≥42 weeks; 3) weight for gestational age: small for gestational age (< -2SD), appropriate for gestational age (-2SD-2SD) (reference) and large for gestational age (>2SD) – weight for gestational age was calculated according to

national, sex-specific weight distribution standards at a given gestational age among children born in Finland from 1996-2008 (Sankilampi et al., 2013); 4) Apgar scores at 1 minute: 9-10 (reference), 7-8, 0-6; 5) neonatal treatment: normal follow-up (reference), monitoring either in maternal post-partum unit or intensive care unit.

4.7 Parental psychiatric disorders and TS/CT (study IV)

Mothers of the cases and controls were identified from the FMBR and the fathers of the cases and controls were identified from the Population Information System. A man married to the child's mother at the time of the child´s birth is registered as the father. The paternity is registered by the acknowledgement of the father if the mother is unmarried. DNA testing for the paternity is also available free of charge. The fathers of 98.1% of the cases and 99.1% of the controls were identified in this study.

Parental psychiatric diagnoses were derived from the FHDR. The parents were followed from January 1969 to December 2010. Table 8 lists the psychiatric diagnoses according to International classification of disease (ICD) ICD-10, ICD-9 and ICD-8 codes.

First, maternal and paternal psychiatric diagnoses were categorised as absent or present (yes/no), respectively. Second, maternal and paternal psychiatric diagnoses separately were divided into specific diagnostic groups: 1) schizophrenia and other psychosis, 2) affective disorders, 3) OCD, 4) anxiety disorders, 5) personality disorders, 6) other psychiatric disorder, and 7) alcohol and other drug addiction or abuse. Table 8 presents the diagnoses included in each category. Parents diagnosed with schizophrenia or other psychotic disorders were not assigned in the other groups, because of the chronic, severe and pervasive nature of schizophrenia. Other parents could be assigned to several groups if they had diagnoses from several groups.

The sample was stratified by sex in additional analyses, and associations between any maternal and any paternal psychiatric diagnoses and TS/CT were examined separately for males and females. Any maternal and paternal diagnoses were also stratified into diagnoses given prior and after the offspring's birth. Parents with comorbid alcohol or other drug addiction diagnoses were excluded in one model. Any maternal and paternal diagnoses were also pooled together: no psychiatric diagnosis in either parent, maternal psychiatric diagnosis without paternal diagnoses, paternal psychiatric diagnosis without maternal psychiatric diagnosis and both parents having psychiatric diagnosis.

These disorders were examined jointly for mothers and fathers due to the low numbers of parents diagnosed with developmental, emotional and behavioral disorders typically occurring in childhood, i.e., tic disorders, ADHD, Autism Spectrum Disorder (ASD) and other developmental disorders.

Table 8. Diagnostic codes for parental psychiatric disorders.

	DIAGNOSTIC CODES		
DIAGNOSTIC CATEGORY	ICD-10 (1996 ONWARDS)	ICD-9 (1987-1995)	ICD-8 (1969-1986)
Schizophrenia and other psychosis	F20 Schizophrenia, F21 Schizotypal disorder, F22 delusional disorder, F23 acute and transient psychotic disorders, F24 induced delusional disorder, F25 schizoaffective disorder, F28 other nonorganic psychotic disorder, F29 unspecified nonorganic psychosis	295, 297, 2989X, 3012C	295, 297, 298.20, 298.30, 298.99, 299
Affective disorders	F30 hypomania, F31 bipolar affective disorder, F32 depressive episode, F33 recurrent depressive disorder, F34 persistent mood (affective) disorders (including cyclothymia and dysthymia), F38 other single mood (affective) disorder, F39 unspecified mood (affective) disorder	2988A, 296, 3004A	296, 298.00, 298.10, 300.41
OCD	F42 OCD	3003A	300.30
Anxiety disorders	F40 phobic anxiety disorders, F41 other anxiety disorders	3000A, 3000B, 3000C, 3002B, 3002C, 3002D, 3002X,	300.00, 300.20,
Personality disorders	F60 specific personality disorders, F61 mixed and other personality disorders	3010A, 3012A, 3012C, 3014A, 3015A, 3016A, 3017A, 3018B, 3018C, 3018D, 3018E, 3018X	301.00, 301.10, 301.20, 301.30, 301.40, 301.50, 301.70, 301.80, 301.88, 301.99
Tic disorder	F95	3072	306.20
ADHD	F90	314	
ASD	F84	299	
Alcohol and drug addiction	Mental and behavioral disorders due to use of F10 alcohol, F11 opioids, F12 cannabinoids, F13 sedatives or hypnotics, F14 cocaine, F15 other stimulants including caffeine, F16 hallucinogens, F17 tobacco, F18 volatile solvents, F19 multiple drug use and use of other psychoactive substances	303, 304, 305, 291, 292	303, 304, 291, 294.30

Other psychiatric disorders	F43 reaction to severe stress and adjustment disorders, F44 dissociative amnesia, F45 somatoform disorders, F48 other neurotic disorders, F50 eating disorders, F51 nonorganic sleep disorders, F52 lack or loss of sexual desire, F53 mental and behavioural disorders associated with the puerperium, not elsewhere classified, F54 psychological and behavioral factors associated with disorders or diseases classified elsewhere, F55 abuse of substances not producing dependence, F59 unspecified behavioural syndromes associated with psychological disturbances, F62 enduring personality changes, not attributable to brain damage and diseases, F63 habit and impulse disorders, F64 gender identity disorders, F65 fetishism, F66 psychological and behavioral disorders associated with sexual development and orientation, F68 other disorders of adult personality and behaviour, F69 unspecified disorder of adult personality and behavior, F99 mental disorder not otherwise specified	300-302 (excluding 3010A, 3012AC, 3015-3017A, 3018BCDEX,3014A, 3000A, 3000B, 3000C, 3002B, 3002C, 3002D, 3002X. 3003A, 3004A ja 3012C), 3071A, 3074A, 3074F, 3074H, 3075A, 3075B, 3075C, 3075E, 3078A, 3079X, 309 (excluding 3092A, 3092B, 3093A, 3094A) 312 (excluding 3120A, 3123D)	300-302 (excluding 300.00, 300.20, 300.30, 300.41301.00, 301.10, 301.20, 301.30, 301.50, 301.60, 301.7, 301.80, 301.88, 301.99, 301.40), 305, 306.40, 306.50, 306.98, 307.99
Other childhood onset disorder	Mental retardation F70-F79, specific developmental disorders of speech and language F80, specific developmental disorders of motor function F82, mixed specific developmental disorders F83, other disorders of psychological development F88, unspecified disorder of psychological development F89, conduct disorders F91, mixed disorders of conduct and emotions F92, emotional disorders with onset specific to childhood F93, other behavioural and emotional disorders with onset usually occurring in childhood and adolescence F98	313, 315, 317-319, 3120A, 3123D, 3070A, 3070B, 3073A, 3074G, 3075D, 3076A, 3076B, 3076C, 3077A, 3092A, 3092B, 3093A, 3094A	310-315, 306.00, 306.10, 306.30, 306.60, 306.70, 308.99

4.8 Confounding factors

The trend of association between potential confounding factors and both exposures and TS were tested. The variables showing a trend of association at level $p<0.10$ were included in to adjusted analyses in studies II-IV.

Maternal and paternal age were included as confounding in studies II-IV. Parental age has been associated with prenatal maternal smoking (Ekblad et al. 2014), some of the obstetric or neonatal factors (Newburn-Cook CV, Onyskiew JE. 2005) and TS (Khalifa N. and von Knorring A-L., 2005, Burd et al., 1999). The data on maternal age were derived from the FMBR and divided into four categories (<20, 20-29 (reference), 30-39, ≥ 40 years) in study II, into five categories (<20, 20-24, 25-34, 35-39, ≥ 40 years) in study III and as a binary variable in study IV (< median and ≥ median). Paternal age was derived from the Population Information System and was divided into categories similar to maternal age.

Maternal socioeconomic status (SES), which was included in studies II-IV, was derived from the FMBR. The latest data on the mother's occupation is collected at the birth hospital. SES is categorised as upper white collar, lower white collar, blue collar and others. The category 'no information on SES' was added in study IV. The measure of SES followed national classifications on occupations (Statistics Finland, 1987).

The studied variables were also included as confounders in the analyses of other factors: Maternal smoking during pregnancy (yes/no) was included as a confounding factor in studies III and IV, birth weight (< 2500 or ≥ 2500 grams), gestational age (< 37 weeks or ≥ 37weeks) were included in study II, maternal psychiatric history (yes/no) and paternal psychiatric history (yes/no) were included in studies II and III. Parity was included as a confounding factor in study IV and categorised as 0 and ≥1.

Parental immigrations status, co-occurring maternal/paternal OCD, ADHD/tic disorder (present/absent) and the other parent's psychiatric disorder (present/absent) were also included as confounding factors in study IV. Data on parental immigration status were obtained from the Population Information System. The immigration status was defined by using mother tongue and country of birth. Parents who were born abroad and whose mother tongue was other than Finnish were defined as immigrants. Parents born in Finland or who were born abroad but had Finnish as a mother tongue were defined as Finnish. Parental immigration status was studied as a binary variable: at least one of the parents was immigrant.

4.9 Ethics

The validation study (I) was authorised by Helsinki University Hospital, Turku University Hospital, Mikkeli Central Hospital, Jyväskylä Central Hospital and Rovaniemi Central Hospital. The study was approved by the ethics committee of the

Hospital District of Helsinki and Uusimaa. Informed and signed consent was obtained from the children over 12 years whose guardians participated in the interview and also from the guardians.

Register study (I-IV) was authorised by the Ministry of Social Affairs and Health (STM/1528/2007) and the National Institute of Health and Welfare. The study was approved by the ethics committee of the Hospital District of South-West Finland.

4.10 Statistical analyses

All statistical analyses were performed using SAS statistical software (SAS version 9.3) (SAS Institute Inc.; Cary, NC, USA).

Pearson´s $\chi 2$-test was used in study I to analyse if there were differences in the frequencies of sex or comorbidities between TS, chronic tic disorders and other tic disorders. The variance method was used to analyse the differences in mean age. The Poisson regression model, assuming a Poisson error distribution, was used to estimate the incidence rates and the corresponding 95% confidence intervals for the children born in 1991, 1995 and 1999. The number of diagnosed children was divided by the number of live births in the respective year, which was ascertained from the Medical Birth Register. Incidence rates were also calculated for northern, eastern, southern and western Finland. The Bonferroni correction was used due to multiple comparisons in geographical analyses. For all testing, p-value <0.05 was considered to be statistically significant.

Conditional logistic regression models were used in studies II-IV to examine the association between the exposures and TS. At first the unadjusted odds ratios and 95% confidence intervals were calculated in all three studies. P-values < 0.05 were considered statistically significant. Pearson $\chi 2$-test was used in study II to calculate the trend of association ($p<0.10$) between covariates and maternal smoking during pregnancy as a binary variable. Condition logistic regression models were used to analyse the association between covariates and TS. Seven covariates showing a trend of association with both maternal smoking during pregnancy and TS were included in the adjusted model examining the association between exposure and TS. Cases were also stratified in study II by diagnoses if hyperkinetic disorders and the unadjusted and adjusted odds ratios with 95% confidence intervals were estimated for cases diagnosed with hyperkinetic disorders and cases without hyperkinetic disorder diagnosis separately. The final model in study III included the exposure factors that were associated with TS by statistical significance level of $p<0.05$ and five parental factors that have shown a trend of association ($p<0.10$) with TS in this sample as covariates. Maternal age, paternal age, maternal immigration status, paternal immigrations status, maternal SES, maternal psychiatric diagnoses (yes/no) and paternal psychiatric diagnoses (yes/no) were analysed first in study IV. The final

model included the examined exposure factors showing a statistical significance $p<0.05$ and the socioeconomic status of mother, in addition to parental psychiatric disorders in specific categories, as described earlier. The final model was adjusted with the other parent's psychiatric history as a binary variable and maternal age, paternal age, paternal immigration and maternal SES.

5 Results

5.1 Characteristics of diagnosed Tourette syndrome and other tic disorders

Altogether 3003 children with tic disorders were identified from the Finnish Hospital Discharge Register (FHDR). Tourette syndrome (TS) was diagnosed in 767, chronic tic disorder (CT) in 390 and other tic disorders in 1846 children and adolescents. The majority of the diagnosed children were males: 16.6% of TS diagnoses, 22.6% of CT diagnoses and 27.4% of other tic disorders were registered for females ($p<0.001$). The mean age for the first tic diagnoses was 7.9 years (SD 3.1, range 0-19). Age at first tic diagnoses varied from 7.3 years (SD 3.1) for the ones diagnosed with other tic disorders compared to 9.0 years (SD 2.8, range 3-19) for the ones diagnosed with Tourette syndrome. The mean age for the first TS diagnoses was 9.3 years (SD 2.8, range 3-19).

Table 9 shows the frequencies of comorbid hyperkinetic disorder, obsessive compulsive disorder (OCD), Autism spectrum disorder (ASD) and conduct/oppositional disorder. Hyperkinetic disorder was the most frequently diagnosed comorbidity. Of the children diagnosed with TS, 28.2% were also diagnosed with hyperkinetic disorder, 16.8% with ASD, 8% with OCD and 6.8% with conduct/oppositional disorder. Comorbidities were less frequent in children diagnosed with CT or other tic disorders. Other developmental disorders, for example, specific language impairment, developmental co-ordination disorder or learning disorders were not examined. Of other psychiatric comorbidities, affective disorder was diagnosed in 58 (7.8%) children diagnosed with TS. Anxiety disorders were similarly diagnosed in 36 (4.9%) and schizophrenia and other psychosis were diagnosed in 18 (2.4%) children diagnosed with TS.

Table 9. Comorbidities of the children diagnosed with tic disorders.

	TOURETTE SYNDROME	CHRONIC TIC DISORDER	OTHER TIC DISORDERS	P-VALUE
	n=767 (%)	n=390 (%)	n=1846(%)	
COMORBIDITIES				
Hyperkinetic disorders	216 (28.2)	63 (16.2)	106 (5.7)	<.001
OCD	61 (8.0)	10 (2.6)	19 (1.0)	<.001
ASD	129 (16.8)	34 (8.7)	81 (4.4)	<.001
Conduct/Oppositional disorder	52 (6.8)	17 (4.4)	38 (2.1)	<.001

5.2 Incidence rates for birth cohorts born in 1991, 1995 and 1999

Figure 3 presents the incidence rates of diagnosed TS, CT and other tic disorders by the age of eleven for the ones born in 1991, 1995 and 1999. By the age of 15, the incidence rates for TS were 5.2 (95% CI 3.7-7.3) for the cases born 1991 and 11.5 (95% CI 9.1-14.4) for the cases born 1995 ($p<0.001$). The incidences of four geographical areas of birth cohort born 1991 were 9.2 (95% CI 6.2-13.8) in southern Finland, 7.4 (95% CI 3.5-15.6) in northern Finland, 6.6 (95% CI 4.0-11.x) in western Finland and 17.6 (95% CI 10.2-30.4) in eastern Finland. No statistically significant differences were found in the incidence rates between different regions.

5.3 Validation of Tourette syndrome diagnoses

5.3.1 The chart review

The paediatric, child psychiatric and child neurologic charts of all 88 subjects were assessed to determine if the child had multiple motor tics and at least one vocal tic reported on the charts. The information on tics was incomplete in five cases; thus, the evaluation was not possible, and these five cases were excluded. Both motor and vocal tics were described in 79 (95%) out of 83 cases; the motor tics were described in the chart in two cases, but according to the chart, the subject did not have vocal tics. The symptoms were not considered to be tics in two cases. Tic duration was often described poorly, and whether there was an over two months lasting pause in the symptom was often unclear. Therefore, this criterion was not included in the evaluation.

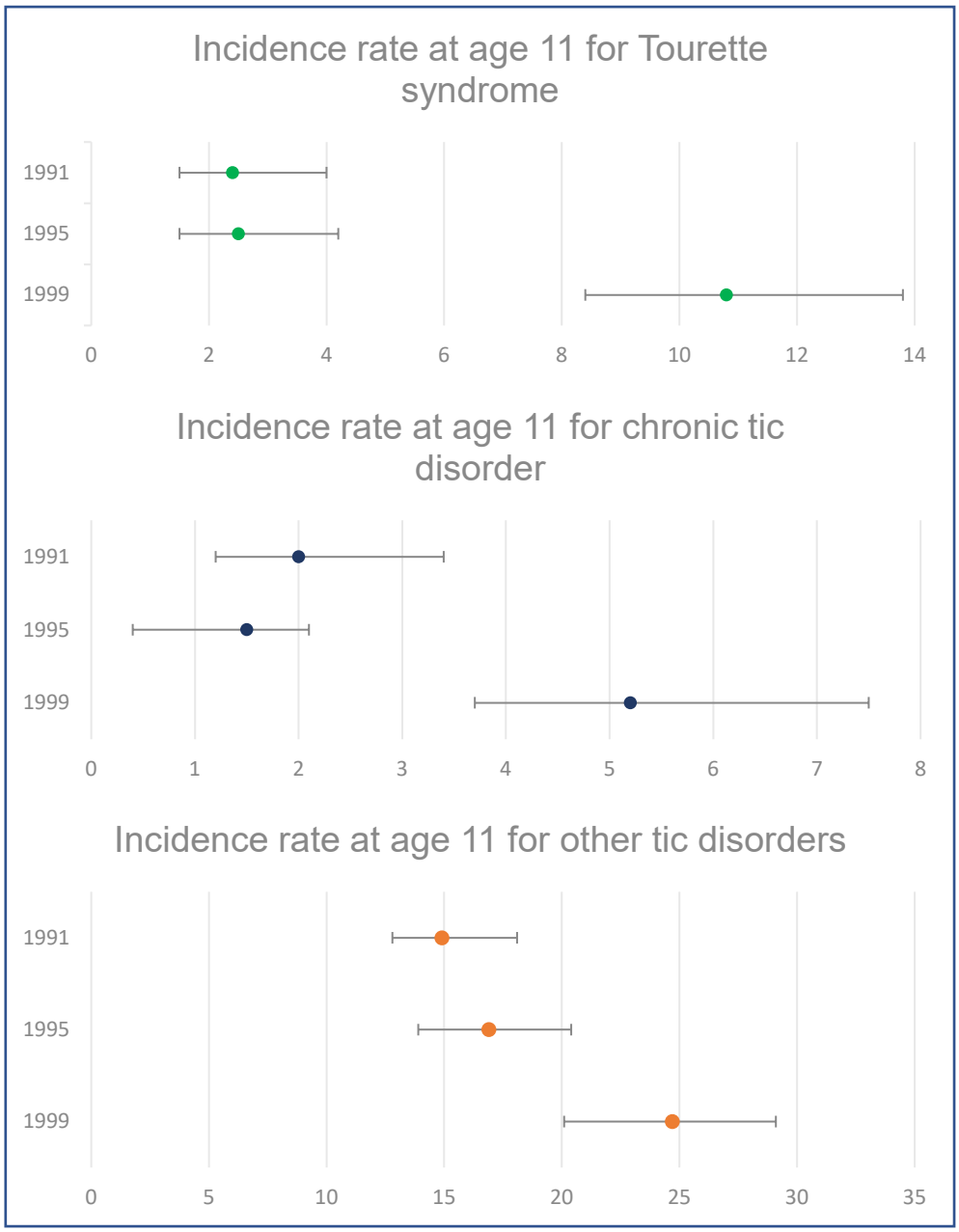

Figure 3. Incidence rates for TS, chronic tic disorders and other tic disorders by age 11 for children born 1991, 1995, 1999.

5.3.2 Interview study

Guardians of 55 subjects (63%) of the 88 cases participated in the interview study. Eleven (20%) of the participating subjects were female. The participants' mean age was 11 years (SD 2.6). The mean age by the motor symptom onset was 5.0 years (SD 2.1) and phonic symptoms start by 5.3 years (SD 2.2). The mean score in the tic severity scale was 43 (range 0-87, SD 24.5). Five subjects scored 0 in the severity scale, and 21 (38%) subjects scored 50 or more at the moment of the interview. Medication was given to 26 (47%) subjects at the time of the interview.

Fifty-three (96%) cases had multiple motor tics, one or more vocal tics, symptom duration was more than one year and the symptom onset was before the age of 18 years. These 53 cases were considered to meet the TS criteria. Eight of them had remission of the symptoms longer than two months by the time of the interview, but the guardians of these eight reported that the remission was ongoing at the time of the interview and not by the time the diagnosis was set. Seven of the guardians were unsure if remissions were longer than two months. These cases were, however, considered to have TS, despite the recall problem. The symptoms of two cases were not considered to be tics. A majority (n= 44, 80%) of the guardians felt that the TS diagnosis was beneficial, and 10 had a neutral opinion. One (2%) found no benefits in diagnosing TS.

5.4 Prenatal maternal smoking

Data on prenatal maternal smoking were found in 723 of the 742 (97.4%) cases and on 2698 of 2854 (94.5%) controls that were included in the analyses. Table 10 first shows the frequencies of the exposed and unexposed cases and controls among all cases and controls, and thereafter among the cases with and without diagnosed hyperkinetic disorder. Among all the cases, 18.9%, and among the controls, 14.7% were exposed to prenatal smoking during pregnancy. The figures for cases with and without hyperkinetic disorders were 27.1% and 15.8%, respectively. The majority of the exposed cases and controls were exposed throughout the pregnancy. Figure 5 shows the results of the unadjusted and adjusted analyses between maternal smoking during the first trimester or throughout pregnancy and TS. Prenatal maternal smoking during pregnancy was associated with TS in the unadjusted analyses (OR 1.3, 95% CI 1.1–1.7, p=0.010).

After adjusting with for the seven confounding factors (maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal age, paternal age, birth weight, gestational age and maternal socioeconomic status), no statistically significant association was found between prenatal maternal smoking either during the first trimester or throughout pregnancy and TS. Figure 4 shows the associations between maternal smoking during pregnancy and TS with ADHD. Prenatal maternal smoking

was associated with TS and comorbid ADHD both in unadjusted and adjusted analyses. In the adjusted analyses ORs with 95% confidence intervals were 4.0 (1.2-13.5) and 1.7 (1.1 -2.7) for smoking during first trimester and throughout pregnancy, respectively. No associations were found between prenatal maternal smoking and TS without ADHD.

Table 10. The frequencies of cases and controls who were unexposed and exposed to maternal smoking during the first trimester or throughout pregnancy.

MATERNAL SMOKING	TOURETTE SYNDROME		TS AND ADHD		TS WITHOUT ADHD	
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)
No	586 (81.1)	2301 (85.3)	148 (72.9)	855 (86.9)	438 (84.7)	1646 (84.7)
First trimester	16 (2.2)	41 (1.5)	9 (4.4)	8 (1.1)	7 (1.4)	33 (1.7)
Throughout pregnancy	121 (16.7)	356 (13.2)	46 (22.7)	91 (12.1)	75 (14.4)	265 (13.6)

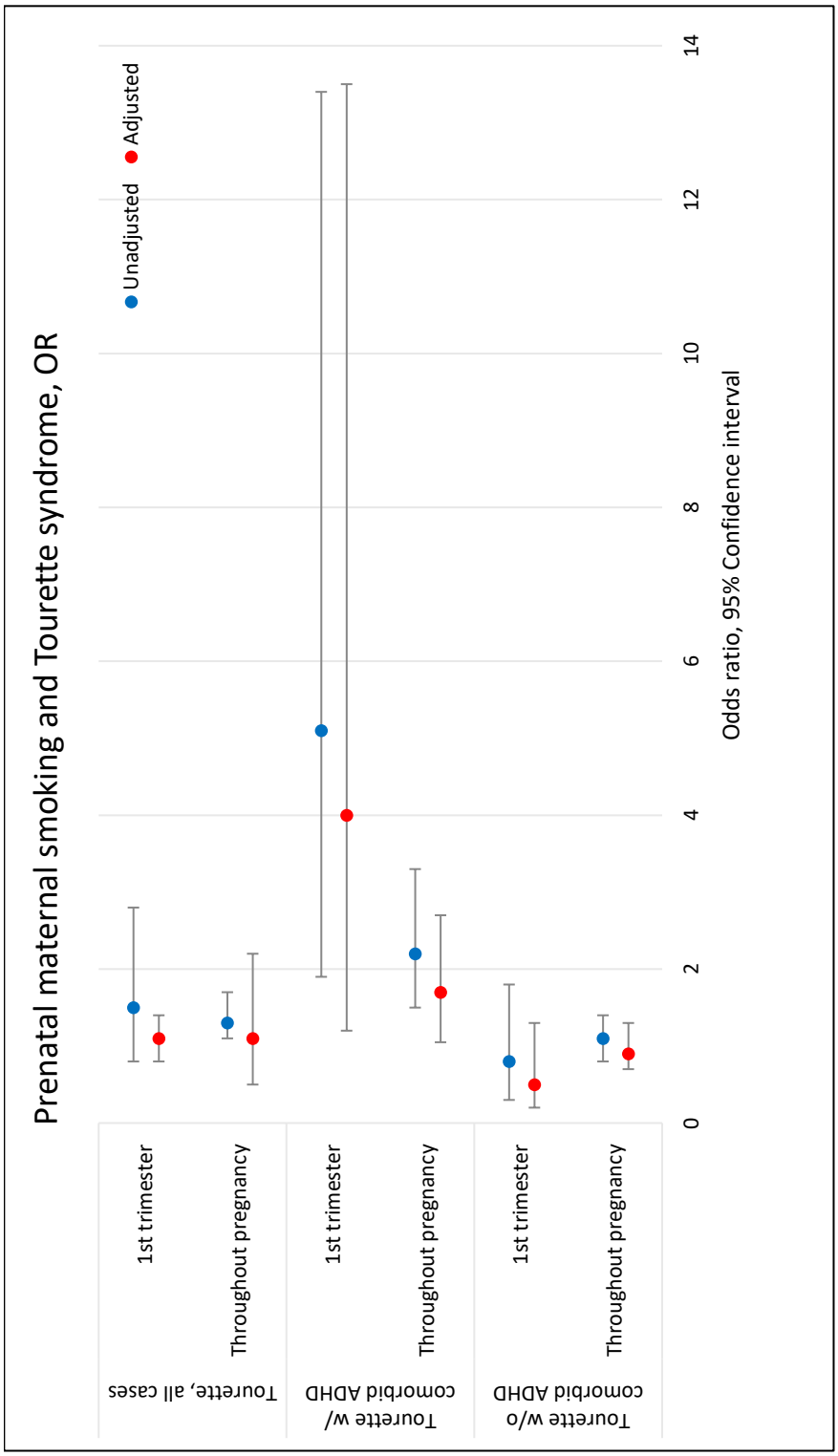

Figure 4. The association between maternal smoking during pregnancy and Tourette syndrome with and without comorbid ADHD.

5.5 Maternal, obstetric and neonatal factors

Data on perinatal factors were available for 738 of 742 (99.5%) cases and for 2810 of 2825 controls (99.5%).

Table 11a shows the frequencies of maternal high blood pressure and numbers of previous births. Maternal high blood pressure was not associated with TS in the offspring. Nulliparity was associated with an increased risk for TS in offspring, and the association remained strong after adjusting with the possible confounders (OR 1.8, 95% CI 1.5-2.2). Parity ≥ 3 was associated with decreased risk for offspring TS compared with parity 1-2.

Table 11a. Frequencies of maternal factors including high bloodpressure and parity and the associations between these factors and TS both in unadjusted (OR1) model and adjusted model (OR2).

	CASES (%)	CONTROLS (%)	OR1	P	OR2*	P
HIGH BLOOD PRESSURE						
Yes	39 (5.3)	116 (4.1)	1.3 (0.9-1.9	.189	1.2 (0.8-1.8)	.384
No	699 (94.7)	2694 (95.9)	1.0			
PARITY						
0	414 (56.1)	1150 (41.0)	1.7 (1.4-2.0)	<.001	1.8 (1.5-2.2)	<.001
1-2	296 (40.1)	1406 (50.1)	1.0			
≥3	28 (3.8)	248 (8.8)	0.5 (0.3-0.8)	.002	0.5 (0.3-0.7)	.001

*OR2 was adjusted with maternal age, maternal SES, maternal psychiatric history, paternal age, and paternal psychiatric history

Table 11b shows the frequencies of the obstetric factors including induced labor, birth type and birth presentation. Birth type–vacuum extractor/forceps/vaginal breech–was associated with TS (unadjusted OR 1.4, 95% CI 1.04-1.9 and adjusted OR 1.5, 95% CI 1.1-2.1). No other associations were found.

Table 11b. Frequencies of obstetric factors including induced labor, birth type and birth presentation and the associations between these factors and associations between these factors and TS in unadjusted and adjusted model.

	CASES (%)	CONTROLS (%)	OR1	P	OR2	P
INDUCED LABOR						
No	617 (83.6)	2360 (84.0)	1.0		1.0	
Yes	121 (16.4)	571 (16.1)	1.0 (0.8-1.3)	.747	1.1 (0.9-1.4)	.408
BIRTH TYPE						
Vaginal cephalic	547 (74.1)	2173 (77.3)	1.0		1.0	
Vacuum extractor/forceps/ vaginal breech	63 (8.5)	178 (6.3)	1.4 (1.04-1.9)	.028	1.5 (1.1-2.1)	.020
Planned cesarean	58 (7.9)	220 (7.8)	1.0 (0.8-1.4)	.792	1.0 (0.7-1.4)	.982
Emergency/urgent cesarean	70 (9.5)	233 (8.3)		.204	1.1 (0.8-1.6)	.435
Unknown	0	6 (0.2)				
BIRTH PRESENTATION						
Cephalic	695 (94.2)	2646 (94.2)	1.0		1.0	
Breech	23 (3.1)	66 (2.4)	1.3 (0.8-2.2)	.236	1.2 (0.7-2.0)	.536
Other	20 (2.7)	98 (3.5)	0.8 (0.5-1.3)	.294	0.8 (0.4-1.4)	.379

*OR2 was adjusted with maternal age, maternal SES, maternal psychiatric history, paternal age, and paternal psychiatric history

Table 11c shows the frequencies and associations between neonatal factors including birth weight, gestational age, weight for gestational age, Apgar score at 1 minute and monitoring or treatment at the Neonatal intensive care unit (NICU) and TS. Birth weight 4000-4499 and >4500 were associated with TS in unadjusted analyses (OR 0.7, 95%CI 0.5-0.8 and OR 0.5, 95% CI 0.3-0.8, respectively). After controlling for the confounding factors birth weight 4000-4499g remained associated with TS (OR, 95% CI). Apgar score 0-6 and LGA were also associated with TS in the unadjusted model, but the associations did not remain significant after controlling with the covariates.

Table 11c. Frequencies of neonatal factors including birth weight, gestational age, weight for gestational age, Apgar at 1 minute and monitoring/NICU and the associations between these factors and TS in unadjusted and adjusted models.

	CASES N (%)	CONTROLS N (%)	OR1	P	OR2	P
BIRTH WEIGHT (G)						
<1500	6 (0.8)	16 (0.6)	1.3 (0.5-3.4)	.566	1.1 (0.4-3.0)	.847
1500-2499	26 (3.5)	68 (2.4)	1.4 (0.8-2.2)	.204	1.3(0.7-2.1)	.403
2500-3999	588 (79.7)	2074 (73.8)	1.0		1.0	
4000-4499	101 (13.7)	527 (18.8)	0.7 (0.5-0.8)	.001	0.7 (0.5 -0.9)	.002
≥4500	17 (2.3)	125 (4.5)	0.5 (0.3-0.8)	.005	0.6 (0.3-1.1)	.084
GESTATIONAL AGE (WK)						
≤31	8 (1.1)	14 (0.5)	2.2 (0.9-1.6)	.074	1.8 (0.7-4.7)	.264
32-37	76 (10.3)	248 (8.8)	1.2 (0.9-1.6)	.207	1.2 (0.9-1.6)	.312
38-41	624 (84.6)	2421 (86.2)	1.0		1.0	
≥42	30 (4.1)	127 (4.5)	0.9 (0.6-1.4)	.684	0.9 (0.6-1.5)	.788
WEIGHT FOR GESTATIONAL AGE						
SGA	21 (2.9)	80 (2.9)	1.0 (0.6-1.6)	.998	1.0 (0.5-1.2)	.913
AGA	702 (95.1)	2628 (93.5)	1.0			
LGA	15 (2.0)	102 (3.6)	0.5 (0.3-0.96)	.034	0.7 (0.4-1.2)	.171
APGAR AT 1 MINUTE						
9-10	547 (74.1)	2147 (76.4)	1.0		1.0	
7-8	152 (20.6)	561 (20.0)	1.1 (0.9-1.4)	.549	1.0 (0.8-1.3)	.828
0-6	39 (5.3)	102 (3.6)	1.5 (1.01-2.2)	.044	1.5 (0.98-2.3)	.062
MONITORING/NICU						
No	665 (90.1)	2583 (91.9)	1.0		1.0	
Yes	73 (9.9)	227 (8.1)	1.3 (0.95-1.7)	.104	1.2 (0.9-1.6)	.210

*OR2 was adjusted with maternal age, maternal SES, maternal psychiatric history, paternal age, and paternal psychiatric history

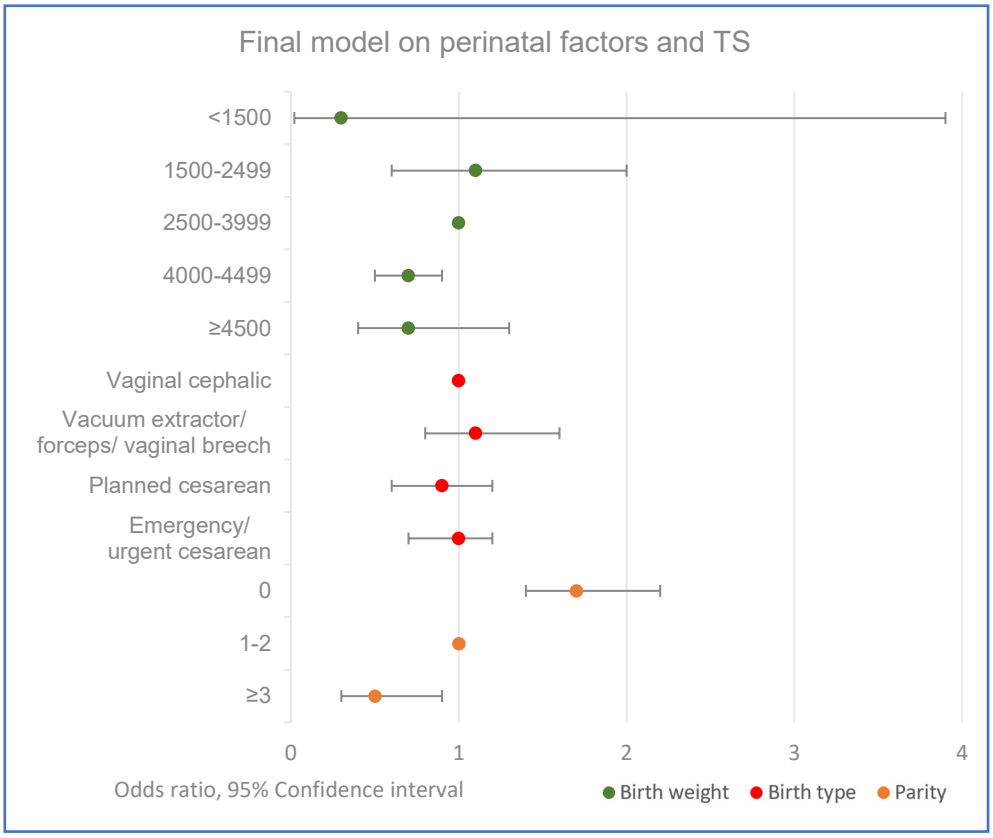

Figure 5. Final model including the factors associated with Tourette syndrome and covariates.

5.6 Parental psychiatric disorders and TS/CT

Maternal and paternal psychiatric diagnoses of all TS/CT cases and controls, 279 (24.9%) and 516 (12%), respectively, had a mother with psychiatric diagnosis. Similarly, 196 (17.9%) cases and 550 (12.9%) controls had a father with a psychiatric diagnosis. Table 12 shows the distribution of frequencies of maternal and paternal psychiatric diagnoses by specific diagnostic groups. Table 13 shows the frequencies of parents diagnosed with childhood onset neuropsychiatric disorders.

Table 12. Frequencies of mothers and fathers of cases and controls having a specific psychiatric diagnoses.

PSYCHIATRIC DIAGNOSES	MATERNAL		PATERNAL	
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)
Schizophrenia and other psychosis	32 (2.9)	47(1.1)	16 (1,5)	38 (0,9)
Affective disorders	145 (13)	249 (5.8)	81 (7.4)	216 (5.1)
OCD	6 (0.5)	0 (0.0)	4 (0.4)	2 (0.1)
Anxiety disorders	83 (7.4)	119 (2.8)	44 (4.0)	101 (2.4)
Personality disorders	34 (3.0)	43 (1.0)	29 (2.7)	94 (2.2)
Other psychiatric disorder	93 (8.3)	188 (4.4)	47 (4.3)	141 (3.3)
Alcohol and drug addiction	38 (3.4)	75 (1.7)	68 (6.2)	221 (5.2)

Table 13. Frequencies of childhood onset neuropsychiatric disorders among parents of cases and controls.

CHILDHOOD ONSET DISORDERS	CASES N (%)	CONTROLS N (%)
Tic disorder	10 (0.9)	2 (0.1)
ADHD	8 (0.7)	9 (0.2)
Autism spectrum disorder	3 (0.3)	0 (0.0)
Other developmental/ childhood onset disorders	23 (2.1)	50 (1.2)

Any maternal and any paternal psychiatric diagnosis was associated with TS/CT (OR 2.4, 95% CI 2.0-2.8, p< 0.001 and OR 1.5, 95% CI 1.2-1.8), p=<.0.001, respectively) in the unadjusted analyses. The associations between any maternal psychiatric diagnosis and any paternal psychiatric diagnosis and TS/CT remained statistically significant (OR 2.3, 1.9-2.7 95% CI, p<0.001; OR 1.2, 95% CI 1.01-1.5, respectively) after controlling with maternal/paternal psychiatric disorder, maternal age, paternal age, maternal SES, maternal/paternal co-occurring OCD/ADHD/tic disorder and parity. The association between any maternal psychiatric disorder and TS/CT was stronger than the association between any paternal psychiatric diagnosis and TS/CT (p< 0.001)

Figures 6a and 6b, respectively, show the unadjusted and adjusted ORs with 95% CIs for the associations between maternal and paternal specific diagnostic groups and TS/CT. Maternal schizophrenia and other psychosis (OR 2.0, 95%CI 1.2-3.3), anxiety disorders (OR 2.6, 95% CI 1.9-3.5), personality disorders (OR 3.1, 95% CI1.9-5.1), affective disorders (OR 2.3, 95% CI1.8-2.9), other psychiatric disorders (OR 2.0, 95% CI 1.5-2.6) and alcohol/drug addiction (OR 1.8, 95% CI 1.1-2.8) were associated with TS/CT in the final model. Paternal OCD was associated with TS (OR 6.5, 95% CI 1.1-39.5) and paternal anxiety disorders (OR 1.5, 95% CI 1.06-2.3). No significant association was detected between other specific paternal psychiatric diagnoses and TS/CT.

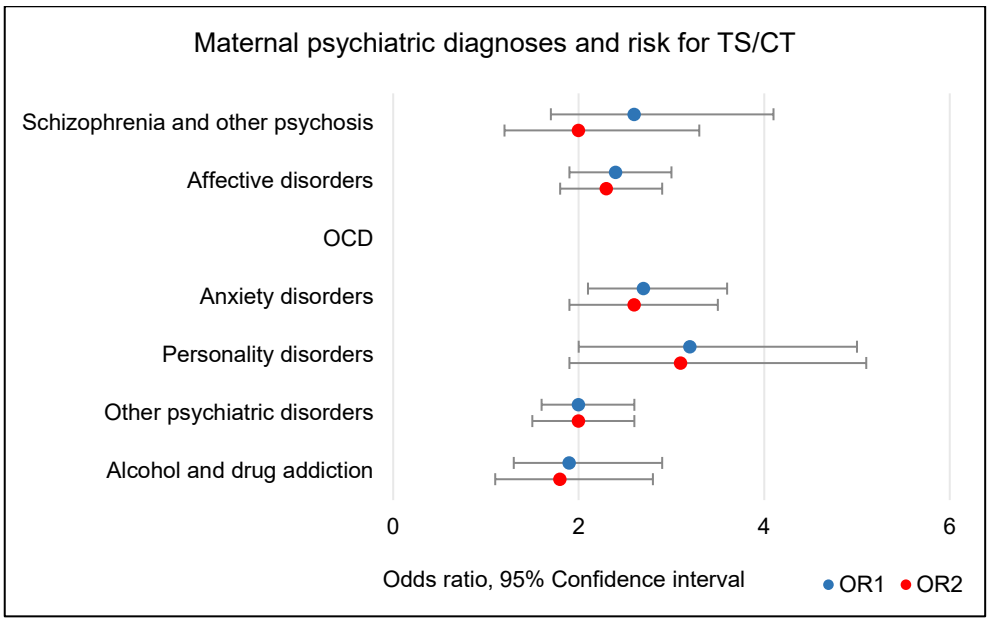

Figure 6a. The associations between specific maternal psychiatric diagnoses and offspring TS/CT. OR1 = unadjusted analyses, OR2 = adjusted with paternal psychiatric disorders, maternal age, paternal age, co-occurring OCD, parity and maternal SES.

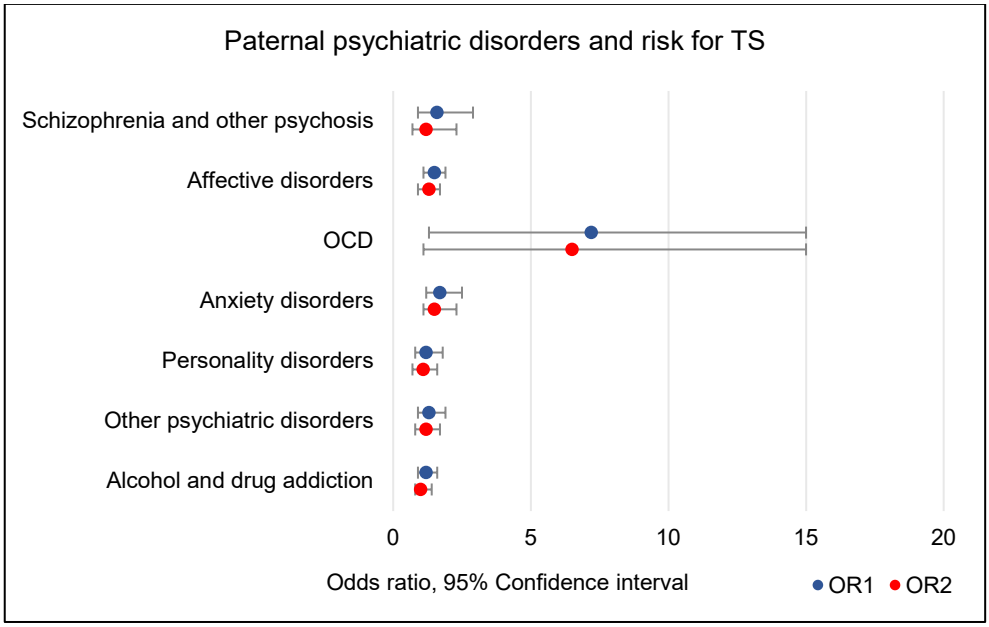

Figure 6b. The associations between specific paternal psychiatric disorders and offspring TS/CT. OR1 = unadjusted analyses, OR2 = adjusted with paternal psychiatric disorders, maternal age, paternal age, co-occurring OCD, parity and maternal SES.

Any maternal psychiatric disorder was associated with TS/CT in both females (OR 2.2, 95% CI 1.5-3.3) and males (OR 2.3, 95% CI 1.9-2.8) in the adjusted models when the cases and controls were stratified by sex. Any paternal psychiatric disorder was not associated with TS/CT in females (OR 1.3, 95% CI 0.8-2.1) or males (OR 1.2, 95% CI 0.97-1.5).

There were no notable changes compared with the original analyses when the parents with comorbid alcohol or drug addiction were excluded.

There were no significant differences between any maternal or paternal psychiatric diagnoses given prior versus after an offspring's birth (p=0.09 and 0.50), respectively.

Of disorders often diagnosed in childhood, parental tic disorder and other developmental disorders were associated with offspring TS/CT (OR 2.7 95% CI 1.8-4.1, OR 20, 95% CI 4.4-91.3 and OR 1.8, 95% CI 1.1-3.1, respectively). The frequencies of parental ASD were low, and no association between parental ASD and offspring TS/CT was detected.

6 Discussion

6.1 Main findings

This thesis aimed to enhance the knowledge of prenatal, perinatal and parental factors contributing to the development of Tourette syndrome (TS) in Finland. An additional aim was to describe the characteristics of the children diagnosed with tic disorders in Finnish specialised health care, report the incidence of diagnosed tic disorders and examine the suitability of the register-based sample to be used in further studies. The main findings of the thesis are:

1 The incidence rates for diagnosed tic disorders increased during the study period. The registered diagnoses of TS correspond well to the TS diagnostic criteria; thus, it is meaningful to utilise register-based data for TS research.

2 Prenatal maternal smoking is associated with Tourette syndrome when comorbid with Attention deficit/hyperactivity disorder (ADHD), but no association between prenatal maternal smoking and TS without comorbid ADHD was found.

3 Increasing parity and high birthweight were associated with decreased odds for TS, while several obstetric and neonatal adversities were not associated with TS.

4 Maternal psychiatric disorders were strongly and independently associated with TS/CT in offspring. The association was found between all the specific diagnostic groups and TS/CT (Chronic tic disorder). The association between paternal psychiatric disorders and TS/CT was less strong, and out of the specific disorders, only anxiety disorders and Obsessive compulsive disorder (OCD) were associated with an increased risk for TS/CT.

6.2 Methodological considerations

6.2.1 Study design of the register-based studies

Studies II-IV were based on a nested case-control design. Cases with disease were identified in a defined cohort. A number of controls were selected in a cohort among

those who have not developed the disease by the time of diseases' occurrence in the case (Ernster 1994). The main advantage of the nested case-control design in comparison with full cohort is its cost-effectiveness. The data are collected for only the fraction of individuals in the cohort. For example, in this study the original cohort included over 1 million children and using the nested case-control design limited the number of examined individuals to 3003 cases and four controls for each case.

Table 14 summarises the methodological strengths and limitations of the register-based studies (I-IV)

6.2.2 Register-based data source

This study utilised nationwide registers as a data source. Studies based on linking data in nationwide registers, mainly in Nordic countries, have provided significant contributions to etiological psychiatric research (Munk-Jorgensent et al., 2011). Table 14 lists the strengths of a register-based design.

However, there are also some methodological concerns for a register-based design. First, the expression of TS varies from mild to severe, and not all the children with symptoms that fulfill the diagnostic criteria of TS are diagnosed in the specialised health-care system; thus, they are not found in the FHDR. This may be a limitation for the generalisability of the results. It is possible that the sample consists of more severely affected TS cases. Second, the outpatient services were first added to the FHDR in 1998. It is possible, therefore, that there are cases that visited the outpatient services 1991-1997 and, thus, were not registered. However, it is unlikely that many cases are lost due to this limitation due to mean age at the diagnosis and the fact that most of the children visited the specialised services several times. Third, despite the nationwide data collection and large sample size, some of the exposures were rare, so the statistical power was limited.

Table 14. Strengths and limitatios of the study design.

	STRENGTHS	**LIMITATION**
A matched, nested case-control design	Less expensive compared with cohort design	Cohort design may be more precise.
Register-based design	Representative for the entire country Sample size Validated diagnoses Prospectively collected data Data on several potential confounders is available Cases and controls are not lost for follow-up	The diagnoses are limited to children and youth who visited specialised health care. Outpatient data were available from 1998 onwards. Despite the large sample size in total, the power is limited to examine rare exposures and it was not possible to stratify children with TS.

6.2.3 Confounding factors

Confounding factors are an association between exposure and outcome that can be related to a third factor that is associated with the exposure and has an effect on outcome. Several means exist to control for possible confounding, including 1) matching 2) stratification 3) multivariate techniques 4) restriction (Pourhoseingholi et al., 2012). Matching makes it possible to prevent confounding. The controls in our studies II-IV were matched to cases by sex, date of birth and place of birth. This was preferable because TS is more common in boys compared to girls (Knight et al., 2012), the cases and controls had an equally long time to be diagnosed with TS and potentially there can be geographical differences in the prevalences of the psychiatric disorders in different areas or there may be local differences in the diagnosing procedures.

Multivariate modelling was used in studies II-IV to control for the potential confounding. Potential confounders that have been associated with both exposure and the outcome (TS and, in some cases, some other childhood onset neurodevelopmental disorders were selected based on the literature; thereafter, it was tested whether the potential confounder was associated with both exposure and TS ($p<0.10$).

The association between prenatal maternal smoking and TS was first examined in all cases and controls. Thereafter, the cases were stratified into children with TS with comorbid hyperkinetic disorder and children with TS without comorbid hyperkinetic disorder. Stratification was also applied in study IV in the additional analyses when mothers with substance abuse diagnoses were excluded from the analyses. This did not alter the results.

6.2.4 Validation study

The validation study consisted of both chart review and telephone interview. The validation study's strengths were 1) combining two different methods, 2) including five different hospitals from different geographical areas, 3) including both university and central hospitals.

The limitation of both telephone and chart reviews was that the studies were conducted by one interviewer/reviewer; thus, no inter/intra-rater agreement was studied. Several interviewers or reviewers would have been more time and resource consuming. Consultation by an experienced child neurologist/child psychiatrist, who also supervised the study, was available for unclear stages. The study focused on examining whether there were false positives among the registered diagnoses. Possible false negatives were not studied. A Swedish study by Rück et al. (2015) found no false negatives individuals with tic disorders among persons who were diagnosed with epilepsy or depression (Rück et al., 2015).

Two major methodological limitations of a telephone interview were 1) symptoms were not observed in person, and 2) potential recall bias. A Swedish study validating a parent telephone interview on neuropsychiatric disorders has shown good validity (Larson et al., 2010). Using telephone interviews has also shown good reliability for other neurological conditions (Savio K. et al., 2013). We included children who visited the clinic two years before the start of the study in an attempt to reduce recall bias.

Using the Yale Global Tic Severity Scale (YGTSS) as a structure for telephone interviews has also strengths and limitations. The YGTSS is designed to evaluate tic severity and impairment but not directly for diagnostic purposes. It has not been designed or validated to be used for a telephone interview (Leckman et al., 1987). However, it is one of the most widely used instruments in TS studies, and it includes a comprehensive structured list of both motor and vocal tic disorders (Leckman et al., 1987). It thus provides a description of a wide spectrum of different tics (Leckman et al., 1987) that was beneficial for mapping out tics in this study. A recent study by Ho C-S et al. (2010) indicated also that the parent-reported YGTSS is a valuable tool, because the differences between parent evaluation and physician evaluation were small.

A retrospective chart review overcame some of the limitations in the telephone interview. An advantage of a chart review was to avoid the recall bias, considering the symptoms at the time of the diagnosis. Chart review is also a less expensive and time-consuming method. There are also several methodological limitations regarding a retrospective chart review: 1) study data have not been originally collected for research purposes, 2) the documentations may be incomplete or some of the information may be unrecorded, 3) there may be difficulties in interpreting the data and there is variance in the data quality, depending on the reporter (Gearing et al., 2006, Worster and Heines 2004). The intra-rater nor interrater reliability was not examined in this study.

6.3 Characteristics of the register-based tic disorder diagnoses in Finland

The disorder has been more prevalent in male than females since Dr. Gilles de la Tourette's first observations (Freeman et al., 2000, Knight et al., 2012), thus the sex ratio of the children diagnosed with tic disorders in the FHDR was expected: 16.6 % of TS cases, 22.6% of CT cases and 27.4% of other tic disorder cases were females). The sex ratio of the cases has been similar in other Nordic register-based studies: 16.9% of the cases with TS were females in a Danish register-based sample; the prevalence of TS was 0.71% for boys and 0.15% for girls in a Norwegian study; and

23.4% of the cases diagnosed with TS/CT were females in a Swedish register-based study (Dalsgaard et al., 2015; Mataix-Cols et al., 2015, Suren et al., 2019).

The explanation for the constant sex-ratio difference is unclear, but it also applies for some other neurodevelopmental disorders, e.g., and Autism Spectrum Disorder (ASD) as well (Loomes R., et al. 2017). It has been hypothesised that, for example, sexual dimorphism in basal ganglia pathways and hormonal factors could explain the different susceptibility of the female and male brain (Smith and Dahodwala., 2014).

The mean age for the first TS diagnoses was 9.3 years (SD 2.8, range 3-19), as the mean ages for the first tic diagnoses varied from 7.3 to 9.0 for other tic disorders and TS, respectively. Of note, our data are skewed towards a younger diagnosis age due to inclusion of younger cases; thus, it is possible that the true mean age of the diagnosis is higher. A common onset age for tic symptoms is 4-6 years, and lead time to diagnosis may be several years (Leckman, 2014, Shilon Y et al., 2008) A large international database showed that approximately half of the TS diagnoses are given when the child is from 6 to ten years old (Freeman et al., 2000).

ADHD was the most prevalent of the examined comorbidities. Comorbid ADHD was diagnosed in 28.2% of the children with TS and 16.2% and 5.7% of those with CT and other tic disorders, respectively. ASD was diagnosed among 16.8% of the children with TS and among 8.7% and 4.4% in children diagnosed with CT and other tic disorders, respectively. OCD frequency was 8%, 2.6% and 1% for TS, CT and other tic disorders, respectively. ADHD and OCD have been the most reported comorbidities in several studies (Hirchtritt et al., 2015, Freeman et al., 2000 et al., Suren et al., 2019). The frequency of comorbid ADHD was somewhat lower in our study than in the most clinical studies. Some population studies suggest lower frequencies (Scharf et al., 2015). Frequency of comorbid OCD in individuals with TS has varied considerably across studies, and most studies have reported higher frequencies of comorbid OCD among the individuals with TS (Khalifa N. and von Knorring A-L., 2006). Two main reasons may explain the low frequency of comorbid OCD in this sample compared with some of the previous studies. First, TS is often diagnosed earlier than OCD, and it is possible that some of the children will develop OCD and be diagnosed in the future due to the study sample's age distribution and limited follow-up time. Second, the registration of comorbid diagnoses may be less consistent.

6.4 Incidence

The incidence rates of diagnosed TS increased from 2.4 to 10.8 per 10 000 during the study years. All the children with symptoms of TS are not diagnosed and registered in the FHDR; thus, our results rather describe the increase in the service

use than the increase of true incidence of the disorder. The results may reflect increased public awareness, availability of the services and increased diagnostic accuracy. It is also possible that some of the cases born 1991 were lost because the outpatient services were first added to the FHDR in 1998. TS prevalence is 0,5% according to meta-analyses (Scharf et al., 2015). A Swedish population-based study that used both screening and register-based methods showed that the prevalence of TS was 1% in a school population while 0.15% of the children were diagnosed with TS in (Kadesjö and Gillberg., 2000).

Our findings are in line with a Danish register-based cohort study that showed a cumulative incidence of 4.5 (95% CI 1.4-3.1) for a cohort born in 1990-91 by age 11. By age 9 there was a statistically significant change in the cumulative incidence when comparing birth cohort 1994-95 to birth cohorts 1990-91 (p 0.005) and 1992-93 (p=0.006) (Atladottir et al., 2007). The most recent Nordic incidence study from Norway showed a notably higher cumulative incidence of 0,43% at age 12; that study included all children born in Norway from 2002-2010, and its follow up time was until 2016. The incidences of the register-based neurodevelopmental diagnoses have been increasing in Nordic countries (Atladottir et al., 2015); it is possible that the different timeframe could partly explain the difference between our study and the Norwegian study. Another explanation could be differences of awareness and diagnostic pathways between Finland and Norway.

6.5 Validity of the TS diagnoses in the FHDR

The number of the false positives among the TS diagnoses in the FHDR is low, indicating that the FHDR is a suitable data source for TS epidemiological studies. The results are in line with the studies examining the validity of childhood autism diagnosis and ADHD in the FHDR that showed that 96% and 88% of the examined cases fulfilled the diagnostic criteria, respectively (Lampi et al., 2010; Joelsson et al., 2015). A study examining the validity of tic disorder diagnoses in the Swedish National Patient Register showed a positive predictive value of 92%; furthermore, 43 files of patients with diagnosed epilepsy were examined and no false negatives were found (Ruck et al., 2015).

The validation study showed that the register-based TS diagnoses correlate to the clinical diagnoses to a good extent despite its methodological limitations. This is also in line with the validity of other psychiatric diagnoses in the FHDR, and the registries in the Finnish registers and the tic disorder diagnoses have been shown to also have good validity in the Swedish registers (Ruck et al., 2015). The registers are thus useful sources of data for epidemiological studies also examining tic disorders.

6.6 Maternal smoking

Maternal smoking during pregnancy was associated with TS when comorbid with ADHD after adjusting with the confounding factors, but no association was found between prenatal maternal smoking and TS without comorbid ADHD. The association between maternal smoking during pregnancy and TS with comorbid ADHD can be explained by the comorbidity. Several studies have reported that children exposed to maternal smoking during pregnancy have around a twofold increased risk for ADHD compared with unexposed children (Obel et al., 2015). The explanation for this association is unclear: Direct biological mechanisms are plausible, but several studies have also indicated that the association may be explained by shared genetic risk factors (Obel et al., 2015). This study did not address this question, and an attempt to address that would require a different kind of study design. This study was also unable to compare the association between maternal smoking during pregnancy and TS with ADHD and ADHD only in this sample. This was because this study was part of the thesis aiming to examine risk factors for TS and did not include a group consisting of children diagnosed with ADHD only. The data on maternal smoking were based on self-reports and not on quantified measures. Another study using Finnish register data showed an association between prenatal maternal smoking and ADHD (OR 1.75, 95% CI 1.65-1.86) that is similar to the association between prenatal maternal smoking and TS and ADHD in this study (Joelsson et al., 2016).

Data on maternal alcohol use or substance use that can be associated with maternal smoking during pregnancy were not available.

We were unable in our study to stratify by the quantity of smoking due to the lack of this data in the register. Interestingly, a recent Danish birth cohort study (including 89189 births and 531 children with TS/CT) showed an association between heavy maternal smoking and TS/CT. This study suggested a dose-response relationship between prenatal maternal smoking and TS/CT (Browne et al., 2016). A recently published Swedish register-based cohort study, including over 5500 individuals with diagnosed TS/CT, found a similar association between prenatal maternal smoking and TS/CT in a dose-responsive manner, but the association was no longer significant when the children with comorbid ADHD were excluded. The association also attenuated in the sibling-comparison models, suggesting that the possible association between prenatal maternal smoking and TS is likely to be explained by familial factors or comorbid ADHD (Brander et al., 2017).

Recently published meta-analyses of seven studies examining prenatal maternal smoking and TS included one of the original articles of this thesis, and reported an overall adjusted RR 1.35 (95% CI 1.17-1.56) (Ayubi et al., 2021).

Quantifying maternal smoking during the pregnancy by using biomarkers, e.g., cotinine, is important in the future to confirm the studies based on interviews on smoking and quantities of smoking.

6.7 Maternal, obstetric and neonatal adversities and TS

Our study showed that increasing parity is associated with decreasing risk for TS. The underlying mechanisms explaining this finding are unclear. Parity is generally associated with several physiological changes in females (e.g., cardiac function, pre-eclampsia, altered hormone levels) and may also change health behaviour (e.g., smoking and alcohol consumption) (Clifton et al., 2012). Primiparity has also previously been associated with TS in a smaller population-based study (Mathews et al., 2014), and other neurodevelopmental disorders, e.g., autism (Cheslack-Postava et al., 2014). It has also been suggested that the association describes rather the family planning stoppage in reproduction than is causal. However, even if this would be the case considering autism, TS is diagnosed later in most cases and may have less effect on family size. We did also adjust for the number of the siblings in the sibship that did not attenuate the association.

Another finding was that a birth weight of 4000-4499 was associated with decreased risk for TS. Birth weight is an indicator of prenatal well-being, and both low and high birth weight have been associated with adverse, long-term consequences. Birth weight is mediated by genetic and environmental factors. Birth weight also correlates with gestational age; weight for gestational age is thus used as a proxy for foetal growth restriction (Lunde et al., 2007). Low birth weight or prematurity did not increase the risk for TS in our study, and neither did small or large size for gestational age. Since these exposures are relatively rare, it is possible that our study lacked statistical power to detect the possible associations. These factors were not included in the final model examining the association between birth weight and TS, but it is likely that babies with higher birth weight are at least nearly full term. A recently published Swedish study having a larger sample size of over 5000 individuals with TS/CT showed that breech presentation, caesarean section, gestational age and impaired foetal growth were associated with a higher risk for TS/CT (Brander et al., 2017). It is possible that a larger sample size explains the differences.

Data on Apgar scores at 5 minutes were available for only 1 % of the sample; we were thus unable to study the association between Apgar score at 5 minutes, although it would have been a better indicator for long-term outcomes (Leinonen et al., 2018).

The exposures (e.g., birth weight < 1500g) are uncommon. Thus, we were thus unable to stratify the cases based on comorbidities despite the large sample size, and our power to detect subtle associations was limited.

6.8 Parental psychiatric disorders and TS/CT

The study showed that any maternal and any paternal psychiatric disorder is associated with an increased risk for TS/CT. The association between maternal psychiatric disorders and TS/CT was stronger than the association between paternal psychiatric disorders and TS/CT. All maternal-specific diagnostic categories were associated with TS/CT. Of paternal psychiatric disorders, OCD and anxiety disorders were associated with offspring TS/CT.

A familial aggregation of TS and OCD has been established, and these two disorders seem to have shared genetic factors (Browne et al., 2015, Hirschtritt et al., 2015). First-degree female relatives of individuals with TS are more likely to have OCD than first-degree male relatives (Debes et al., 2010). Therefore, a maternal OCD comorbid with another examined psychiatric disorder could represent a sex-influenced genetic risk factor for TS. The co-occurring OCD was included as a covariate in our study. This did not alter the results. However, it must be noted that OCD is not necessarily diagnosed in specialised health care and registered in the FHDR, and some residual confounding may exist.

Maternal-specific, non-genetic effects on the child may arise from direct intrauterine mechanisms, e.g., maternal medication use, substance use, other health related issues, e.g., nutrition, obstetric complications or stress. Maternal psychotropic medication during pregnancy has been associated with neurodevelopmental disorders, e.g., autism and ADHD, although the studies are not consistent (Clements et al., 2015, Malm et al., 2016, Hviid et al., 2013, Croen et al., 2011). The studies examining maternal psychotropic medication use and TS are lacking. Exposure to cannabis and alcohol during pregnancy have been associated with TS (Mathews et al., 2014). Maternal smoking during pregnancy was associated with TS only when comorbid with hyperkinetic disorder in this sample, although it has been suggested to be associated with TS in other studies (Browne et al., 2016, Mathews et al., 2006). Obstetric or neonatal adversities were not associated with TS in this sample.

Maternal stress may affect prenatal programming through foetal exposure to glucocorticoids, inflammation, or placental modification (Kim et al., 2015). Maternal stress as well as the neuroendocrine mechanisms have been suggested to be associated with TS (Hoekstra et al., 2012, Martino et al., 2013). Increased inflammatory biomarkers have been associated with other neurodevelopmental disorders such as autism and schizophrenia (Brown et al., 2014, Canetta et al., 2014);

however, such studies on TS are still lacking. A Danish register-based study has shown an association between maternal autoimmune disorders and TS (Dalsgaard et al., 2015). Postnatal infections have also been suggested to trigger or modulate tic disorders in some individuals (Macerollo and Martino, 2013).

Specific maternal psychiatric disorders increased the risk for TS approximately 2.5-fold, indicating the non-specific association between maternal psychiatric disorders and TS/CT. This could be due to 1) aggregation of several disorders in the family, for example, TS has genetic correlations with mood disorders, anxiety disorders and disruptive behaviour disorders, however, these correlations are mediated through the presence of OCD and ADHD in these families (Hirschtritt et al., 2015); 2) several psychiatric/neurodevelopmental disorders partly share a genetic origin (Pettersson et al., 2016, Pettersson et al., 2013); or 3) prenatal factors shared across psychiatric disorders that were discussed earlier.

Data on parental childhood onset disorders were scarce in this sample. This can be due to a lack of outpatient data before 1998 as well as a limited awareness of these disorders in Finland during the childhood of these parents. Diagnosing these disorders has increased in Finland during the last decades (Atladottir et al., 2015).

The strong association between maternal psychiatric disorders and offspring TS/CT encourages us to explore more maternal specific factors, either environmental, genetic or combination of these, that could underlie the finding.

7 Summary/Conclusions

This thesis aimed to increase the knowledge on prenatal, perinatal and parental factors associated with the development of Tourette syndrome (TS). The characteristics of the register-based sample and validity of the TS diagnoses were also examined. The thesis had several findings, both contributing to the etiologic research of TS and describing the clinically diagnosed children with TS and other tic disorders in Finland.

First, the incidence of registered TS diagnoses has increased during the study period, possibly reflecting the increased awareness of this disorder.

Second, the TS diagnoses registered in the Finnish Hospital Discharge Register (FHDR) are correct for almost all the cases (95%). This encourages to utilization of FHDR as a source for epidemiological studies of TS.

Third, maternal smoking during pregnancy was associated with TS when comorbid with ADHD but not with TS without comorbid Attention deficit/hyperactivity disorder (ADHD). Considering the literature (Obel et al., 2015), it seems likely that the found association is explained by the established relationship between prenatal maternal smoking and ADHD familial confounding. However, the mechanisms behind comorbidity between TS and ADHD are as yet unclear, and it requires further research regarding whether prenatal maternal smoking increases the risk of ADHD in children with TS. Studies using biological measures of prenatal maternal smoking are also desirable.

Fourth, increasing parity and higher birth weight decrease the risk for TS. The mechanisms explaining these associations are unclear. Further examination of the factors associated with parity and prenatal growth, including prenatal exposure to infections, toxins, nutrition, and maternal hormones, could lead to a better understanding of the detected associations.

Finally, the fifth finding of a wide range of maternal psychiatric diagnoses that are associated with offspring TS suggests there are unspecific maternal factors shared across disorders that are likely to explain this association. These could be shared genetic factors, or intrauterine exposure to substance abuse or stress that have previously been shown to be associated with TS (Mathews et al., 2015) or maternal

medication or inflammation that have been shown to be associated with other neurodevelopmental disorders, but those studies in TS are waiting to be conducted.

TS likely arises from a complex interplay between multiple genetic and non-genetic risk factors. Identifying each risk factor – either genetic or non-genetic – adds its own important piece to the complicated picture of this disorder's etiology. Each step leading to the next one is necessary. Discovering the non-genetic risk factors – along with the genetic risk factors – is a step needed to go forward before examining the gene by environment interaction that may reveal the more detailed picture of this intriguing disorder's etiology.

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