



**UNIVERSITY
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Tourette's Syndrome and the Risk of Psychiatric and Neurodevelopmental Disorders in Siblings

MDP in Human Neuroscience/Faculty of Medicine

Master's thesis

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12.05.2026

Turku

The originality of this thesis has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

Master's thesis

Subject: MDP in Human Neuroscience

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Title: Tourette's Syndrome and the Risk of Psychiatric and Neurodevelopmental Disorders in Siblings

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Number of pages: 60 pages

Date: 12.05.2026

Tourette's Syndrome (TS) is a neurodevelopmental disorder that affects up to 1% of the global population. It is typically characterised by the presence of both motor and vocal tics, but encompasses a variety of additional symptoms. This study aims to be the first to explore the likelihoods of specific mental and neurodevelopmental disorders in the siblings of people with TS.

A dataset comprised of 35,295 individuals, of which 21,414 were siblings, born between 1991-2010 and 1977-2013 respectively was compiled. It was populated with data from three national registers: the Finnish Care Register for Health Care (CRHC), the Finnish Digital and Population Data Services Agency (DPDSA), and the Finnish Medical Birth Register (MBR).

A nested case-control design was then used and each sibling case (n=2188) was matched to four controls (n=6963) within the dataset. The included covariates were parity, parental age, parental psychiatric diagnoses, maternal socioeconomic status, and parental immigration. Sibling psychiatric disorders were also taken from registers. A conditional logistic regression using generalised estimating equations (GEEs) was used to create three models from the data: an unadjusted model and two models adjusted for all covariates.

The siblings of people with TS were shown to have a significantly increased incidence of mental and neurodevelopmental disorders, with the likelihood being 1.4 times that of the average for the sibling of a person without TS. Of the investigated disorders, the ones with a significantly increased incidence were mood/affective disorders (adjusted odds ratio (aOR) 1.4, 95% CI 1.2-1.6), anxiety-derived disorders (1.3 aOR, 95% CI 1.1-1.6), autism spectrum disorder (aOR 2.2, 95% CI 1.5-3.2), attention deficit hyperactivity disorder (aOR 1.6, 95% CI 1.2-2.1), and other neurodevelopmental disorders (aOR 1.4, 95% CI 1.2-1.6 and aOR 1.5, 95% CI 1.3-1.7).

The clustering of psychiatric disorders among siblings could imply a shared genetic or environmental factor in these disorders, setting up a groundwork for future genetic and comparative studies.

Keywords: Tourette's syndrome, TS, sibling study, mental disorders

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1 Introduction

1.1 History of Tourette's Syndrome

Tourette's syndrome (TS) is a typically childhood-onset neurodevelopmental disorder (Johnson et al., 2023) that is diagnosed in up to 1% of children (and in 0.01% of adults) worldwide (Stern, 2018), (Yilmaz & Jankovic, 2025). Despite descriptions of TS dating back as far as 1486 (Germiniani et al., 2012), the first published medical description only arose in 1885 (Pauls, Hurst, et al., 1986). Little research has since been conducted regarding the causes behind TS, with initial hopes for locating a gene ('Definitions and Classification of Tic Disorders', 1993) being replaced by the idea that multiple genes may work in concert to result in a Tourettic phenotype (Willsey et al., 2017).

1.2 Diagnosis of Tourette's Syndrome

Initially, TS was classified as a motor disorder (as per the DSM-5 in 2013). This view has since evolved into describing it as a neurodevelopmental neuropsychiatric disorder (Jones et al., 2026). It is currently grouped under tic disorders, which are also not well understood at this time (Grossen et al., 2024).

Currently, the ICD-10 diagnoses TS with regards to the presence of tics (*ICD-10 Version:2019, 2019*):

Combined vocal and multiple motor tic disorder [de la Tourette's syndrome]

A form of tic disorder in which there are, or have been, multiple motor tics and one or more vocal tics, although these need not have occurred concurrently. Onset is almost always in childhood or adolescence. A history of motor tics before development of vocal tics is common; the symptoms frequently worsen during adolescence, and it is common for the disorder to persist into adult life.

The vocal tics are often multiple with explosive repetitive vocalizations, throat-clearing, and grunting, and there may be the use of obscene words or phrases. Sometimes there is associated gestural echopraxia, which also may be of an obscene nature (copropraxia). As with motor tics, the vocal tics may be voluntarily suppressed for short periods, be exacerbated by stress, and disappear during sleep.

However, there are many non-tic symptoms that characterise the disorder and therefore inform our understanding of it. Social cognition is thought to be altered in TS (Eddy &

Cavanna, 2013). This is often paired with findings that inhibitory control is often impaired in TS, though verbal inhibition does not appear to be universally affected either (Morand-Beaulieu et al., 2017), (Ritter et al., 2022). Sensory hypersensitivity has also been commonly observed in subjects with TS, not just with regards to disorder-specific phenomena such as premonitory urges (Leckman et al., 1993), but also when concerning general external sensory input (Isaacs & Riordan, 2020). A significantly increased probability of sleep problems has also been reported in TS (Jiménez-Jiménez et al., 2022), though it remains unclear how much of this is attributable to the effect of tics on sleep or rather to TS itself (Blaty & DelRosso, 2022). Another common symptom of TS are rage attacks, which are present in up to 67% of Tourette individuals (Conte et al., 2020). One study found that the average IQ scores of children with TS was lower than those of their non-Tourette peers (Debes et al., 2011), while others have found an elevated level of cognitive control over motor output (Jung et al., 2013). Furthermore, the primary symptom of tics can themselves be divided into subcategories depending on their manifestation: they can be simple or complex, they can be motor or phonic at their most vague, but have been recorded as existing in mental, written, and other forms as well (Zanaboni Dina et al., 2016). They can stem from external influences or internal sensations (Baizabal-Carvallo & Jankovic, 2025), and an individual will likely exhibit many different tics over the course of their life.

1.3 Current Treatments for Tourette's Syndrome

No TS-specific treatment exists, and all current medications and therapies only address the tic symptom. For those with co-occurring obsessive-compulsive disorder (OCD), selective serotonin reuptake inhibitors (SSRIs) have been shown to have an effect in reducing tics (Jiménez-Jiménez & García-Ruiz, 2001). Otherwise, the attention deficit hyperactivity disorder (ADHD) medications clonidine and guanfacine, and antipsychotics haloperidol, pimozide, aripiprazole, and risperidone have been shown to have some tic suppressing ability in people with TS (Seideman & Seideman, 2020). Comprehensive Behavioural Intervention for Tic (CBIT) disorders is the primary non-pharmacological therapy for those with TS (Kohler et al., 2025), though deep brain stimulation is often cited as a candidate for tic treatment in the future (Casagrande et al., 2019).

1.4 Comorbidities in Tourette's Syndrome

One of the challenges inherent to studying TS comes from its high propensity for comorbid conditions, making it difficult to find isolated instances of the disorder. Up to 86% of individuals with TS have at least one comorbid condition and up to 58% have two or more (Hirschtritt et al., 2015). ADHD is the most prevalent comorbidity of TS (Oluwabusi et al., 2016), followed and often overlapped by OCD (Yan et al., 2022). Autism spectrum disorder (ASD) (Kalyva et al., 2016) and oppositional defiant disorder (ODD) (Kumar et al., 2016) have also been found to have an elevated rate of incidence among individuals with TS. Non-neurodevelopmental conditions have also been observed in higher rates in TS, particularly in the cases of anxiety and depression (Abbasi et al., 2023). Of these, OCD has been noted to provide a unique challenge to clinicians and researchers alike, as the phenotype of comorbid TS and OCD is distinct, with symptoms often “blending” to create novel features that are not present in either disorder when alone (Katz et al., 2022).

1.5 Pedigree of Tourette's Syndrome

The genetic and environmental factors leading to the development of TS in an individual are not yet understood, but studies have found that most cases of the disorder involve a hereditary element. First degree relatives of a person with TS have a 10-1000 times greater risk of also developing TS when compared to the general population (Pauls et al., 2014). Furthermore, those with comorbid OCD are more likely to have their relatives develop OCD than patients with OCD alone (Brander et al., 2021). Although this study focused only on psychiatric and neurodevelopmental diagnoses in siblings, it is worth noting that a possible link between TS and autoimmune diseases (ADs) in families exists, with one study finding that the risk for ADs increased in both patients with TS and their first-degree relatives, but not their second or third-degree relatives (Mataix-Cols et al., 2015). The mechanics of all these hereditary patterns remain unknown and require further research and investigation before any relationships between their and TS' development can be characterised properly.

1.6 Previous Sibling Studies

To date, no studies have investigated the likelihoods of psychiatric and neurodevelopmental disorder diagnoses in the siblings of people with TS. Two previous sibling studies have looked

at the symptoms present in siblings of those with TS, (Sidiropoulou et al., 2024) and (Mathews & Grados, 2011). Both studies were register-based, with Sidiropoulou et al.'s European dataset being comprised of 196 Tourette individuals and their 220 full siblings, while Mathews & Grados' contained 952 individuals from 222 TS-affected sibling-pair families from the United States of America, Canada, Germany, the Netherlands, and the United Kingdom.

One found a significantly increased incidence of ASD, ADHD, and ODD symptoms in the siblings of Tourette individuals by way of generalised linear mixed-effect negative binomial regression models, (Sidiropoulou et al., 2024). The other found a significantly increased heritability of OCD and ADHD in TS families, (Mathews & Grados, 2011). These are all common comorbidities of TS, which further reinforces the theory that these conditions may share an aetiological link. Furthermore, previous sibling studies on other neurodevelopmental disorders have shown similar clustering, with the siblings of those with ADHD and ASD having an increased likelihood of having a tic disorder (Jokiranta-Olkonieni et al., 2019), (Jokiranta-Olkonieni et al., 2016). However, the prevalences of specific mental and neurodevelopmental disorders in the siblings of people with TS have yet to be explored. This study aimed to do that by compiling and analysing a dataset from Finnish registers, benefitting from their completeness and minimisation of selection bias.

1.7 Aims and Objectives

The major aim of this study was to investigate the wide-ranging psychiatric and neurodevelopmental morbidities that may affect the siblings of children with TS and their frequencies in comparison to non-Tourette controls. Our hypothesis presumed that there would indeed be an elevated likelihood of mental and neurodevelopmental conditions in the siblings of those with TS when compared to their counterparts. The goal was to contribute to the production of research for this poorly-understood neurodevelopmental disorder.

2 Method

2.1 Dataset

The dataset was built from the information found in three national Finnish registers: the Care Register for Health Care (CRHC) – formerly known as the Finnish Hospital Discharge Register (FHDR), the Medical Birth Register (MBR), and the Digital and Population Data Services Agency (DPDSA) – formerly known as the Finnish Population Register (FPR).

The CRHC contains information on all medical diagnoses made in Finnish hospitals, inpatient wards in public hospitals, psychiatric hospitals, military wards, local health centres, prison wards and hospitals, and private hospitals since 1969. Starting from 1998, it also contains diagnostic information from outpatient care in public hospitals. Additional relevant information found in the CRHC extends to personal identity codes (PICs), dates of admission, dates of discharge, possible subsidiary diagnoses, and further details on the care and admission of psychiatric patients (*Care Register for Health Care*, 2023). Between 1969-1986, the diagnoses in the CRHC were recorded in terms of the ICD-8, then ICD-9 between 1987-1995, and ICD-10 from 1996 until now (Leivonen et al., 2014). The validity of the diagnoses found in the CRHC has been investigated, with positive predictive values of 75%-99% having been found (Sund, 2012).

The MBR was established in 1987 and, like the CRHC, is maintained by the Finnish Institute for Health and Welfare (THL). It contains comprehensive and standardised data on the perinatal period of all live births and stillbirths of fetuses with birth weights over 500g and gestational ages over 22 weeks in Finland. Further information in the MBR includes data on maternal background, pregnancies, the perinatal period of the current pregnancy up to 7 days after birth, and the neonatal period (*Medical Birth Register*, 2023). In this study, information on maternal socioeconomic status (SES), maternal age, and parity was obtained from the MBR.

The DPDSA is a computerised national register containing information on Finnish citizens and permanent residents in Finland. It is maintained by the Finnish population centre and local register offices and includes details on each individual's PIC, address, citizenship status, native languages, family relations, dates and countries of immigration and emigration, birth

date, death date, and countries of origin. Furthermore, a person's PIC – issued to every citizen and permanent resident of Finland since the 1960s – includes information on their date of birth, sex, and provides a unique control number for each individual, allowing their profiles across all three registers to be linked. This was also used to identify full siblings through their parents.

2.2 Subjects and Controls

Subjects were those born in Finland between 1st January 1991-31st December 2009, with TS diagnoses given between birth or 1st January 1991 and death or 31st December 2010.

Comorbid diagnoses were taken until the end of the follow-up period on 31st December 2016. A diagnosis of TS was defined as either an ICD-9 code 307.23, a Finnish ICD-9 code 3072D, or an ICD-10 code F95.2. Non-singletons (n=98) were excluded in order to avoid skewing the results and due to the difficulty in finding controls with which to match them. Subjects with diagnoses of severe or profound intellectual disability (n=1) – ICD-9 318.1 and 318.2, Finnish ICD-9 3181 and 3182, ICD-10 F72 and F73 – were also excluded for the same reasons and in order to ensure that no other factors relating to these risk pregnancies influenced the results. Individuals who had emigrated from Finland before the end of the 31st December 2016 follow-up period (n=9) and those who were deceased before the end of this period (n=3) were excluded due to their inherent missing information.

Controls were taken from between the same time period. Non-singletons (n=433) were excluded, as were those with TS diagnoses (n=7). Those diagnosed with other tic disorders (n=11), (ICD-9 307.2X without 307.23, Finnish ICD-9 3072X without 3072D, and ICD-10 F95X without F95.2) were excluded, as it is not uncommon for a child diagnosed with, for example, transient tic disorder to later be diagnosed with TS. Controls diagnosed with severe or profound intellectual disability (n=1) were excluded following the same diagnostic criteria used for the subjects.

2.3 Siblings

The dataset included full siblings born between 1st January 1977-31st December 2012. Siblings born outside of this timeframe (n=599 before 1977) were excluded, as were those who died or emigrated from Finland before the age of 3 (n=107) or immigrated to Finland

after the age of 3 (n=84). This is, once again, due to the incompleteness of such records. The remainder of the exclusions were the same as those for the cases with the addition of excluding half-siblings that only shared a mother (n=3933), half-siblings that only shared a father (n=3800), and any siblings with an unknown parent. The follow-up time for the siblings and their diagnoses was from the birth of the sibling or 1st January 1987 until the death of the sibling or 31st December 2016.

Subjects and controls were matched in a 1:4 ratio by their dates of birth (+/- 30 days), sex, place of birth, and living status at time of diagnosis. This led to the further exclusion of cases without matched controls (n=3), and controls without matched cases (n=701). Complete matched sets of cases and controls were included if the case and at least one of its controls had a full sibling within the criteria. This resulted in a final dataset consisting of 35,295 total individuals.

2.3.1 Sibling Diagnoses

The diagnostic groups for siblings were based on the 2019 ICD-10's chapter 5 structure for mental and behavioural disorders (*ICD-10 Version:2019*, 2019). Additional splitting and grouping of diagnoses was done based on previous studies that have utilised a similar methodology (Koskela et al., 2024), previous studies looking into the common comorbidities of TS (Kumar et al., 2016), and symptoms observed in the siblings of those with TS (Sidiropoulou et al., 2024), (Mathews & Grados, 2011).

Table 1. Categorisation and grouping of sibling disorders in terms of the ICD-10 and ICD-9

X is used to include all disorders covered by the preceding code. For example, 307.2X includes 307.20, 307.21, 307.22, and 307.23 (unless otherwise specified).

Similarly, codes include all their sub-codes. For example, F11 includes F11.1 through to F11.99 (unless otherwise specified).

The Finnish ICD-9 codes are included for legibility. The general ICD-9 was used in the study itself.

Sibling Diagnostic Category	ICD-10	ICD-9	Finnish ICD-9
No psychiatric or neurodevelopmental diagnoses	No diagnoses within F00-F99	No diagnoses within 290-319	No diagnoses within 290-319
Any psychiatric or neurodevelopmental diagnoses	Any diagnoses within F00-F99	Any diagnoses within 290-319	Any diagnoses within 290-319
Organic mental disorders	F00-F09 F00, F01, F02, F03, F04, F05, F06, F07, F09	290, 293, 294, 310	290, 293, 294, 310
Disorders due to substance use	F10-F19 F10, F11, F12, F13, F14, F15, F16, F17, F18, F19	291, 292, 303, 304, 305	291, 292, 303, 304, 305
Schizophrenia spectrum disorders	F20-F29 F20, F21, F22, F23, F24, F25, F28, F29	295, 297, 298, 301.2X	295, 297, 298, 3012X
Mood/affective disorders	F30-F39 F30, F31, F32, F33, F34, F38, F39	296, 311	296
Anxiety-derived disorders	F40-F48, excluding F42 F40, F41, F43, F44, F45, F48	300 (excluding 300.3), 308, 309	300 (excluding 3003A), 309
OCD	F42	300.3	3003A
ASD	F84	299	299
ADHD	F90	314	314
Non-TS tic disorders	F95, excluding F95.2	307.2X, excluding 307.23	3072X, excluding 3072D
Neurodevelopmental disorders group 1 (mental retardation, learning disorders, and disorders of cognitive development)	F70-F83, excluding F84	315, 317, 318, 319	315, 317, 318, 319
Neurodevelopmental disorders group 2 (often childhood onset, psychiatric, developmental, and emotional disorders)	F88-F98, excluding F90 and F95	313	313
Other psychiatric or neurodevelopmental diagnoses	F50-F69, F99	301 (excluding 301.2X), 302, 306, 307 (excluding 307.2X), 312, 316	301 (excluding 3012X), 302, 307, (excluding 3072X), 312, 316

2.4 Covariates

The covariates chosen for this study were parity, maternal age at childbirth, paternal age, paternal and maternal psychiatric history, maternal socioeconomic status, and parental immigration. Their categorisation can be seen in Table 2, while the coding for the entire dataset can be seen in detail in appendix 1.

Table 2. Covariate coding

Variable	Variable Range	Number of Objects	Number of Missing Values	Coding
Parity	0-1	35,295	0	0="No", 2="Yes"
Mother's age	14-47	35,295	0	
Father's age	15-67	35,133	162	
Mother mental condition diagnosis	0-1	35,295	0	0="No", 2="Yes"
Father mental condition diagnosis	0-1	35,295	0	0="No", 2="Yes"
Mother's socioeconomic status		32,776	2519	1="Upper white-collar workers", 2="Lower white-collar workers", 3="Blue-collar workers", 4="Others"
Mother's immigration status	1-3	35,295	0	1="Finnish", 2="1 st generation immigrant", 3="2 nd + generation immigrant"
Father's immigration status	1-3	35,133	162	1="Finnish", 2="1 st generation immigrant", 3="2 nd + generation immigrant"

Covariates were chosen with respect to previous literature linking them to TS. Increased parity has been connected to decreased odds of developing TS, while nulliparity has been associated with increased odds (Leivonen et al., 2016). Younger maternal age and older paternal age have previously been implicated in the onset of TS (Choi et al., 2023), as has incidence of TS in at least one of the parents (Lin et al., 2022). Higher incidences of TS have

been associated with a lower SES (Miller et al., 2014), and while no direct link has yet been made between immigration status and TS, it is well-known that different cultural environments can have effects on the intensity of some symptoms (Richter et al., 2020), (Lei et al., 2025) and the presence of comorbidities (Côté-Olijnyk et al., 2024) in TS.

2.5 Statistical Analyses

The analysis conducted was a nested sibling analysis with a matched case-control sample design with the siblings as the unit of analysis. Regression models were made separately for each outcome and were fitted to estimate the association between TS in individuals and psychiatric or neurodevelopmental disorders in their siblings versus that between non-TS individuals and psychiatric or neurodevelopmental disorders in their siblings.

A conditional logistic regression using generalised estimating equations (GEEs) was used to create three models from the data. GEEs are best applied to longitudinal data such as this and account for correlations in individuals over time. Furthermore, they do not assume a normal distribution in the dataset.

The association between TS in cases (classified as exposure) and each psychiatric disorder in siblings (classified as outcome) was estimated separately. This accounted for siblings within the same family, the dependency between cases and their matched controls, and individual follow-up times. Each stratum was defined by one matched case-control set, therefore each stratum included the siblings of 1 case and of their matched controls.

The first model was unadjusted for all covariates, while models 2 and 3 were adjusted for all covariates. Where model 2 considered maternal marital status “married” and “in a relationship” as two separate values, model 3 treated them as one and the same. Otherwise, the models were identical in their treatment of the covariates.

All statistical modelling was conducted using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

3 Results

The final totals used for the study are presented in Table 3. The data was comprised of 2188 cases with 3789 siblings and 6963 controls with 13,478 siblings. Among cases and their siblings (n=3789), the average age of siblings at the end of the follow-up period was 19.6 with a standard deviation (SD) of 6.8 and a range of 4.2-39.8 years. For the controls and their siblings (n=13,478), the average age of siblings at the end of the follow-up period was 20.3 with an SD of 7.0 and a range of 3.2-40.0 years.

Table 3. Final totals used for the study with their sex frequencies

	Number of Individuals
Cases	2188
Controls	6963
Cases and their siblings	3789
Controls and their siblings	13,478

The descriptive information of the siblings is detailed in Table 4. On average, those with TS had fewer (1.7) siblings than those without TS (1.9). The distribution of sibling sexes between cases and controls was almost identical, with 23.9% (n=522) of the case siblings being female and 23.8% (n=1660) of the control siblings being female. The male sibling frequencies were 76.1% (n=1666) and 76.2% (n=5303) for cases and controls respectively.

Table 4. Descriptive information on the siblings of cases with TS and controls without TS

Values rounded to 1 decimal place (DP) where relevant.

IQR = interquartile range

	Cases (n=2188)	Controls (n=6963)
Number of full siblings		
<i>1</i>	1240 (56.7%)	3479 (50.0%)
<i>2</i>	652 (29.8%)	2213 (31.8%)
<i>3</i>	173 (7.9%)	696 (10.0%)
<i>4 or more</i>	123 (5.6%)	575 (8.3%)
<i>Mean</i>	1.7	1.9
<i>Range</i>	1-16	1-17
<i>Median (IQR)</i>	1 (1-2)	2 (1-2)
Sex of the siblings		
<i>Female</i>	522 (23.9%)	1660 (23.8%)
<i>Male</i>	1666 (76.1%)	5303 (76.2%)

Table 5 contains information on the covariates considered in the analysis. Most frequencies across cases and controls were similar. On average, the mothers of cases had more psychiatric disorder diagnoses than those of controls, with 17.1% (n=374) in cases compared to 10.8% (n=751) in controls. This was less apparent with regards to the paternal psychiatric diagnoses, where 13.0% (n=284) of the cases' fathers had at least 1 psychiatric diagnosis compared to 11.0% (n=768) in controls. On average, cases with TS were more likely to be their mother's firstborn child in comparison to controls without TS – 37.3% (n=815) compared to 28.6% (n=1990).

Table 5. Descriptive information of covariates in cases and controls

SD = standard deviation

Rounded to 1 DP where relevant

	Cases (n=2188)	Controls (n=6963)
Maternal Age		
<i>Mean (SD)</i>	28.9 (5.0)	29.1 (4.9)
<i>Range</i>	17-47	16-46
Paternal Age		
<i>Mean (SD)</i>	31.3 (5.7)	31.5 (5.6)
<i>Range</i>	17-56	15-58
Maternal socioeconomic status		
<i>Upper white-collar workers</i>	376 (17.2%)	1065 (15.3%)
<i>Lower white-collar workers</i>	936 (42.8%)	3093 (44.4%)
<i>Blue-collar workers</i>	362 (16.5%)	1175 (16.9%)
<i>Others</i>	360 (16.5%)	1117 (16.0%)
<i>Information Missing</i>	154 (7.0%)	513 (7.4%)
Maternal marital status		
<i>Married</i>	1474 (67.4%)	4787 (68.8%)
<i>In a relationship</i>	507 (23.2%)	1627 (23.4%)
<i>Single</i>	53 (2.4%)	135 (1.9%)
<i>Unknown</i>	154 (7.0%)	414 (6.0%)
Maternal psychiatric disorders		
<i>Yes</i>	374 (17.1%)	751 (10.8%)
<i>No</i>	1814 (82.9%)	6212 (89.2%)
Paternal psychiatric disorders		
<i>Yes</i>	284 (13.0%)	768 (11.0%)
<i>No</i>	1904 (87.0%)	6195 (89%)
Parity		
<i>Yes</i>	1373 (62.8%)	4973 (71.4%)
<i>No</i>	815 (37.3%)	1990 (28.6%)

Table 6 presents the frequency of diagnoses among siblings in cases and controls alongside the sibling analysis proper. It shows that 27.9% (n=611) of the cases with TS had a sibling with a psychiatric or neurodevelopmental diagnosis, while 22.2% (n=1543) of the controls' siblings had a sibling with a psychiatric or neurodevelopmental diagnosis.

In the unadjusted model, siblings of cases with TS had a significantly increased risk of being diagnosed with a psychiatric or neurodevelopmental disorder. All diagnostic categories had significant ORs except for organic mental disorders, disorders due to substance use, and schizophrenia spectrum disorders. The highest ORs were seen for non-TS tic disorders (8.1), ASD (2.4), OCD (1.8), and ADHD (1.8).

The sample sizes for OCD and non-TS tic disorders were too small for adjusted models. The prevalence of anxiety-derived disorders in the siblings of those with TS lost significance in adjusted model 1, while all other significant results remained as such. In adjusted model 1, siblings of cases with TS had a significantly increased risk of being diagnosed with a psychiatric or neurodevelopmental disorder. The highest ORs were seen for ASD (2.2), ADHD (1.6), and neurodevelopmental disorders group 2 (1.5).

In adjusted model 2, the ORs from adjusted model 1 were maintained, with the only notable change being that the prevalence of anxiety-derived disorders in the siblings of those with TS regained significance.

Table 6. Associations between TS and mental and neurodevelopmental diagnoses among siblings of people with TS and matched controls

All values rounded to 1 DP with the exception of those that would round to 0.0, which have been kept at 2 DP

*: $p < 0.05$, **: $p < 0.001$, ***: $p < 0.0001$

Adjusted model 1: adjusted for all covariates

Adjusted model 2: adjusted for all covariates but with maternal marital status “married” and “in a relationship” treated as the same

Sibling Diagnoses	Cases (n=2188)	Controls (n=6963)	Unadjusted Model	Adjusted Model 1	Adjusted Model 2
Any psychiatric or neurodevelopmental diagnoses	611 (27.9%)	1543 (22.2%)	1.4 (1.3-1.6)**	1.4 (1.3-1.5)***	1.4 (1.3-1.5)***
Organic mental disorders	1 (0.1%)	10 (0.1%)	0.4 (0.05-2.9)	N/A	N/A
Disorders due to substance use	45 (2.1%)	159 (2.3%)	1.1 (0.8-1.5)	1.0 (0.7-1.5)	1.0 (0.7-1.4)
Schizophrenia spectrum disorders	23 (1.1%)	87 (1.3%)	0.9 (0.6-1.4)	0.9 (0.6-1.5)	0.9 (0.6-1.5)
Mood/affective disorders	180 (8.2%)	466 (6.7%)	1.4 (1.2-1.7)***	1.4 (1.2-1.6)**	1.4 (1.2-1.6)***
Anxiety-derived disorders	164 (7.5%)	456 (6.6%)	1.3 (1.1-1.6)*	1.3 (1.1-1.6)	1.3 (1.1-1.6)*
OCD	18 (0.8%)	37 (0.5%)	1.8 (1.0-3.1)*	N/A	N/A
ASD	48 (2.2%)	78 (1.1%)	2.4 (1.7-3.4)***	2.2 (1.5-3.2)***	2.2 (1.5-3.2)***
ADHD	87 (4.0%)	172 (2.5%)	1.8 (1.4-2.3)***	1.6 (1.3-2.2)**	1.6 (1.2-2.1)**
Non-TS tic disorders	22 (1.0%)	10 (0.1%)	8.1 (3.9-17.1)***	N/A	N/A
Neurodevelopmental disorders group 1 (mental retardation, learning disorders and disorders of cognitive development)	210 (9.6%)	550 (7.9%)	1.4 (1.2-1.6)***	1.4 (1.2-1.6)**	1.4 (1.2-1.6)**
Neurodevelopmental disorders group 2 (often childhood onset; psychiatric, developmental, and emotional disorders)	219 (10.0%)	493 (7.1%)	1.6 (1.4-1.9)***	1.5 (1.3-1.7)***	1.5 (1.3-1.7)***
Other psychiatric or neurodevelopmental diagnoses	110 (5.0%)	281 (4.0%)	1.4 (1.1-1.8)*	1.4 (1.1-1.8)*	1.4 (1.1-1.8)*

4 Discussion

In our dataset of 2188 cases and their matched 6963 controls, the siblings of people with TS were shown to have a significantly increased incidence of mental and neurodevelopmental disorder diagnoses. Their likelihood of having a diagnosis of a mental or neurodevelopmental disorder was 1.4 times that of a sibling of someone without TS. Of the investigated disorder categories, those that proved to have significantly higher odds after adjusting for covariates were ASD, ADHD, neurodevelopmental disorders classed under often childhood onset, psychiatric, developmental, and emotional disorders, mood/affective disorders, neurodevelopmental disorders classed under mental retardation, learning disorders, and disorders of cognitive development, other neurodevelopmental disorders, and anxiety-derived disorders. Due to the small sample size of the study, adjusted models for incidences of OCD and non-TS tic disorders in siblings could not be made. In the unadjusted model, these remained significantly more common in the siblings of those with TS. In the adjusted analyses, ASD was the most common diagnosis in siblings of people with TS, with a 2.2 times increased chance when compared to the siblings of controls.

A similar study looked at the neuropsychiatric symptoms of siblings of cases with TS (Sidiropoulou et al., 2024) using data from the European Multicentre Tics in Children Study (EMTICS) (Schrag et al., 2019). Despite the smaller sample size of this study, similar results were found, with siblings exhibiting a significantly increased incidence of ASD, ADHD, and ODD symptoms. This is in line with our findings of the increased prevalence of ASD and ADHD diagnoses in the siblings of people with TS.

The majority of previous research on the prevalence of ADHD in the relatives of those with TS supports an aetiological link between the conditions (O'Rourke et al., 2011). Some studies have even suggested that TS itself occurs in different genetic variants, in which one has ADHD as a secondary, dependent occurrence (Pauls et al., 1993). However, the hypothesis that there are different subtypes of TS remains uncertain without further research and understanding of the disorder as whole (Eapen & Robertson, 2015). Previous work found no evidence for a genetic relationship between ADHD and TS (Pauls, Hurst, et al., 1986), stating that the increased prevalence of ADHD in Tourettic families arises from the effect of separate, inherited instances of TS, but other papers have supported the more recent idea of

different variations of TS and ADHD having different inheritability mechanics (Knell & Comings, 1993).

To the best of our knowledge, no other studies on the incidence of ASD in the siblings or relatives of those with TS have been conducted. The opposite has been investigated, indicating that tic disorders are significantly more common in the siblings of those with ASD compared to the siblings of those without ASD (Jokiranta-Olkonieni et al., 2016). While this does not prove that the relationship is reciprocal, other studies on the significantly elevated rate of ASD as a comorbidity of TS (Kalyva et al., 2016) suggest that the two conditions share an aetiological tie.

Aside from genetics, other factors have also been implicated in the aetiology of TS. Numerous studies have linked environmental conditions to higher rates of TS diagnosis, such as older paternal age, maternal psychosocial stress, maternal smoking, and lower Apgar scores (Hoekstra et al., 2013). It was also noted that higher rates of some comorbidities have been linked to environmental pressures, with ADHD appearing more commonly in Tourette people whose weights at birth were low or whose mothers smoked while pregnant, and OCD appearing more in those who were delivered with forceps, had older fathers, or whose mothers used cigarettes, alcohol, or coffee while pregnant. Some tenuous links also exist between the development of TS and the presence of maternal infection during pregnancy, particularly with regards to group A streptococcal pharyngitis (Rizzo et al., 2006). While it is known that stress can worsen the severity of tics (Leisman & Sheldon, 2022), some theories exist as to its direct relationship with TS. It has been suggested that genetics combined with a vulnerability for psychosocial stress may lead to TS, which in turn exacerbates the stress, which then worsens the symptoms, and so on (Hoekstra et al., 2013). Maternal stress while pregnant is also thought to contribute to this predisposition for TS, though more research is needed before this can be stated conclusively (Ben-Shlomo et al., 2016). One of our covariates – parity – is also thought to play a part in the aetiology of TS. Firstborns have been associated with a higher risk for TS (Scharf, 2016), with subsequent children by the same mother having a lower chance of being diagnosed with TS (Leivonen et al., 2016). Overall, it is widely agreed upon that TS has a complex aetiology that, while genetic to some extent, also depends heavily on environmental and parental factors. It is likely the interplay of these

that leads to TS, though more investigation is necessary in order to understand the nature of the relationships.

In our study, ODD was included under the neurodevelopmental disorders group 2 sibling diagnostic category and also showed significance among siblings. Like ASD, there are no other studies linking the incidence of ODD in the siblings or relatives of those with TS. While anecdotal claims exist for ODD as a comorbidity of TS, these are largely made in the context of children with TS as viewed by an adult without TS ('Co-Occurring Conditions', n.d.), and thus should be investigated properly before resulting in assertions of comorbidity. That being said, our study did find an association and, therefore, further studies are needed.

Furthermore, Sidiropoulou et al. revealed a significant interaction between the sex of the proband and the symptoms of the siblings. Female siblings displayed more symptoms of ADHD and ODD compared to males. Our study did not account for sex as a variable beyond assigning it as one of the covariates in the GEE, so no comment can be made on whether this result is shared. The EMTICS TS diagnoses were confirmed with hospital visits rather than through telephone interviews. Ideally, the diagnosis of TS is conducted in person and addresses symptoms beyond those found in the ICD-10, such as the presence of comorbid conditions (Cohen et al., 2013). While neither our registers nor the EMTICS conform to the latter, the EMTICS diagnoses were carried out in person, thus reducing the likelihood of misdiagnosis, to which TS is clinically prone (Wand et al., 1992). Sidiropoulou et al. considered the effect of tic severity on sibling symptoms, using the subjects' YGTSS results as a measure of tic severity. On the other hand, our registers improperly used the YGTSS to diagnose TS and did not keep a record of the score. With the scores, we could have carried out a similar analysis to see the effect of case tic severity on their siblings' diagnoses, if any. Otherwise, the YGTSS has been shown to be a consistently adequate measure of tic severity with strong correlations between parent-rated and subject-rated tic severities (Storch et al., 2005). As both studies relied on parental reporting of tic severity, these can be assumed to be accurate.

Covariates in our study were obtained from medical record databases, and information on individuals across registers and time were matched through their PICs. Sidiropoulou et al.

sourced their covariates through interview rather than from a database, which may introduce bias into the responses given (West & Kreuter, 2018).

Another study looked at the heritability of OCD and ADHD in Tourettic families among sibling pairs and found results reinforcing the theory that these conditions have an aetiological link (Mathews & Grados, 2011). They found significant genetic correlations between TS and OCD, which previous literature has also supported as having a possible genetic tie (Leckman et al., 2003), (Sheppard et al., 1999). It has been posited that TS may have an OCD-like phenotype (Pauls, Towbin, et al., 1986), with the most recent example being that of Tourettic OCD, which suggests that individuals with both TS and OCD present different versions of the same symptoms in comparison to their TS-only and OCD-only counterparts (Katz et al., 2022). While Matthews & Grados did not explore this relationship between siblings, our results show that the prevalence of OCD in Tourettic families may extend to the siblings of affected individuals. Further research exploring how this differs when considering parental diagnostics may reveal more about the extent to which two disorders are linked.

Matthews & Grados also found a significant genetic correlation between OCD and ADHD, but not one between TS and ADHD. Other studies have argued in favour of a shared genetic basis for TS and ADHD (Tsetsos et al., 2016), but stress that the link remains complex and unknown in nature (Yang et al., 2021). Environmental correlations between TS and ADHD, and OCD and ADHD were also observed, along with a high heritability of both OCD and ADHD in families with TS. As we did not investigate parental diagnostics in sufficient detail to assess the effect of their specific diagnoses on the diagnoses of the probands' siblings, this is not something we can comment on. Future research may benefit from looking into these relationships and seeing the effect of specific parental diagnoses across the siblings of those with TS.

Lastly, the diagnoses from Matthews & Grados were collected by the Tourette Syndrome Association International Consortium on Genetics ('A Complete Genome Screen in Sib Pairs Affected by Gilles de La Tourette Syndrome', 1999) by subjecting all participants to the same psychological tests. In our covariates, we tried to account for factors that may affect an individual's likelihood of being diagnosed or of seeking diagnosis in the first place (Staples et al., 2025), (Rantakallio, 1979).

While no other papers have explored sibling risk in TS, similar studies have been conducted for other disorders. One such study used the same Finnish registers to explore the prevalences of mental and neurodevelopmental diagnoses among the siblings of those with selective mutism (SM) (Koskela et al., 2024). Another utilised these registers to explore the same question with regards to ASD (Jokiranta-Olkonieni et al., 2016). Additional analyses in the style of these papers would have strengthened and informed our results further had time allowed. Dividing parental diagnoses into more granular categories (such as those assigned to the sibling diagnoses) may have provided insight into the relationship between parental diagnoses and their offspring's diagnoses.

Our findings correspond to the initial prediction that siblings of those with TS would potentially be more at risk of developing conditions commonly comorbid to TS. This extended to mood disorders (Robertson, 2006) and others, though no previous literature on their prevalence in siblings exists. Once again, this suggests a potentially shared aetiology or set of risk factors between TS and disorders such as depression.

The prevalences of ODD and avoidant/restrictive food intake disorder (ARFID) in siblings were not investigated separately, though both disorders have been reported as being more common in individuals with TS (Smith et al., 2022). Similarly to other comorbidities of TS, they may also have an increased prevalence among siblings. This is supported by the significant aORs found in the sibling diagnostic categories pertaining to them (neurodevelopmental disorders group 2 for ODD and other psychiatric or developmental diagnoses for ARFID). In the future, a similar study with these diagnoses in their own distinct categories could reveal whether they too are more common in the siblings of those with TS when compared to the siblings of those without TS.

In general, further research on the aetiology and genetics of TS and related disorders is required before anything definitive can be said about the links between these disorders. TS remains a relatively unknown disorder, with the majority of focus around the condition being concentrated exclusively on the tic symptom. Outside of this, little is known about the inheritance pattern (Pauls et al., 2014), genetic background (Lin et al., 2022), (Fernandez, 2025), causes (Jiang et al., 2022), and mechanisms of TS (Lamanna et al., 2023). This, combined with similar gaps in knowledge regarding related conditions such as ASD (Sauer et

al., 2021) and ADHD (Thapar et al., 2012), makes it challenging to adequately compare them at this point. In the future, with more aetiological studies and thus more aetiological information available for TS and its comorbidities, the relationships between their developments may become easier to identify and describe.

This is the first study to investigate the likelihoods of mental disorder diagnoses in the siblings of those with TS. Additional studies using other datasets – such as those in Sweden (Brand et al., 2020) – would contribute to knowledge in this field.

4.1 Limitations

The diagnoses of TS within the CRHC were validated by chart reviews and telephone interviews using the Yale Global Tic Severity Scale (YGTSS). It is worth noting that the YGTSS is used to assess the severity of the tic symptom in an individual with tics, but it is not a valid tool when it comes to the diagnosis of TS (Haas et al., 2021), which is typically conducted via the ICD-10 or other diagnostic manuals. Ideally, an individual with TS would be seen and assessed by a clinician in person where tics – the only current symptom used in diagnosis – can be observed and discussed (Johnson et al., 2023). That being said, the validity of the CRHC's TS diagnoses has been evaluated (Leivonen et al., 2014) and found to be approximately 95%. Undiagnosed or incorrectly diagnosed individuals cannot be accounted for, however (Wand et al., 1992). Furthermore, TS' high rate of comorbidities can further confound the diagnostic process (Cavanna et al., 2025), especially in cases of comorbid OCD (Szejko & Müller-Vahl, 2021) and other disorder combinations that clinicians may not be equipped to recognise (Parker et al., 2024).

The sibling method relies on assumptions that cannot be verified by the existing data. Using only full siblings assumes that they grew up together in the same environment, and the registers do not contain information on whether or not this occurred for each pair (Pettersson et al., 2019).

As not all individuals in the dataset were adults by the end of the follow-up period, some non-significant results may be as such due to this. For example, substance use disorders (Thomasius et al., 2022), and schizophrenia spectrum disorders (Gogtay et al., 2011), are

usually diagnosed in adulthood, so individuals who developed these disorders after the end of the follow-up period have not been noted as such.

This study has included diagnostic categories that were used historically in order to obtain a complete dataset. It acknowledges that some of these are inappropriate when considered in a modern clinical context, such as transsexualism (ICD-9 302.5X) and sadomasochism (ICD-10 F65.5).

Until 2023, the forced sterilisation of transgender individuals in Finland was required in order for them to obtain a change in their legal gender marker ('Finland', 2023), therefore all birthing individuals in the MBR are recorded as being of the female sex. While this study uses the terms "maternal" and "mother" to refer to the information regarding the birthing parent, and "paternal" and "father" to describe the other parent, it acknowledges that these may not be accurate descriptors of the demographics themselves.

Similarly, all siblings have been assigned as being of either the male or female sex in the dataset. Statistically, it is thought that up to 1.7% of the general population is born with intersex traits such as Klinefelter syndrome, Turner syndrome, oestrogen insensitivity syndrome, and more. This is not reflected in the registers and was therefore not accounted for.

Paternal SES, like its maternal counterpart, is relevant as a covariate of TS diagnosis. This information is not available in the registers however, and is therefore missing from the study.

5 Conclusion

TS is a disorder with a high rate of comorbidities and a strong, if relatively undescribed, set of contributing genetic factors. The offspring of those with TS are likely to inherit the condition, though it is not uncommon for it to not be inherited either. The reasons why are not known, and until now the conditions and potential vulnerabilities in those that did not inherit or develop the TS remained unexplored. This thesis aimed to set up a groundwork for future studies by identifying the prevalence of different mental and neurodevelopmental disorder diagnoses in the full siblings of people diagnosed with TS. We found that there was a significantly increased occurrence of some mental and neurodevelopmental disorders in the siblings of people with TS, notably in the categories of mood/affective disorders, anxiety-derived disorders, autism spectrum disorder, attention deficit hyperactivity disorder, and other neurodevelopmental disorders. These are common comorbidities found in people with TS, reinforcing the idea that the aetiologies of these conditions may be linked to that of TS. Future studies between the development of TS and these disorders in individuals may reveal the nature of these links and why, even in siblings that did not inherit the TS itself, there appears to be a higher risk of developing these other disorders. In the future, further familial studies using other registers will provide further information on the likelihoods of these conditions in the siblings of those with TS.

6 Acknowledgements

I would like to thank my supervisors, Subina Upadhyaya, PhD, and particularly Miina Koskela, MD, PhD, for their support and feedback on this thesis.

My gratitude extends to the University of Turku's Department of Child Psychiatry, who kindly gave me a workstation in their office for the duration of the project work.

A special thank-you is extended to Auli Suominen, MSc, for her invaluable guidance and patience regarding all things SAS and statistics.

I would like to thank the University of Turku's Human Neuroscience programme for an incredible degree experience. Finally, I wish to thank my friends and peers – I could not have asked for a better group of people to study alongside.

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Appendices

Appendix 1

Table 7. Raw dataset codebook

Variable	Variable Range	Number of Objects	Number of Missing Values	Coding
Child's ID		35,295	0	
Child's date of birth	01.01.1991-30.12.2009	35,295	0	
Case/control	0-1	35,295	0	0="Control", 1="Case"
Sibling's ID		35,295	0	
Sibling's date of birth	10.01.1977-16.11.2012	21,414	13,881	
Sibling type	0-4	35,295	0	0="Control", 1="Case", 2="Mother", 3="Father", 4="Full sibling", 5="Mother's child", 6="Father's child"
Sibling case/control	0-1	35,295	0	0="Control", 1="Case"
Mother's ID		35,295	0	
Father's ID		35,133	162	
Case code (strata)	1001-4103	35,295	0	
Date of first TS diagnosis	02.02.1994-31.12.2010	35,295	0	
Mother's age	14-47	35,295	0	
Father's age	15-67	35,133	162	
Anaemia (=100g/L)		35,295	0	
Number of fetuses	1-1	35,295	0	
Mother's socioeconomical status		32,776	2519	1="Upper white-collar workers", 2="Lower white-collar workers", 3="Blue-collar workers", 4="Others"
Sex		35,295	0	1="Male", 2="Female", 3="Not Known"

Variable	Variable Range	Number of Objects	Number of Missing Values	Coding
Birth weight for gestational age	1-3	35,111	184	1="Small", 2="Appropriate", 3="Large"
Mother's immigration status	1-3	35,295	0	1="Finnish", 2="1 st generation immigrant", 3="2 nd + generation immigrant"
Father's immigration status	1-3	35,133	162	1="Finnish", 2="1 st generation immigrant", 3="2 nd + generation immigrant"
Maternal marital status	1-9	35,295	0	1="Married", 2="In a relationship", 3="Single", 9="Unknown"
Date of mother's first mental condition diagnosis	18.11.1970-25.02.2011	4577	30,718	
Date of father's first mental condition diagnosis	01.04.1969-30.12.2010	4152	31,143	
Mother mental condition diagnosis	0-1	35,295	0	0="No", 2="Yes"
Father mental condition diagnosis	0-1	35,295	0	0="No", 2="Yes"
Parity	0-1	35,295	0	0="No", 2="Yes"
Maternal smoking	0-1	34,439	856	0="No", 2="Yes"
Date of emigration		0	35,295	
Date of immigration	28.04.2000-28.12.2010	4	35,291	
Date of death	30.07.1988-07.09.2012	59	35,236	
Age of death	3.16-29.70	59	35,236	
Age of immigration	1.22-2.56	4	35,291	
Siblings with any psychiatric diagnosis	0-1	35,295	0	0="No", 2="Yes"
Siblings with organic mental disorder diagnoses	0-1	35,295	0	0="No", 2="Yes"
Siblings with disorders due to substance use	0-1	35,295	0	0="No", 2="Yes"

Variable	Variable Range	Number of Objects	Number of Missing Values	Coding
Siblings with schizophrenia spectrum disorder diagnoses	0-1	35,295	0	0="No", 2="Yes"
Siblings with mood/affective disorder diagnoses	0-1	35,295	0	0="No", 2="Yes"
Siblings with anxiety-derived disorder diagnoses	0-1	35,295	0	0="No", 2="Yes"
Siblings with OCD diagnoses	0-1	35,295	0	0="No", 2="Yes"
Siblings with ASD diagnoses	0-1	35,295	0	0="No", 2="Yes"
Siblings with ADHD diagnoses	0-1	35,295	0	0="No", 2="Yes"
Siblings with non-TS tic disorder diagnoses	0-1	35,295	0	0="No", 2="Yes"
Siblings with diagnoses from neurodevelopmental group 1	0-1	35,295	0	0="No", 2="Yes"
Siblings with diagnoses from neurodevelopmental group 2	0-1	35,295	0	0="No", 2="Yes"
Siblings with other psychiatric or neurodevelopmental diagnoses	0-1	35,295	0	0="No", 2="Yes"

Appendix 2

Code for sibling descriptive data

```

1. *file:  siblings_mental_freq.sas *
2. *aim:   raportoidaan Tourett-tapausten ja kontrollien sisarusten mielenterveydelliset
diagnoosit (icd10,9) ryhmittäin frekvenssit**
3. *date:  12.3.2026 *
4. *author: Auli * ;
5. *obs.   18.3.26 lisätty dataan seuranta-ajat;
6. *obs:   lisätty 24.3.26 sisarusten määrän ja ikien tunnuslukuja;
7.
8.
9. *****;
10. *VASTEET:
11. *****;
12.
13. proc datasets lib=work kill;
14. run;quit;
15. title;footnote;
16.
17. *****;
18.
19. options nocenter nodate orientation=portrait;
20. libname sib "\\utu.fi\verkkolevyt\FIPS-data\Tourette\Maite";
21. %include '\\utu.fi\verkkolevyt\FIPS-data\Tourette\Data\formats.sas';
22.
23.
24. proc format;
25. value grf
26. 0=""
27. 1=""
28. 2="";
29. run;
30.
31.
32.
33. proc sort data=sib.tourette_sibling_thesis_data out=full3;by id_child;run;
34.
35.
36. proc sort data=full3;by id_child;run;
37. /*Liitetään tähän tutkimushenkilökohtaiset K/E -muuttujat, eli jos yhdelläkin on, niin
K=kyllä*/
38. proc freq data=full3 noprint;
39. by id_child;
40. tables sibl_anypsy /out=any;
41. run;*10386 joista osalla lapsista on sekä kyllä että ei -luokat;
42. proc sort data=any (keep=id_child sibl_anypsy);by id_child descending
sibl_anypsy;run;/*etusijalla siis että jos on psyk, niin tulee ekaksi*/
43. proc sort data=any nodupkey;by id_child;run;*10386->9151;
44.
45. %macro yhd(no);
46. proc freq data=full3 noprint;
47. by id_child;
48. tables &no. /out=&no.;
49. run;
50. proc sort data=&no. (keep=id_child &no.);by id_child descending &no.;run;
51. proc sort data=&no. nodupkey;by id_child;run;*9151;
52. %mend;
53.
%yhd(sibl_organic);%yhd(sibl_substance);%yhd(sibl_schizo);%yhd(sibl_mood);%yhd(sibl_anxiety);%yhd
(sibl OCD);%yhd(sibl ASD);
54. %yhd(sibl_adhd);%yhd(sibl_tic);%yhd(sibl_neuro_g1);%yhd(sibl_neuro_g2);%yhd(sibl_other_psy);
55.
56.
57. /*tieto yes/no tutkimushenkilötason dataan*/
58. proc sort data=full3 out=full_by_subject nodupkey;by id_child;run;*9151;
59.

```

```

60. data full_by_subject;
61.     merge full_by_subject any sibl_organic sibl_substance sibl_schizo sibl_mood
sibl_anxiety sibl OCD sibl_asd
62.     sibl_adhd sibl_tic sibl_neuro_g1 sibl_neuro_g2 sibl_other_psy;
63.     by id_child;
64. run;*9151;
65.
66. proc contents data=full3 order=varnum;run;
67.
68. /*lisätty 24.3.26*/
69. ods pdf file='\\utu.fi\verkkolevyt\fips-data\tourette\maite\programs\sib_means_24032026.pdf
';
70.
71. title1 "Descriptives of Total number of siblings by case and control";
72. proc sort data=full3 out=nfullsib nodupkey;by id_child;run;*17267->9151=2188 cases + 6963
controls;
73. proc sort data=nfullsib;by caco;run;*17267->9151=2188 cases + 6963 controls;
74. proc means data=nfullsib ndec=2 n median mean std min max p25 p75;by caco; var
n_fullsib;run;
75.
76. *lasketaan sisarusten ikä seurannan päättyessä;
77.
78. data full4;set full3;
79.     seurloppu=mdy(12,31,2016);
80.     age_sibl=yrdif(dob_sibl,seurloppu);
81.     /*syntymästä kuolemaan*/
82.     if death_date ne . and death_date lt seurloppu then do;
83.         age_sibl=yrdif(dob_sibl,death_date);
84.     end;
85.     format seurloppu yymmdd10.;
86. run;
87.
88. proc sort data=full4;by caco;run;*17267->9151=2188 cases + 6963 controls;
89. title1 "Descriptives of age of siblings at the end of follow-up period (31.12.2016 or death
date) by case and control";
90. proc means data=full4 ndec=2 n median mean std min max p25 p75;by caco; var age_sibl;run;
91.
92. ods pdf close;
93.
94. ods pdf file='\\utu.fi\verkkolevyt\fips-data\tourette\maite\programs\sib_freqs_12032026.pdf
';
95.
96. title1 "Total number of siblings by case and control";
97. proc sort data=full3 out=nfullsib nodupkey;by id_child;run;*17267->9151=2188 cases + 6963
controls;
98. proc freq data=nfullsib order=formatted;tables caco*n_fullsib;run;
99.
100. title1 "Number of siblings and cases and controls (one row for all siblings and
cases/controls without siblings)";
101. proc freq data=cases_controls order=formatted;tables caco;run;*6686 ca + 28609 co;
102.
103. title1 "Number of rows by fullsiblings of cases and controls (one row for all
fullsiblings)";
104. proc freq data=full order=formatted;tables caco;run;*3793 ca + 17621 co;
105.
106. title1 "Number of rows by fullsiblings of cases and controls (one row for all fullsiblings)
after matching checked";
107. proc freq data=full3 order=formatted;tables caco;run;*3791 ca + 13478 co;
108.
109. title1 "Gender, SES, smoking, parity, mental status for cases and controls with at least one
fullsibling after matching checked";
110. proc sort data=full3 out=full4 ;by id_child;run;*17267;
111. proc sort data=full4 nodupkey;by id_child;run;*2188 ca + 6963 co;
112.
113. proc freq data=full4 order=formatted;tables caco*soseco_cat caco*parity caco*gender
caco*m_status caco*mental_mother caco*mental_father / missing;run;*3791 ca + 13478 co;
114. proc means data=full4 ndec=3; class caco; var age_mother age_father;run;*2188 ca + 6963 co;
115.
116.
117. proc sort data=full_by_subject; by caco; run;

```

```

118.
119. /*Käytetään K/E luokitusta*/
120. title "Tourette Number of CASES/CONTROLS WHO HAS at least one diagnosed sibs OR NOT any";
121. title2 "Dgs: Any psychiatric/ neurodevelopmental disorder";
122. title3 'FULL-siblings';
123. proc freq data=full_by_subject order=formatted ;
124.     tables sibl_anypsy*caco / norow;
125. run;
126.
127. /*Käytetään tarkempaa luokitusta*/
128. title1 "Tourette Number of CASES/CONTROLS WHO HAS at least one diagnosed sibs OR NOT any";
129. %macro fre(var);
130. title2 'FULL-siblings';
131. proc freq data=full_by_subject order=formatted;
132.     tables &var.*caco / norow;
133. run;
134. %mend;
135.
136. %fre(var=sibl_organic);
137. %fre(var=sibl_substance);
138. %fre(var=sibl_schizo);
139. %fre(var=sibl_mood);
140. %fre(var=sibl_anxiety);
141. %fre(var=sibl OCD);
142. %fre(var=sibl_asd);
143. %fre(var=sibl_adhd);
144. %fre(var=sibl_tic);
145. %fre(var=sibl_neuro_g1);
146. %fre(var=sibl_neuro_g2);
147. %fre(var=sibl_other_psy);
148.
149. title;
150.
151. ods pdf close;
152.
153.
154.
155.
156.
157.
158.
159. /****** Jos tarvitaan by sex*/
160.
161. ods pdf file='\\utu.fi\verkkolevyt\fips-data\tourette\maite\programs\sib_freqs_sex.pdf ';
162.
163.
164. proc sort data=full_by_subject; by sex; run;
165.
166. /*Käytetään K/E luokitusta*/
167. title "Mutism Number of CASES/CONTROLS WHO HAS at least one diagnosed sibs OR NOT any";
168. title2 "Dgs: Any psychiatric/ neurodevelopmental disorder";
169. title3 'FULL-siblings';
170. proc freq data=full_by_subject order=formatted;
171.     by sex;
172.     tables any*caco;
173. run;
174. title2 "Dgs: Any disorder usually diagnosed in childhood";
175. title3 'FULL-siblings';
176. proc freq data=full_by_subject order=formatted;
177.     by sex;
178.     tables any_childhood*caco;
179. run;
180.
181. /*Käytetään tarkempaa luokitusta*/
182. title2 "1. Schizophrenia spectrum disorders";
183. title3 'FULL-siblings';
184. proc freq data=full_by_subject order=formatted;
185.     by sex;
186.     tables S_G1*caco;
187. run;

```

```
188. title2 "2. Affective disorder";
189. title3 'FULL-siblings';
190. proc freq data=full_by_subject order=formatted;
191.     by sex;
192.     tables S_G2*caco;
193. run;
194. title2 "3. Bipolar disorder";
195. title3 'FULL-siblings';
196. proc freq data=full_by_subject order=formatted;
197.     by sex;
198.     tables S_G3*caco;
199. run;
200. title2 "4. Unipolar disorders";
201. title3 'FULL-siblings';
202. proc freq data=full_by_subject order=formatted;
203.     by sex;
204.     tables S_G4*caco;
205. run;
206. title2 "5. Anxiety disorders";
207. title3 'FULL-siblings';
208. proc freq data=full_by_subject order=formatted;
209.     by sex;
210.     tables S_G5*caco;
211. run;
212. title2 "6. Other neurotic and personality disorders";
213. title3 'FULL-siblings';
214. proc freq data=full_by_subject order=formatted;
215.     by sex;
216.     tables S_G6*caco;
217. run;
218. title2 "7. Substance abuse disorder";
219. title3 'FULL-siblings';
220. proc freq data=full_by_subject order=formatted;
221.     by sex;
222.     tables S_G7*caco;
223. run;
224. title2 "8. Autism spectrum disorders";
225. title3 'FULL-siblings';
226. proc freq data=full_by_subject order=formatted;
227.     by sex;
228.     tables S_G8*caco;
229. run;
230. title2 "9. Attention deficit hyperactivity disorder";
231. title3 'FULL-siblings';
232. proc freq data=full_by_subject order=formatted;
233.     by sex;
234.     tables S_G9*caco;
235. run;
236. title2 "10. Intellectual disability";
237. title3 'FULL-siblings';
238. proc freq data=full_by_subject order=formatted;
239.     by sex;
240.     tables S_G10*caco;
241. run;
242. title2 "11. Childhood emotional disorders";
243. title3 'FULL-siblings';
244. proc freq data=full_by_subject order=formatted;
245.     by sex;
246.     tables S_G11*caco;
247. run;
248. title2 "12. Conduct and oppositional disorders";
249. title3 'FULL-siblings';
250. proc freq data=full_by_subject order=formatted;
251.     by sex;
252.     tables S_G12*caco;
253. run;
254. title2 "13. Tic disorders";
255. title3 'FULL-siblings';
256. proc freq data=full_by_subject order=formatted;
257.     by sex;
```

```
258.     tables S_G13*caco;
259. run;
260. title2 "14. Learning and coordination disorders ";
261. title3 'FULL-siblings';
262. proc freq data=full_by_subject order=formatted;
263.     by sex;
264.     tables S_G14*caco;
265. run;title;
266.
267. ods pdf close;
```

Appendix 3

Code for additional sibling descriptive data

```

1. *file:  siblings_mental_freq.sas *
2. *aim:   raportoidaan Tourett-tapausten ja kontrollien sisarusten mielenterveydelliset
diagnosoit (icd10,9) ryhmittäin frekvenssit**
3. *date:  12.3.2026 *
4. *author: Auli * ;
5. *obs.   18.3.26 lisätty dataan seuranta-ajat;
6.
7. *****;
8. *VASTEET:
9. *****;
10.
11. proc datasets lib=work kill;
12. run;quit;
13. title;footnote;
14.
15. *****;
16.
17. options nocenter nodate orientation=portrait;
18. %include '\\utu.fi\verkkolevyt\FIPS-data\mutism\Data\formats.sas';
19. libname sib "\\utu.fi\verkkolevyt\FIPS-data\Tourette\Maite";
20. %include '\\utu.fi\verkkolevyt\FIPS-data\Tourette\Data\formats.sas';
21.
22.
23. proc format;
24. value grf
25. 0=""
26. 1=""
27. 2="";
28. run;
29.
30. /** */
31. proc sort data=sib.tourette_sibling_thesis_analysis out=a;by id_child;run;*35295;
32. /*proc contents data=a order=varnum;run;*/
33.
34. /*proc freq data=a;tables sibl;run;*/
35. /*proc freq data=a;tables caco_sibl;run;*/
36.
37. /*puuttuuko jollain sisaruksella seuranta-aika?*/
38. data b;set a;if sibl not in (0 1) and follow_up=.;run;/*0 sisarus riviltä puuttuu*/
39. data b;set a;if sibl in (0 1) and follow_up=.;run;/*13881=2893 ca + 10988 co, eli 13881
riviltä puuttuu. OK!*/
40. /*proc freq data=b;tables caco;run;2893 ca +10988 co*/
41.
42. proc sort data=a out=cases_controls;by code_case caco;run;*35295;
43. proc freq data=cases_controls;tables caco;run;*6686 ca&sisarusta + 28609 co&sisarusta;
44.
45. /*Matsaus tarkistettu? Yksi tietue per tutkimushenkilö. OK!*/
46. /*only fullsiblings*/
47. data full;
48.     set cases_controls;
49.     if sibl=4;
50. run;
51. /*N=21414*/
52.
53. /*Lasketaan tähän sisarusten määrä per henkilö*/
54. proc sort data=full;by id_child;run;
55. proc freq data=full noprint;
56. tables id_child / out=n_sib;
57. run;
58. data n_sib;set n_sib;rename count=n_fullsib;drop percent;run;
59. data full_;merge full n_sib;by id_child;run;
60. proc freq data=full_ order=formatted;table caco*n_fullsib;run;
61.

```

```

62. /**** uusinta kaltaistuksen tarkastus*/
63. /*pidetään mukana jokainen code_case, yksi case ja yksi control jokaisesta. Jos ei ole, niin
silloin kaltaistus tarkistettava.*/
64. proc sort data=full_;by code_case descending caco;run;
65. data full_ekat_caseja;
66. set full_;
67. by code_case;
68. if first.code_case;
69. keep id_child code_case caco;
70. run;*jos eka on caco=0 eli kontrolli, niin silloin casella ei sisaruksia;
71. proc freq data=full_ekat_caseja;tables caco;run;*2191 casea ja 701 kontrollia eli 701:ssa
ositteessa ei tapauksella sisaruksia;
72. /*NÄMÄ ositteet kokonaan pois, koska ei tapausta n=701*/
73. data pois_osite;set full_ekat_caseja;if caco=0;keep code_case;run;
74.
75. proc sort data=full_;by code_case caco;run;
76. data full_ekat_ctrls;
77. set full_;
78. by code_case;
79. if first.code_case;
80. keep id_child code_case caco;
81. run;*jos eka on caco=1 eli tapaus, niin silloin yhdelläkään kontrolleista ei sisaruksia;
82. proc freq data=full_ekat_ctrls;tables caco;run;*3 casea ja 2889 kontrollia eli 3:ssa
ositteessa kontrolleilla ei ole yhtään sisaruksia;
83. /*NÄMÄ ositteet kokonaan pois, koska ei sisaruksellista kontrollia n=3*/
84. data pois_osite_case;set full_ekat_ctrls;if caco=1;keep code_case;run;
85.
86. /*poistetaan 701 + 3 ositetta*/
87.
88. /*lähtötilanne: proc sort data=full_ out=t nodupkey;by code_case;run;*2892 ositetta;*/
89.
90. proc sort data=full_;by code_case;run;*21414;
91. proc sort data=pois_osite;by code_case;run;*701;
92. proc sort data=pois_osite_case;by code_case;run;*3;
93. data full_clean;
94. merge full_(in=a) /*pois_osite*/ pois_osite_case(in=b);
95. by code_Case;
96. if a and not b;
97. run;*21414->21410;
98. /*lähtötilanne: proc sort data=full_clean out=t nodupkey;by code_case;run;*2892-3=2889
ositetta OK;*/
99. data full_totalclean;
100. merge full_clean(in=a) pois_osite(in=b) /*pois_osite_case(in=b)*/;
101. by code_Case;
102. if a and not b;
103. run;*21414->21410->17267;
104. /*lähtötilanne: proc sort data=full_totalclean out=t nodupkey;by code_case;run;*2892-3-=2188
ositetta OK OK;*/
105.
106. proc freq data=full_totalclean;tables caco_sibl;run;
107. proc sort data=full_totalclean;by code_case descending caco_sibl;run;*17267 yhteensä;
108. data cases;set full_totalclean;by code_case;if first.code_case;run;*2188 cases;
109. proc sort data=full_totalclean;by code_case caco_sibl;run;*17267 yhteensä;
110. data ctrl;set full_totalclean;by code_case;if not first.code_case and caco_sibl ne
1;run;*11290 ctrl;
111. /***** saadaan samat 17267 tutkimushenkilöä **/
112. /** kaltaistuksen tarkastus päättyy **/
113.
114. /* tämä on tehty aiemmin ja on oikein!!! */
115. /*Tarkastetaan vielä case-control kaltaistus*/
116. proc sort data=full_;by code_case descending caco;run;
117. proc sort data=full_ out=full_1;by code_case caco;run;
118.
119. /*ei toimi oikein jos mukana useampi rivi per tutkimushenkilö, full_2 on vain yksi per case
ja per control*/
120. proc sort data=full_1 out=full_2 nodupkey;by code_case caco;run;*5080;
121. proc sort data=full_2;by code_case descending caco;run;
122.
123. /*kaltaistuksen tarkistus*/
124. proc sort data=full_2;by code_case descending caco;run;

```

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125. data full2;
126. set full_2;
127. by code_case;
128. retain pois;
129. if first.code_case then do;
130.     pois=0;
131.     if last.code_case or caco=0 then pois=1;
132. end;
133. if pois=1 then delete;
134. drop pois;
135. run;*5080->4376;
136. * tämä tehty 1 ca ja 1 co per code_case: 4376 tapausta ja kontrollia;
137. * jätetään poimimista varten vain yksi code_case per case-control pari;
138. data codecaset;set full2;by code_case;if first.code_case;keep code_case;run;*2188;
139.
140. proc sort data=codecaset;by code_case;run;
141. proc sort data=full_;by code_case;run;
142. data full3;
143. merge full_(in=a) codecaset(in=b);
144. by code_case;
145. if b;
146. run;
147. /*17267 OK!*/
148.
149. /******
150. /******
151. /******
152. /*pysyvä data jossa kaltaistus ok*/
153. proc sort data=full3 out=veryfinalfull;by id_child;run;
154. proc compare data=veryfinalfull compare=sib.tourette_sibling_thesis_analysis;run;
155.
156. proc sort data=veryfinalfull out=sib.tourette_sibling_thesis_data;by id_child;run;
157. /*17267;*/
158.
159. /******
160. /******
161. /******
162.
163.
164.
165. proc sort data=sib.tourette_sibling_thesis_data out=full3;by id_child;run;
166.
167.
168. proc sort data=full3;by id_child;run;
169. /*Liitetään tähän tutkimushenkilökohtaiset K/E -muuttujat, eli jos yhdelläkin on, niin
K=kyllä*/
170. proc freq data=full3 noprint;
171. by id_child;
172. tables sibl_anpsy /out=any;
173. run;*10386 joista osalla lapsista on sekä kyllä että ei -luokat;
174. proc sort data=any (keep=id_child sibl_anpsy);by id_child descending
sibl_anpsy;run;/*etusijalla siis että jos on psyk, niin tulee ekaksi*/
175. proc sort data=any nodupkey;by id_child;run;*10386->9151;
176.
177. %macro yhd(no);
178. proc freq data=full3 noprint;
179. by id_child;
180. tables &no. /out=&no.;
181. run;
182. proc sort data=&no. (keep=id_child &no.);by id_child descending &no.;run;
183. proc sort data=&no. nodupkey;by id_child;run;*9151;
184. %mend;
185.
%yhd(sibl_organic);%yhd(sibl_substance);%yhd(sibl_schizo);%yhd(sibl_mood);%yhd(sibl_anxiety);%yhd
(sibl OCD);%yhd(sibl ASD);
186. %yhd(sibl ADHD);%yhd(sibl TIC);%yhd(sibl_neuro_g1);%yhd(sibl_neuro_g2);%yhd(sibl_other_psy);
187.
188.
189. /*tieto yes/no tutkimushenkilötason dataan*/
190. proc sort data=full3 out=full_by_subject nodupkey;by id_child;run;*9151;

```

```

191.
192. data full_by_subject;
193.     merge full_by_subject any sibl_organic sibl_substance sibl_schizo sibl_mood
sibl_anxiety sibl OCD sibl_asd
194.     sibl_adhd sibl_tic sibl_neuro_g1 sibl_neuro_g2 sibl_other_psy;
195.     by id_child;
196. run;*9151;
197.
198.
199.
200. ods pdf file='\\utu.fi\verkkolevyt\fips-data\tourette\maite\programs\sib_freqs_12032026.pdf
';
201.
202. title1 "Total number of siblings by case and control";
203. proc sort data=full3 out=nfullsib nodupkey;by id_child;run;*17267->9151=2188 cases + 6963
controls;
204. proc freq data=nfullsib order=formatted;tables caco*n_fullsib;run;
205.
206. title1 "Number of siblings and cases and controls (one row for all siblings and
cases/controls without siblings)";
207. proc freq data=cases_controls order=formatted;tables caco;run;*6686 ca + 28609 co;
208.
209. title1 "Number of rows by fullsiblings of cases and controls (one row for all
fullsiblings)";
210. proc freq data=full order=formatted;tables caco;run;*3793 ca + 17621 co;
211.
212. title1 "Number of rows by fullsiblings of cases and controls (one row for all fullsiblings)
after matching checked";
213. proc freq data=full3 order=formatted;tables caco;run;*3791 ca + 13478 co;
214.
215. title1 "Gender, SES, smoking, parity, mental status for cases and controls with at least one
fullsibling after matching checked";
216. proc sort data=full3 out=full4 ;by id_child;run;*17267;
217. proc sort data=full4 nodupkey;by id_child;run;*2188 ca + 6963 co;
218.
219. proc freq data=full4 order=formatted;tables caco*soseco_cat caco*parity caco*gender
caco*m_status caco*mental_mother caco*mental_father / missing;run;*3791 ca + 13478 co;
220. proc means data=full4 ndec=3; class caco; var age_mother age_father;run;*2188 ca + 6963 co;
221.
222.
223. proc sort data=full_by_subject; by caco; run;
224.
225. /*Käytetään K/E luokitusta*/
226. title "Tourette Number of CASES/CONTROLS WHO HAS at least one diagnosed sibs OR NOT any";
227. title2 "Dgs: Any psychiatric/ neurodevelopmental disorder";
228. title3 'FULL-siblings';
229. proc freq data=full_by_subject order=formatted ;
230.     tables sibl_anpsy*caco / norow;
231. run;
232.
233. /*Käytetään tarkempaa luokitusta*/
234. title1 "Tourette Number of CASES/CONTROLS WHO HAS at least one diagnosed sibs OR NOT any";
235. %macro fre(var);
236. title2 'FULL-siblings';
237. proc freq data=full_by_subject order=formatted;
238.     tables &var.*caco / norow;
239. run;
240. %mend;
241.
242. %fre(var=sibl_organic);
243. %fre(var=sibl_substance);
244. %fre(var=sibl_schizo);
245. %fre(var=sibl_mood);
246. %fre(var=sibl_anxiety);
247. %fre(var=sibl OCD);
248. %fre(var=sibl_asd);
249. %fre(var=sibl_adhd);
250. %fre(var=sibl_tic);
251. %fre(var=sibl_neuro_g1);
252. %fre(var=sibl_neuro_g2);

```

```
253. %fre(var=sibl_other_psy);
254.
255. title;
256.
257. ods pdf close;
258.
259.
260.
261.
262.
263.
264.
265. /***** Jos tarvitaan by sex*/
266.
267. ods pdf file='\\utu.fi\verkkolevyt\fips-data\tourette\maite\programs\sib_freqs_sex.pdf ';
268.
269.
270. proc sort data=full_by_subject; by sex; run;
271.
272. /*Käytetään K/E luokitusta*/
273. title "Mutism Number of CASES/CONTROLS WHO HAS at least one diagnosed sibs OR NOT any";
274. title2 "Dgs: Any psychiatric/ neurodevelopmental disorder";
275. title3 'FULL-siblings';
276. proc freq data=full_by_subject order=formatted;
277.     by sex;
278.     tables any*caco;
279. run;
280. title2 "Dgs: Any disorder usually diagnosed in childhood";
281. title3 'FULL-siblings';
282. proc freq data=full_by_subject order=formatted;
283.     by sex;
284.     tables any_childhood*caco;
285. run;
286.
287. /*Käytetään tarkempaa luokitusta*/
288. title2 "1. Schizophrenia spectrum disorders";
289. title3 'FULL-siblings';
290. proc freq data=full_by_subject order=formatted;
291.     by sex;
292.     tables S_G1*caco;
293. run;
294. title2 "2. Affective disorder";
295. title3 'FULL-siblings';
296. proc freq data=full_by_subject order=formatted;
297.     by sex;
298.     tables S_G2*caco;
299. run;
300. title2 "3. Bipolar disorder";
301. title3 'FULL-siblings';
302. proc freq data=full_by_subject order=formatted;
303.     by sex;
304.     tables S_G3*caco;
305. run;
306. title2 "4. Unipolar disorders";
307. title3 'FULL-siblings';
308. proc freq data=full_by_subject order=formatted;
309.     by sex;
310.     tables S_G4*caco;
311. run;
312. title2 "5. Anxiety disorders";
313. title3 'FULL-siblings';
314. proc freq data=full_by_subject order=formatted;
315.     by sex;
316.     tables S_G5*caco;
317. run;
318. title2 "6. Other neurotic and personality disorders";
319. title3 'FULL-siblings';
320. proc freq data=full_by_subject order=formatted;
321.     by sex;
322.     tables S_G6*caco;
```

```
323. run;
324. title2 "7. Substance abuse disorder";
325. title3 'FULL-siblings';
326. proc freq data=full_by_subject order=formatted;
327.     by sex;
328.     tables S_G7*caco;
329. run;
330. title2 "8. Autism spectrum disorders";
331. title3 'FULL-siblings';
332. proc freq data=full_by_subject order=formatted;
333.     by sex;
334.     tables S_G8*caco;
335. run;
336. title2 "9. Attention deficit hyperactivity disorder";
337. title3 'FULL-siblings';
338. proc freq data=full_by_subject order=formatted;
339.     by sex;
340.     tables S_G9*caco;
341. run;
342. title2 "10. Intellectual disability";
343. title3 'FULL-siblings';
344. proc freq data=full_by_subject order=formatted;
345.     by sex;
346.     tables S_G10*caco;
347. run;
348. title2 "11. Childhood emotional disorders";
349. title3 'FULL-siblings';
350. proc freq data=full_by_subject order=formatted;
351.     by sex;
352.     tables S_G11*caco;
353. run;
354. title2 "12. Conduct and oppositional disorders";
355. title3 'FULL-siblings';
356. proc freq data=full_by_subject order=formatted;
357.     by sex;
358.     tables S_G12*caco;
359. run;
360. title2 "13. Tic disorders";
361. title3 'FULL-siblings';
362. proc freq data=full_by_subject order=formatted;
363.     by sex;
364.     tables S_G13*caco;
365. run;
366. title2 "14. Learning and coordination disorders ";
367. title3 'FULL-siblings';
368. proc freq data=full_by_subject order=formatted;
369.     by sex;
370.     tables S_G14*caco;
371. run;title;
372.
373. ods pdf close;
374.
```

Appendix 4

Code for unadjusted model

```

1. *file:   siblings_mental_nonadj.sas *
2. *aim:   raportoidaan tourette sisarusten mieleninterveydelliset diagnoosit (icd10 ja 9) OR:t*
3. *aim:   mallitetaan individuaalitalason seuranta-aika dataa*
4. *date:  18.3.2026 *
5. *author: Auli * ;
6. *obs.   *
7. ;
8.
9. *****;
10. *VASTEET:
11. *****;
12.
13. /*proc datasets lib=work kill;
14. run;quit;
15. footnote;*/
16. proc datasets lib=work kill;
17. run;quit;
18. title;footnote;
19.
20. *****;
21.
22. options nocenter nodate orientation=portrait;
23. %include '\\utu.fi\verkkolevyt\FIPS-data\mutism\Data\formats.sas';
24. libname sib "\\utu.fi\verkkolevyt\FIPS-data\Tourette\Maite";
25. %include '\\utu.fi\verkkolevyt\FIPS-data\Tourette\Data\formats.sas';
26.
27.
28. proc format;
29. value grf
30. 0=""
31. 1=""
32. 2="";
33. run;
34.
35. proc sort data=sib.tourette_sibling_thesis_data out=a;by id_child;run;
36. /*proc contents data=a order=varnum;run;*/
37.
38. proc sort data=a out=cases_controls;by code_case caco;run;*;
39. proc freq data=cases_controls;tables caco;run;*3789 ca + 13478 co;
40.
41. *4 = full sibs only in data;
42. proc freq data=cases_controls;
43. where sib1 in (4);
44. tables caco_sibl*sibl;
45. run;*3789 siblings of cases, 13478 sibs of controls;
46.
47.
48. /*Matsaus tarkistettu? OK!*/
49. data full;
50.     set cases_controls;
51.     *drop S_G1_NO--S_G14_NO;
52. run;
53. /**/
54.
55. /*#####*/
56.
57. /**Lasketaan seuranta-ajan luonnollinen logaritmi Poissonin mallia varten */
58. /**Poistetaan case/ctrl -tietueet */
59. data full1;
60.     set full;
61.     if sib1 not in (0 1);
62.     ln_follow_up=log(follow_up);
63. run; /*17267 sisarusta*/

```

```

64.
65. /*negatiiviset*/
66. data aneg;
67. set full1;
68. if follow_up le 0;
69. run;*0;
70.
71. ods rtf file='\\utu.fi\verkkolevyt\fips-data\tourette\maite\programs\annotated_nonadj.rtf ';
72.
73. /* GENMOD, Poisson regressio, GEE-estimointi */
74. /* data yksilötason muodossa */
75. /* diagnoosien lukumäärä on suhteutettu jokaisen tutkittavan henkilökohtaiseen seuranta-
aikaan */
76. title1 "Risk for psychiatric and neurodevelopmental disorders among siblings of tourette";
77. title2 "Dgs: Any psychiatric/ neurodevelopmental disorder";
78. proc genmod data=full1;
79. ods exclude ClassLevels ParmInfo GEEFitCriteria ;
80. class code_case caco / param=glm; /* GLM-parametrisointi, jotta estimate-lauseen vertailut
on helpompi muodostaa */
81. model sibl_anypsy=caco / dist=poisson link=log offset=ln_follow_up;
82. estimate 'Case vs Control' caco 1 -1 / exp;
83. repeated subject=code_case / type=exch;
84. run;
85. ods rtf close;
86.
87. ods pdf file='\\utu.fi\verkkolevyt\fips-
data\tourette\maite\programs\tourette_sibs_nonadj.pdf ';
88.
89. /* GENMOD, Poisson regressio, GEE-estimointi */
90. /* data yksilötason muodossa */
91. /* diagnoosien lukumäärä on suhteutettu jokaisen tutkittavan henkilökohtaiseen seuranta-
aikaan */
92. title1 "Risk for psychiatric and neurodevelopmental disorders among siblings of tourette";
93. title2 "Dgs: Any psychiatric/ neurodevelopmental disorder";
94. proc genmod data=full1;
95. ods exclude ClassLevels ParmInfo GEEFitCriteria ;
96. class code_case caco / param=glm; /* GLM-parametrisointi, jotta estimate-lauseen vertailut
on helpompi muodostaa */
97. model sibl_anypsy=caco / dist=poisson link=log offset=ln_follow_up;
98. estimate 'Case vs Control' caco 1 -1 / exp;
99. repeated subject=code_case / type=exch;
100. run;
101.
102.
103. %macro non(title,var);
104. title2 "Dgs: &title.";
105. proc genmod data=full1;
106. ods exclude ClassLevels ParmInfo GEEFitCriteria ;
107. class code_case caco / param=glm; /* GLM-parametrisointi, jotta estimate-lauseen vertailut
on helpompi muodostaa */
108. model &var.=caco / dist=poisson link=log offset=ln_follow_up;
109. estimate 'Case vs Control' caco 1 -1 / exp;
110. repeated subject=code_case / type=exch;
111. run;
112.
113. %mend;
114.
115.
116. %non(var=sibl_organic);
117. %non(var=sibl_substance);
118. %non(var=sibl_schizo);
119. %non(var=sibl_mood);
120. %non(var=sibl_anxiety);
121. %non(var=sibl OCD);
122. %non(var=sibl_asd);
123. %non(var=sibl_adhd);
124. %non(var=sibl_tic);
125. %non(var=sibl_neuro_g1);
126. %non(var=sibl_neuro_g2);
127. %non(var=sibl_other_psy);

```

```
128.  
129. title;  
130.  
131. ods pdf close;
```

Appendix 5

Code for adjusted models

```

1. *file:   siblings_mental_adjusted.sas *
2. *aim:    raportoidaan tourette sisarusten mieleninterveydelliset diagnoosit (icd10 ja 9) OR:t*
3. *aim:    mallitetaan individuaalitalason seuranta-aika dataa*
4. *date:   18.3.2026 *
5. *author: Auli * ;
6. *obs.    *
7. ;
8.
9. *****;
10. *VASTEET:
11. *****;
12.
13. /*proc datasets lib=work kill;
14. run;quit;
15. footnote;*/
16. proc datasets lib=work kill;
17. run;quit;
18. title;footnote;
19.
20. *****;
21.
22. options nocenter nodate orientation=portrait;
23. %include '\\utu.fi\verkkolevyt\FIPS-data\mutism\Data\formats.sas';
24. libname sib "\\utu.fi\verkkolevyt\FIPS-data\Tourette\Maite";
25. %include '\\utu.fi\verkkolevyt\FIPS-data\Tourette\Data\formats.sas';
26.
27.
28. proc format;
29. value grf
30. 0=""
31. 1=""
32. 2="";
33. run;
34.
35. proc sort data=sib.tourette_sibling_thesis_data out=a;by id_child;run;
36. /*proc contents data=a order=varnum;run;*/
37.
38. proc sort data=a out=cases_controls;by code_case caco;run;*;
39. proc freq data=cases_controls;tables caco;run;*3789 ca + 13478 co;
40.
41. *4 = full sibs only in data;
42. proc freq data=cases_controls;
43. where sibl in (4);
44. tables caco_sibl*sibl;
45. run;*3789 siblings of cases, 13478 sibs of controls;
46.
47. /*m_status as binary*/
48. proc format;
49. value m_status_b
50. 1='Married/In a relationship'
51. 2='Single'
52. 9='Unknown';
53. run;
54. /*value m_status
55. 1='Married'
56. 2='In a relationship'
57. 3='Single'
58. 9='Unknown';*/
59. /*Matsaus tarkistettu? OK!*/
60. data full;
61.     set cases_controls;
62.     *drop S_G1_NO--S_G14_NO;
63.     m_status_bin=m_status;

```

```

64.     if m_status in (1 2) then m_status_bin=1;
65.     if m_status in (3) then m_status_bin=2;
66.     format m_status_bin m_status_b.;
67. run;
68. /**/
69.
70. /*#####*/
71.
72. /**Lasketaan seuranta-ajan luonnollinen logaritmi Poissonin mallia varten */
73. /**Poistetaan case/ctrl -tietueet */
74. data full1;
75.     set full;
76.     if sibl not in (0 1);
77.     ln_follow_up=log(follow_up);
78. run; /*17267 sisarusta*/
79.
80. /*negatiiviset*/
81. data aneg;
82. set full1;
83. if follow_up le 0;
84. run; *0;
85.
86.
87. ods pdf file='\\utu.fi\verkkolevyt\fips-
data\tourette\maite\programs\tourette_sibs_adjusted.pdf ';
88.
89. /* GENMOD, Poisson regressio, GEE-estimointi */
90. /* data yksilötason muodossa */
91. /* diagnoosien lukumäärä on suhteutettu jokaisen tutkittavan henkilökohtaiseen seuranta-
aikaan */
92.
93. title1 "Risk for psychiatric and neurodevelopmental disorders among siblings of tourette";
94. title2 "Dgs: Any psychiatric/ neurodevelopmental disorder";
95. proc genmod data=full1;
96. ods exclude ClassLevels ParmInfo GEEFitCriteria ;
97.
98. class code_case caco soseco_cat(ref='Upper white collar workers') parity(ref='Yes')
m_status(ref='Married') mental_mother(ref='No') mental_father(ref='No') / param=glm; /* GLM-
parametrisointi, jotta estimate-lauseen vertailut on helpompi muodostaa */
99. model sibl_anypsy=caco age_mother age_father soseco_cat parity m_status mental_mother
mental_father / dist=poisson link=log offset=ln_follow_up;
100. estimate 'Case vs Control' caco 1 -1 / exp;
101. repeated subject=code_case / type=exch;
102. run;
103.
104.
105. %macro non(title,var);
106. title2 "Dgs: &title.";
107. proc genmod data=full1;
108. ods exclude ClassLevels ParmInfo GEEFitCriteria ;
109. class code_case caco soseco_cat(ref='Upper white collar workers') parity(ref='Yes')
m_status(ref='Married') mental_mother(ref='No') mental_father(ref='No') / param=glm; /* GLM-
parametrisointi, jotta estimate-lauseen vertailut on helpompi muodostaa */
110. model &var.=caco age_mother age_father soseco_cat parity m_status mental_mother
mental_father / dist=poisson link=log offset=ln_follow_up;
111. estimate 'Case vs Control' caco 1 -1 / exp;
112. repeated subject=code_case / type=exch maxiter=50000;
113. run;
114.
115. %mend;
116.
117.
118. %non(var=sibl_organic);
119. %non(var=sibl_substance);
120. %non(var=sibl_schizo);
121. %non(var=sibl_mood);
122. %non(var=sibl_anxiety);
123. %non(var=sibl OCD);
124. %non(var=sibl_asd);
125. %non(var=sibl_adhd);

```

```

126. %non(var=sibl_tic);
127. %non(var=sibl_neuro_g1);
128. %non(var=sibl_neuro_g2);
129. %non(var=sibl_other_psy);
130.
131. title;
132.
133. ods pdf close;
134.
135.
136. ods pdf file='\\utu.fi\verkkolevyt\fips-
data\tourette\maite\programs\tourette_sibs_adjusted_m_status_option2.pdf ';
137.
138. /* GENMOD, Poisson regressio, GEE-estimointi */
139. /* data yksilötason muodossa */
140. /* diagnoosien lukumäärä on suhteutettu jokaisen tutkittavan henkilökohtaiseen seuranta-
aikaan */
141.
142. title1 "Risk for psychiatric and neurodevelopmental disorders among siblings of tourette";
143. title2 "Dgs: Any psychiatric/ neurodevelopmental disorder";
144. proc genmod data=full1;
145. ods exclude ClassLevels ParmInfo GEEFitCriteria ;
146.
147. class code_case caco soseco_cat(ref='Upper white collar workers') parity(ref='Yes')
m_status_bin(ref='Married/In a relationship') mental_mother(ref='No') mental_father(ref='No') /
param=glm; /* GLM-parametrisointi, jotta estimate-lauseen vertailut on helpompi muodostaa */
148. model sibl_anypsy=caco age_mother age_father soseco_cat parity m_status_bin mental_mother
mental_father / dist=poisson link=log offset=ln_follow_up;
149. estimate 'Case vs Control' caco 1 -1 / exp;
150. repeated subject=code_case / type=exch;
151. run;
152.
153.
154. %macro non(title,var);
155. title2 "Dgs: &title.";
156. proc genmod data=full1;
157. ods exclude ClassLevels ParmInfo GEEFitCriteria ;
158. class code_case caco soseco_cat(ref='Upper white collar workers') parity(ref='Yes')
m_status_bin(ref='Married/In a relationship') mental_mother(ref='No') mental_father(ref='No') /
param=glm; /* GLM-parametrisointi, jotta estimate-lauseen vertailut on helpompi muodostaa */
159. model &var.=caco age_mother age_father soseco_cat parity m_status_bin mental_mother
mental_father / dist=poisson link=log offset=ln_follow_up;
160. estimate 'Case vs Control' caco 1 -1 / exp;
161. repeated subject=code_case / type=exch maxiter=50000;
162. run;
163.
164. %mend;
165.
166.
167. %non(var=sibl_organic);
168. %non(var=sibl_substance);
169. %non(var=sibl_schizo);
170. %non(var=sibl_mood);
171. %non(var=sibl_anxiety);
172. %non(var=sibl OCD);
173. %non(var=sibl_asd);
174. %non(var=sibl_adhd);
175. %non(var=sibl_tic);
176. %non(var=sibl_neuro_g1);
177. %non(var=sibl_neuro_g2);
178. %non(var=sibl_other_psy);
179.
180. title;
181.
182. ods pdf close;

```