ORIGINAL ARTICLE

Perinatal risk factors in Tourette's and chronic tic disorders: a total population sibling comparison study

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Adverse perinatal events may increase the risk of Tourette's and chronic tic disorders (TD/CTD), but previous studies have been unable to control for unmeasured environmental and genetic confounding. We aimed to prospectively investigate potential perinatal risk factors for TD/CTD, taking unmeasured factors shared between full siblings into account. A population-based birth cohort, consisting of all singletons born in Sweden in 1973–2003, was followed until December 2013. A total of 3 026 861 individuals were identified, 5597 of which had a registered TD/CTD diagnosis. We then studied differentially exposed full siblings from 947 942 families; of these, 3563 families included siblings that were discordant for TD/CTD. Perinatal data were collected from the Medical Birth Register and TD/CTD diagnoses were collected from the National Patient Register, using a previously validated algorithm. In the fully adjusted models, impaired fetal growth, preterm birth, breech presentation and cesarean section were associated with a higher risk of TD/CTD, largely independent from shared family confounders and measured covariates. Maternal smoking during pregnancy was associated with risk of TD/CTD in a dose–response manner but the association was no longer statistically significant in the sibling comparison models or after the exclusion of comorbid attention-deficit/hyperactivity disorder. A dose–response relationship between the number of adverse perinatal events and increased risk for TD/CTD was also observed, with hazard ratios ranging from 1.41 (95% confidence interval (CI): 1.33–1.50) for one event to 2.42 (95% CI: 1.65–3.53) for five or more events. These results pave the way for future gene by environment interaction and epigenetic studies in TD/CTD.

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INTRODUCTION

Family[1–5] and molecular[4,6–8] genetic studies suggest that Tourette's disorder (TD) and chronic tic disorders (CTD) are both familial and highly heritable conditions. There is growing evidence that environmental factors are also important in the etiology of these disorders,[9] with at least 23% of the variance being explained by non-shared environmental factors.[1] In addition, emerging evidence suggests potential epigenetic mechanisms in TD/CTD.[10,11] With much of the current research focusing on the identification of common and rare genetic variants involved in TD/CTD,[8,12,13] there is a particular need to identify robust environmental risk factors implicated in these disorders, as some of these factors may be malleable or preventable.

Perinatal risk factors are a logical starting point because they are already known to be associated with a range of neuropsychiatric disorders, such as schizophrenia,[14] bipolar disorder,[15,16] autism spectrum disorder,[17,18] attention-deficit/hyperactivity disorder (ADHD),[18,19] and obsessive-compulsive disorder (OCD).[20] Previous research on the association between adverse perinatal events and TD/CTD has been sparse and methodologically limited, resulting in inconclusive findings.[9,21]

Maternal smoking during pregnancy has been the focus of previous investigations, with conflicting results. For example, a recent Danish prospective population-based study[22] including 531 TD/CTD patients reported an association between heavy smoking

(>10 cigarettes) during pregnancy and a 71% increased risk of TD/CTD, after controlling for a wide range of potential confounders, including birth weight and preterm birth. Maternal smoking during pregnancy has also been associated with TD severity.[23] However, other studies did not find any association between maternal smoking during pregnancy and TD/CTD,[24–26] including a longitudinal study of 6090 children from a pre-birth cohort, 122 of which had TD/CTD.[25] Other studies only found such association in TD cases with comorbid ADHD.[27–29]

In two small studies involving monozygotic twin pairs, lower birth weight was associated with both the presence[30] and the severity[31] of TD. In addition, TD/CTD have been associated with premature birth,[26] inadequate weight gain,[25] low birth weight and preterm birth with comorbid ADHD,[29] birth complications,[32] birth complications in males,[33,34] older paternal age and low Apgar scores.[35] In addition, the severity of TD/CTD symptoms has been associated with delivery complications,[24] and paternal age and negatively associated with birth weight.[23] However, a number of other studies have failed to find such associations.[23,25,27]

All previous studies of perinatal risk factors in TD/CTD were based on relatively small samples, ascertained from specialist TD/CTD clinics and largely relied on retrospectively collected information on perinatal risk factors—except for Browne et al.[22] and Mathews et al.,[25] which analyzed longitudinal data. Crucially, previous studies could not control for unmeasured familial

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confounders, which could result in spurious associations between perinatal events and TD/CTD.[36]

In this large-scale longitudinal population-based cohort study, we aimed to explore the potential causal link between a wide range of perinatal risk factors and TD/CTD. We employed a quasi-experimental family-based design to provide a better control for unmeasured environmental and genetic factors. Specifically, comparison of full siblings discordant for the exposure automatically controls for most shared environmental and a substantial proportion of genetic factors.[37] Because some adverse perinatal events have been associated with comorbid disorders,[26] we performed sensitivity analyses controlling for a range of comorbid disorders to isolate TD/CTD-specific risk factors. Finally, as there is some evidence that perinatal risk factors may act in a gender-specific manner,[33,34] we also examined male and female patients separately.

MATERIALS AND METHODS

The study was approved by the Regional Ethical Review Board in Stockholm (reference number 2013/862-31/5). The requirement for informed consent was waived because the study was register-based and the included individuals were not identifiable at any time.

Study population

The study cohort consisted of all live singleton births in Sweden from 1 January 1973 to 31 December 2003. The cohort was followed from birth until first diagnosis of TD/CTD, emigration, death or end of follow-up (31 December 2013), whichever came first. The data were obtained by linking individuals through their unique personal identification numbers[38] from the following population-based registers: (1) the Medical Birth Register (MBR), which includes data on more than 99% of all pregnancies and deliveries in Sweden since 1973;[39] (2) the Multi-Generation Register (MGR), with information about kinship going back to 1932, containing information on 100% of mothers and 98% of fathers of individuals born after 1961;[40] (3) the Swedish National Patient Register (NPR), which covers inpatient hospital admissions since 1969 and outpatient specialist care since 2001;[41] (4) the Migration Register, providing information about migration in and out of Sweden;[42] and (5) the Cause of Death Register, with information on dates and causes of all deaths since 1961.[43] Information from the Cause of Death Register and the Migration Register was used to calculate censoring time. For the sibling comparison analysis, we identified from the MGR a subsample of families with at least two full siblings (that is, siblings sharing the same biological mother and father) during the same time period.

Exposures

Information about all perinatal exposures was retrieved from the MBR. In this study, unless otherwise specified, we employed data from 1973 until 2003.

Maternal smoking during pregnancy. Information on maternal smoking during pregnancy collected at the first antenatal visit is available in the MBR from 1982, marking the start of cohort inclusion for this exposure ($n = 2\,152\,848$). The variable was categorized as no daily smoking, 1–9 cigarettes per day and 10 or more cigarettes per day.

Labor presentation. Labor presentation was divided into normal presentation, breech and other malpresentations (for example, face or brow presentations or transverse lie).

Obstetric delivery. Obstetric delivery was categorized in three hierarchical categories: cesarean section, assisted (instrumental) vaginal delivery (that is, use of forceps or vacuum extraction) and unassisted (normal) vaginal delivery.

Gestational age and birth weight. Gestational age was categorized into preterm birth (gestational age < 37 weeks), term birth (37–41 weeks) and post-term birth (⩾42 weeks).

Birth weight was analyzed in two ways. First, as a continuous variable, where we included linear and quadratic terms, distributed as every 250 g. Second, as an ordinal variable categorized into ⩽ 2500 g (low birth weight),

2501–3500 g, 3501–4500 g (referent category) and >4500 g (high birth weight).

Small for gestational age and large for gestational age were defined as a birth weight of more than two standard deviations below and above the mean weight for gestational age, respectively, according to the Scandinavian fetal growth curve adjusted for sex.[44]

Apgar score. The Apgar score[45] at 5 min after delivery was categorized as normal (a score of ⩾ 7) or abnormal (< 7). The Apgar score is a tool for evaluating heart rate, respiratory effort, reflex irritability, muscle tone and color after delivery, which are considered to be five useful indicators that could be determined easily without interfering with the care of the infant.

Head circumference. Small head circumference (HC) was defined as the individuals whose HC was below the 10th centile for each gestational week, and large HC as those whose HC was above the 90th centile for each gestational week, according to the World Health Organization standards.[46]

Outcome

The first instance of a recorded TD or CTD diagnosis in the NPR constituted the outcome using the classification of the International Classification of Diseases (ICD) in its 8th (ICD-8 code 306.2), 9th (ICD-9 code 307C) and 10th versions (ICD-10 codes F95.0 (transient tic disorder), F95.1 (chronic motor or vocal tic disorder), F95.2 (TD), F95.8 (other tic disorders) or F95.9 (unspecified tic disorder)). Using a previously validated algorithm,[47] individuals who have transient tics as their only or final diagnostic code within the same year of the initial diagnosis are considered diagnosis-free. Furthermore, individuals who receive an initial diagnosis of transient, other or unspecified tics are only included if they receive at least an additional diagnosis of a tic disorder, except if the last available diagnosis is of a transient tic disorder given within the same year of the initial diagnosis. This approach results in nearly perfect inter-rater reliability and highly valid diagnoses, with a positive predictive value of 0.89 in ICD-8, 0.86 in ICD-9 and 0.97 in ICD-10.[47]

Covariates

Data on all potential, measured confounders were collected from the MBR (year of birth of the index person, sex, parity and maternal age at childbirth) and the MGR (paternal age at childbirth).

Statistical analysis

We performed Cox proportional hazards regression analysis to estimate hazard ratios (HR) and 95% confidence intervals (CI) of the association between perinatal factors and TD/CTD.

We fitted three different Cox regression models for all exposure variables: first, we modeled the crude associations with TD/CTD, separately for each exposure variable; second, we adjusted for sex and year of birth; and third, in the fully adjusted model, we adjusted for all measured confounders, listed above.

For birth weight, we fitted both a linear and a quadratic representation. We used Akaike Information Criterion to determine which model (that is, linear or linear+quadratic) best fitted the data.

The analyses were also replicated in a fixed-effects model of the subsample of clusters of all full siblings using stratified Cox models. By design, these models adjust for shared familial confounders,[48] in particular for genetic factors and unmeasured shared confounders, such as socio-economic status and parental factors, that make siblings similar. Further, we adjusted for all measured confounders, all of which typically vary between full siblings.

To confirm that the associations were not entirely explained by comorbid conditions, we performed sensitivity analyses in subgroups where all individuals with certain comorbid conditions were excluded from analysis. These conditions were organized in six clusters: organic disorders (organic brain disorder and epilepsy), psychotic disorders (schizophrenia and bipolar disorder), OCD, ADHD, pervasive developmental disorders and mental retardation. All disorders were defined as at least one registered diagnosis in the NPR (for ICD codes, Supplementary Table 1). These models adjusted for all measured confounders. To investigate potential differences in risk factors between the sexes, we also ran all models separately by sex.

Finally, a Cox regression analysis was used to determine possible dose–response effects, that is, the association between the accumulated number of adverse perinatal events that remained statistically significant in the fully adjusted models, and the risk for TD/CTD.

All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Descriptive statistics

Descriptive characteristics of the study population are presented in Table 1. In total, 3 026 861 individuals were included in the cohort, 5597 of which were diagnosed with TD/CTD during the study period, resulting in a Kaplan–Meier estimated prevalence of 0.26% by age 40 (Supplementary Figure 1). As expected, individuals with TD/CTD were more likely to be male and to have multiple comorbidities, particularly other neuropsychiatric disorders and OCD (Table 1). Of the 947 942 families with at least two children, 3563 families included full siblings discordant for TD/CTD. This means that the family includes at least two children and at least one of them has a TD/CTD diagnosis and at least one does not.

Maternal smoking during pregnancy

In the fully adjusted model, maternal smoking during pregnancy was associated with an increased risk of offspring with TD/CTD in a dose–response manner (1–9 cigarettes HR = 1.40 (95% CI: 1.29–1.52) and ⩾10 cigarettes HR = 1.88 (95% CI: 1.71–2.06); Table 2). However, this association did not remain when familial factors were controlled for in the full sibling comparison (1–9 cigarettes HR = 0.72 (95% CI: 0.54–0.96) and ⩾10 cigarettes HR = 0.79 (95% CI: 0.55–1.15)).

Labor presentation

An association was observed between breech presentation and an increased risk for TD/CTD in the fully adjusted model (HR = 1.17 (95% CI: 1–1.38)), compared with normal presentation. The estimate increased further in the sibling comparison, but with lower precision (HR = 1.45 (95% CI: 0.96–2.20); Table 2). In the unadjusted and adjusted models, no association between other malpresentations and TD/CTD was observed.

Obstetric delivery

There was an increased risk of TD/CTD among individuals delivered with cesarean section, compared with an unassisted vaginal delivery, in the fully adjusted model (HR = 1.22 (95% CI: 1.13–1.32); Table 2). The results of the sibling comparison yielded a slightly lower and less precise estimate (HR = 1.15 (95% CI: 0.91–1.46)). The association between assisted vaginal delivery and TD/CTD observed in the unadjusted model decreased in the adjusted models, and did not remain statistically significant in the sibling comparison.

Gestational age

Compared with those born at term, the risk for TD/CTD in individuals with preterm births (< 37 weeks) was significantly higher (HR = 1.25 (95% CI: 1.13–1.32)). The results of the sibling comparison yielded a slightly lower and less precise estimate (HR = 1.20 (95% CI: 0.93–1.56)). Post-term births were not associated with an increased risk of TD/CTD (Table 2).

Birth weight

Birth weights below normal were associated with a slightly increased risk for TD/CTD when adjusting for all measured confounders as well as gestational age—known to correlate with birth weight[49] (⩽2500 g HR = 1.26 (95% CI: 1.06–1.51) and 2501–3500 g HR = 1.12 (95% CI: 1.06–1.19); Table 2). The continuous representation mirrored these results (Figure 1). The results from the sibling comparison models yielded estimates with lower precision, with slightly lower estimates for ⩽ 2500 g and slightly higher estimates for 2501–3500 g (HR = 1.20

Table 1. Descriptive characteristics of study population separately for individuals with and without TD/CTD

Variable	Individuals without TD/CTD, n (%) n = 3 021 264 (99.82)	Individuals with TD/CTD, n (%) n = 5597 (0.18)[a]
Mean follow-up time in years ± s.d.[b]	25 ± 9.25	14.48 ± 6.71
Sex[b]		
Males	1 551 468 (51.35)	4437 (79.27)
Females	1 469 796 (48.65)	1160 (20.73)
Mean age of mothers at birth of index person, years ± s.d.[c]	28 ± 5.13	27.78 ± 5.33
Missing	0 (0)	0 (0)
Mean age of fathers at birth of index person, years ± s.d.	31.37 ± 5.99	31.35 ± 6.40
Missing	23 778 (0.79)	52 (0.93)
Parity[b]		
1	1 272 651 (42.12)	2702 (48.28)
2	1 105 644 (36.60)	1778 (31.77)
3	456 494 (15.11)	741 (13.24)
⩾4	186 475 (6.17)	376 (6.72)
Missing	0 (0)	0 (0)
Smoking during pregnancy[b,d]		
No daily smoking	1 562 819 (72.76)	3383 (67.88)
1–9 cigarettes per day	263 063 (12.25)	739 (14.83)
⩾ 10 cigarettes per day	153 840 (7.16)	543 (10.89)
Missing	168 142 (7.83)	319 (6.40)
Labor presentation		
Normal presentation	2 201 726 (72.87)	4117 (73.56)
Breech presentation	70 874 (2.35)	152 (2.72)
Other malpresentation	98 144 (3.25)	184 (3.29)
Missing	650 520 (21.53)	1144 (20.44)
Obstetric delivery[b]		
Unassisted vaginal delivery	2 417 839 (80.03)	4179 (74.66)
Cesarean section	33 275 (11.10)	788 (14.08)
Assisted vaginal delivery[e]	189 009 (6.26)	412 (7.36)
Missing	79 141 (2.62)	218 (3.89)
Gestational age		
Mean gestational age, weeks ± s.d.[b]	39.47 ± 1.87	39.34 ± 1.96
Gestational age[b]		
Preterm birth (< 37 weeks)	150 633 (4.99)	354 (6.32)
Term birth (37–41 weeks)	2 597 377 (85.97)	4759 (85.03)
Post-term birth (⩾42 weeks)	265 489 (8.79)	473 (8.45)
Missing	7765 (0.26)	11 (0.20)
Birth weight		
Mean birth weight, g ± s.d.	3524.71 ± 557.88	3523.97 ± 582.73
Birth weight[c]		
⩽ 2500 g	105 449 (3.49)	228 (4.07)
2501–3500 g	1 323 635 (43.81)	2408 (43.02)
3501–4500 g	1 484 846 (49.15)	2738 (48.92)
> 4500 g	98 208 (3.25)	202 (3.61)
Missing	9126 (0.30)	21 (0.38)

Table 1. (Continued)

Variable	Individuals without TD/CTD, n (%) n = 3 021 264 (99.82)	Individuals with TD/CTD, n (%) n = 5597 (0.18)[a]
Birth weight in relation to gestational age		
Small for gestational age[c]	92 677 (3.07)	217 (3.88)
Normal for gestational age	2 814 340 (93.15)	5195 (92.17)
Large for gestational age	96 548 (3.20)	184 (3.29)
Missing	17 699 (0.59)	37 (0.66)
Apgar score after 5 minutes		
Normal, score ⩾ 7	2 760 313 (91.36)	5356 (95.69)
Abnormal, score < 7	31 282 (1.04)	59 (1.06)
Missing	229 669 (7.60)	182 (3.25)
Head circumference[c]		
Small head circumference (< 10th centile/gestational week)	136 342 (4.51)	225 (4.02)
Normal head circumference	2 627 690 (86.97)	4796 (85.69)
Large head circumference (> 90th centile/gestational week)	162 330 (5.37)	355 (6.34)
Missing	94 902 (3.14)	221 (3.95)
Comorbidity		
Organic disorders[b,f]	41 619 (1.38)	313 (5.59)
Psychotic disorders[b,g]	31 418 (1.04)	388 (6.93)
Obsessive-compulsive disorder[b]	18 173 (0.60)	1036 (18.51)
ADHD[b]	78 398 (2.59)	2949 (52.69)
Pervasive developmental disorder[b]	34 882 (1.15)	1611 (28.78)
Mental retardation[b]	24 734 (0.82)	459 (8.20)
Affective and anxiety disorders[b,h]	238 247 (7.89)	1810 (32.34)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive-compulsive disorder; s.d., standard deviation; TD/CTD, Tourette's disorder/chronic tic disorder. [a]Kaplan–Meier estimate of expected prevalence at 40 years of age: 0.26%, see Supplementary Figure 1. [b]P-value for χ^2 or t-test < 0.0001. [c]P-value for χ^2 or t-test < 0.05. [d]Data available from 1982 and onwards, n = 2 152 848. [e]Use of forceps or vacuum extraction. [f]Organic brain disorder and epilepsy. [g]Schizophrenia and bipolar disorder. [h]Mood disorders except bipolar disorder, and anxiety disorders except OCD.

(95% CI: 0.80–1.80) and HR = 1.23 (95% CI: 1.07–1.41), respectively). High birth weight (> 4500 g) was not associated with an increased risk for tics (Table 2).

Analyses of small for gestational age revealed an association with an increased risk for TD/CTD, both in the fully adjusted model and in the sibling comparison (HR = 1.49 (95% CI: 1.30–1.70) and HR = 1.46 (95% CI: 1.06–2.01), respectively), whereas large for gestational age revealed no such association (Table 2).

Apgar score
No statistically significant association between abnormal 5-min Apgar scores (< 7) and an increased risk for TD/CTD was observed (Table 2).

Head circumference
The observed statistically significant association between small HC and TD/CTD in the fully adjusted model (HR = 1.31 (95% CI: 1.14–1.49)) did not remain in the sibling comparison (HR = 1.03 (95% CI: 0.77–1.36); Table 2). No statistically significant association between large head circumference and TD/CTD was observed.

Number of perinatal events
A dose–response relationship between number of perinatal events and increased risk for TD/CTD was observed, with HRs ranging from 1.41 (95% CI: 1.33–1.50) for one event to 2.42 (95% CI: 1.65–3.53) for five or more events (Table 3).

Sensitivity analyses
The pattern of results remained largely unchanged in magnitude but with lower precision when individuals with comorbid conditions were excluded from the analyses, with the exception of ADHD, where both the magnitude and precision of the estimates tended to decrease for some of the examined risk factors (Table 4).

Gender effects
The pattern of results described above was similar in male and female individuals with TD/CTD, with overlapping CIs (Supplementary Table 2).

DISCUSSION
In this study of the entire Swedish population including over 5000 individuals diagnosed with TD/CTD, we found that maternal smoking during pregnancy, breech presentation, delivery by cesarean section, impaired fetal growth, preterm birth and small head circumference were associated with a higher risk of developing these disorders after adjusting for measured confounders. The sibling comparison analyses, which controlled for shared familial confounders, resulted in reduced precision (wider CIs) but largely unchanged estimates for most perinatal variables. The exceptions to this were maternal smoking during pregnancy and small head circumference, which were no longer associated with TD/CTD in these sibling models. A dose–response relationship was identified for number of perinatal events, whereby the higher the number, the higher the risk for TD/CTD. Having one positive risk factor increased the risk of TD/CTD by 41%, whereas having five or more risk factors more than doubled the risk, compared to having no adverse perinatal events.

An association between maternal smoking during pregnancy and TD/CTD has been inconsistently reported and likely confounded by the presence of comorbidities.[23,27,28] We replicated recent findings from a Danish cohort study, which also identified a dose–response relationship between the number of cigarettes and the risk of TD/CTD.[22] In our study, compared with the offspring of non-smoking mothers, offspring of mothers who reported smoking up to 9 cigarettes per day had a 40% increased risk of TD/CTD, whereas the offspring of heavy smokers (⩾10 cigarettes/day) had an 88% increased risk. However, this association did not remain when controlling for shared familial confounders, which previous studies did not control for. These negative results are in line with other family-based studies suggesting that shared familial confounders explain why maternal smoking during pregnancy is associated with a range of psychosocial outcomes on the offspring (e.g., ADHD, criminality, academic achievement, drug use, adolescent antisocial behavior, adolescent psychological functioning, suicidal behavior, childhood conduct problems and intellectual abilities).[37,50] OCD may be an exception to this general trend.[20]

Table 2. Hazard ratios and 95% CIs of the association between perinatal events and TD/CTD

Perinatal event	Unadjusted model, HR (95% CI)	Partially adjusted[a], HR (95% CI)	Adjusted[b], HR (95% CI)	Full sibling comparison[b], HR (95% CI)
Smoking during pregnancy[c]				
No daily smoking	1	1	1	1
1–9 cigarettes per day	**1.17 (1.08–1.27)**	**1.48 (1.37–1.60)**	**1.40 (1.29–1.52)**	**0.72 (0.54–0.96)**
⩾ 10 cigarettes per day	**1.44 (1.31–1.57)**	**1.94 (1.77–2.13)**	**1.88 (1.71–2.06)**	0.79 (0.55–1.15)
Labor presentation				
Normal presentation	1	1	1	1
Breech	**1.20 (1.02–1.41)**	**1.19 (1.01–1.40)**	**1.17 (1–1.38)**	1.45 (0.96–2.20)
Other malpresentation	1.00 (0.86–1.16)	1.02 (0.88–1.18)	1.00 (0.86–1.16)	1.18 (0.82–1.69)
Obstetric delivery				
Unassisted vaginal delivery	1	1	1	1
Cesarean section	**1.48 (1.37–1.59)**	**1.21 (1.12–1.30)**	**1.22 (1.13–1.32)**	1.15 (0.91–1.46)
Assisted vaginal delivery	**1.32 (1.19–1.46)**	1.08 (0.98–1.20)	1.02 (0.92–1.13)	0.91 (0.71–1.15)
Gestational age				
Preterm birth (< 37 weeks)	**1.35 (1.21–1.51)**	**1.29 (1.16–1.44)**	**1.25 (1.13–1.40)**	1.20 (0.93–1.56)
Term birth (37–41 weeks)	1	1	1	1
Post-term birth (⩾42 weeks)	0.92 (0.84–1.01)	1.05 (0.95–1.15)	1.03 (0.93–1.13)	1.03 (0.84–1.26)
Birth weight[d]				
⩽ 2500 g	0.90 (0.76–1.07)	**1.34 (1.12–1.59)**	**1.26 (1.06–1.51)**	1.20 (0.80–1.80)
2501–3500 g	0.91 (0.86–0.97)	**1.16 (1.10–1.23)**	**1.12 (1.06–1.19)**	**1.23 (1.07–1.41)**
3501–4500 g	1	1	1	1
> 4500 g	**1.20 (1.04–1.39)**	0.93 (0.80–1.07)	0.97 (0.84–1.12)	0.88 (0.65–1.19)
Birth weight in relation to gestational age				
Not small for gestational age	1	1	1	1
Small for gestational age	**1.25 (1.09–1.43)**	**1.54 (1.34–1.76)**	**1.49 (1.30–1.70)**	**1.46 (1.06–2.01)**
Not large for gestational age	1	1	1	1
Large for gestational age	1.07 (0.92–1.24)	0.95 (0.82–1.10)	1 (0.87–1.16)	1.02 (0.75–1.38)
Apgar score after 5 min				
Normal, score ⩾ 7	1	1	1	1
Abnormal, score < 7	1.13 (0.88–1.46)	1.13 (0.87–1.46)	1.10 (0.85–1.42)	0.86 (0.48–1.54)
Head circumference				
Small head circumference (< 10th centile/ gestational week)	0.84 (0.74–0.96)	**1.36 (1.19–1.56)**	**1.31 (1.14–1.49)**	1.03 (0.77–1.36)
Normal head circumference	1	1	1	1
Large head circumference (> 90th centile/ gestational week)	**1.24 (1.11–1.38)**	0.90 (0.81–1.00)	0.93 (0.83–1.04)	0.97 (0.77–1.22)

Abbreviations: CI, confidence interval; HR, hazard ratio; TD/CTD, Tourette's disorder/chronic tic disorder. [a]Model-adjusted model for sex and year of birth. [b]Model-adjusted for sex, year of birth, age of mother and father, and parity. [c]Data available from 1982 and onwards, n = 2 152 848. [d]Additionally adjusted for gestational age, both linear and quadratic terms in all models. Significant predictors are highlighted in bold.

Our results are in line with previous studies reporting an association between impaired fetal growth and birth complications and TD/CTD.[23,24,26,30–32] However, other studies have failed to find such associations.[23,25,27] Of note, all of this prior literature has used much smaller sample sizes than the current study (7–586 cases), likely to be insufficient to determine associations with rare perinatal exposures. In addition, two previous reports in clinical samples indicated that males with TD/CTD had more birth complications than females,[33,34] a finding that we could not replicate in our study. It is possible that previous studies had insufficient number of female patients to test this hypothesis.

In general, the results remained unchanged when other frequent comorbidities were excluded from the analyses, with the exception of ADHD, where both the magnitude and precision of the estimates tended to be attenuated for some of the examined risk factors. Particularly the association with maternal smoking during pregnancy did not survive when excluding individuals with ADHD. However, over half of the individuals with

TD/CTD in our cohort had a comorbid ADHD diagnosis and their exclusion likely introduces a selection bias.

The mechanisms linking adverse perinatal factors and TD/CTD remain to be identified. Adverse fetal environments have been observed to affect brain development.[51–53] Similarly, the fetal programming hypothesis posits that the adaptation to the fetal environment may lead to adverse effects in life.[54,55] Neuroimaging studies have shown a relationship between structural and functional abnormalities within motor cortico-basal ganglia circuits and the occurrence of tics.[56,57] Whereas genetic factors are indisputably important, an emerging body of literature is showing that environmental factors may have an important part in gene expression through epigenetic mechanisms.[10] Recent findings from neuroimaging[58] and transcriptome analyses studies of post-mortem brain tissue[59] have linked TD with the activation of microglia brain cells following neuroinflammation.[58–60]

Many questions remain for the future, including whether and how adverse perinatal events interact with familial or genetic
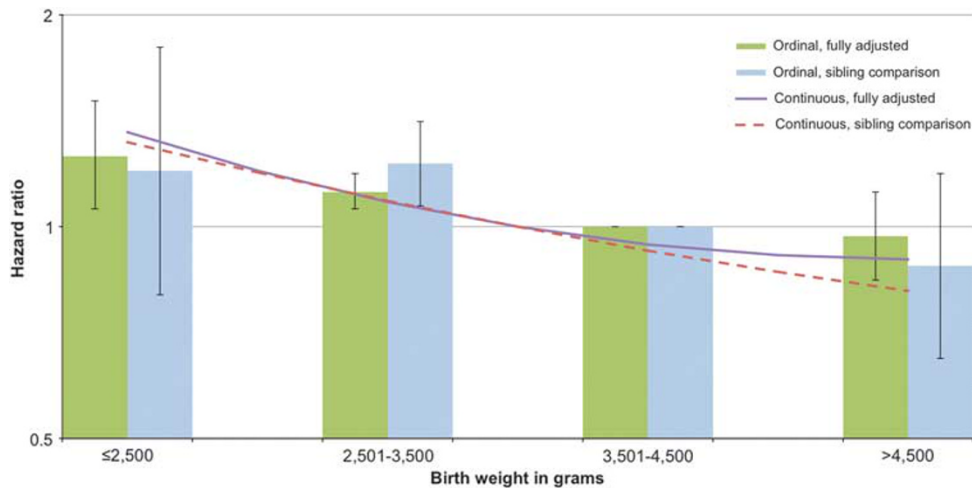
Figure 1. Hazard ratios and 95% confidence intervals (CIs) of the association between birth weight and Tourette's disorder or chronic tic disorders (TD/CTD). Analysis of data as ordinal (columns) and continuous (lines) variables in fully adjusted, baseline, population-wide estimate and sibling comparison models for birth weight (reference group 3501–4500 g) in determination of the risk for TD/CTD in offspring born in Sweden between 1 January 1973 and 31 December 2003. Error bars indicate 95% CI. The y-axis uses a log scale.

Table 3. Association between the number of perinatal events and TD/CTD, expressed as hazard ratios and 95% CIs[a]

Number of perinatal events[a]	Individuals without TD/CTD, n (%)[b]	Individuals with TD/CTD, n (%)[b]	Unadjusted model, HR (95% CI)	Partially adjusted[c], HR (95% CI)	Adjusted[d], HR (95% CI)
0	2 068 047 (68.45)	3287 (58.73)	1	1	1
1	703 282 (23.28)	1689 (30.18)	**1.55 (1.46–1.64)**	**1.45 (1.37–1.54)**	**1.41 (1.33–1.50)**
2	165 930 (5.49)	392 (7.00)	**1.56 (1.40–1.73)**	**1.47 (1.33–1.64)**	**1.43 (1.29–1.59)**
3	54 608 (1.81)	141 (2.52)	**1.74 (1.47–2.06)**	**1.74 (1.47–2.06)**	**1.68 (1.42–1.99)**
4	22 037 (0.73)	61 (1.09)	**1.98 (1.54–2.55)**	**1.84 (1.43–2.37)**	**1.78 (1.37–2.29)**
⩾5	7360 (0.24)	27 (0.48)	**2.74 (1.88–4.00)**	**2.49 (1.71–3.64)**	**2.42 (1.65–3.53)**

Abbreviations: CI, confidence interval; HR, hazard ratio; TD/CTD, Tourette's disorder/chronic tic disorder. [a]Only perinatal events that remain statistically significant in the fully adjusted models are included. The events are defined as follows: daily maternal smoking during pregnancy, breech presentation, delivery by cesarean section, gestational age < 37 weeks, birth weight ⩽2500 g, small for gestational age and small head circumference. [b]P-value for χ^2 < 0.0001. [c]Model-adjusted for sex and year of birth. [d]Model-adjusted for sex, year of birth, age of mother and father, and parity. Maternal smoking during pregnancy was included even though the variable was not introduced in the Medical Birth Register until 1982, but running analyses on the entire cohort excluding smoking, and on a subsample of those born from 1982 did not reveal statistically significant differences in the estimates. Significant predictors are highlighted in bold.

factors and whether perinatal complications predict the persistence of tics beyond young adulthood, alone or in interaction with genetic factors. Additional maternal factors, such as metabolic diseases during pregnancy or maternal immune activation,[61] remain largely unexplored in TD/CTD.

Strengths and limitations

To the best of our knowledge, this is the first study examining a broad range of perinatal risk factors for TD/CTD using a very large population-based cohort with prospectively collected data at the time of birth. By comparing clusters of full siblings discordant for TD/CTD, we could control for many (unmeasured) shared familial confounders (genetic and environmental). In addition, the diagnostic validity and reliability of the TD/CTD diagnoses in the Swedish national registers is high.[47]

The results need to be interpreted in light of some study limitations. Our cohort is weighted towards more severe cases and does not represent the totality of all TD/CTD patients in Sweden. This is because many sufferers with mild symptoms may not seek help, the incomplete coverage of the outpatient register (which started in 2001 and had limited coverage in the early years), and

that patients diagnosed by general practitioners, other non-specialists or non-physicians are not included in the NPR. Some associations need to be interpreted with caution, as the small number of individuals being exposed to some events resulted in relatively imprecise estimates. Sibling comparisons can help inferring, but do not prove, causality. They also have lower statistical power than population-based estimates.[48] Furthermore, sibling comparison designs are sensitive to random measurement error in the exposure, and may be biased due to variables shared by siblings that are related to the exposure but not the outcome.[37,62] The sibling comparison assumes there are no carryover effects from one pregnancy to a later pregnancy.[63,64] Adjusting for parity addresses this partially, but not entirely.

CONCLUSIONS

A number of perinatal factors, namely impaired fetal growth, preterm birth, breech presentation and cesarean section are associated with a higher risk of TD/CTD, independently of shared family confounders and measured covariates, suggesting they may be in the causal pathway to TD/CTD. The association between maternal smoking during pregnancy and TD/CTD is likely to be

Table 4. Hazard ratios and 95% CIs of the association between perinatal events and TD/CTD when excluding common comorbid disorders, adjusted for sex, year of birth, age of mother and father, and parity

Perinatal event	Excluding organic disorders[a]	Excluding psychotic disorders[b]	Excluding OCD	Excluding ADHD	Excluding pervasive developmental disorders	Excluding mental retardation
Smoking during pregnancy[c]						
No daily smoking	1	1	1	1	1	1
1–9 cigarettes per day	**1.38 (1.27–1.50)**	**1.41 (1.30–1.53)**	**1.43 (1.31–1.57)**	1.04 (0.91–1.19)	**1.41 (1.28–1.56)**	**1.39 (1.28–1.52)**
⩾10 cigarettes per day	**1.87 (1.70–2.06)**	**1.89 (1.72–2.08)**	**2.05 (1.86–2.27)**	1.18 (0.99–1.39)	**1.87 (1.67–2.10)**	**1.88 (1.70–2.08)**
Labor presentation						
Normal presentation	1	1	1	1	1	1
Breech	**1.19 (1.01–1.40)**	1.16 (0.98–1.38)	**1.24 (1.04–1.48)**	1.17 (0.93–1.48)	1.09 (0.89–1.33)	1.10 (0.93–1.31)
Other malpresentation	0.98 (0.84–1.15)	1.00 (0.86–1.17)	1.02 (0.86–1.20)	0.94 (0.75–1.18)	1.03 (0.86–1.22)	0.98 (0.84–1.14)
Obstetric delivery						
Unassisted vaginal delivery	1	1	1	1	1	1
Cesarean section	**1.19 (1.10–1.29)**	**1.19 (1.10–1.29)**	**1.26 (1.15–1.37)**	**1.16 (1.03–1.30)**	**1.21 (1.11–1.33)**	**1.19 (1.09–1.29)**
Assisted vaginal delivery	1.01 (0.91–1.13)	1.01 (0.91–1.13)	1 (0.89–1.12)	0.99 (0.85–1.15)	1.06 (0.94–1.20)	1.01 (0.91–1.13)
Gestational age						
Preterm birth (<37 weeks)	**1.24 (1.11–1.39)**	**1.25 (1.12–1.40)**	**1.24 (1.10–1.39)**	1.18 (1.00–1.38)	**1.15 (1.01–1.32)**	**1.24 (1.11–1.39)**
Term birth (37–41 weeks)	1	1	1	1	1	1
Post-term birth (⩾42 weeks)	1.03 (0.93–1.13)	1.02 (0.92–1.12)	1.03 (0.93–1.15)	1.08 (0.94–1.23)	1.02 (0.91–1.14)	1.04 (0.95–1.15)
Birth weight[d]						
⩽2500 g	**1.29 (1.07–1.54)**	**1.27 (1.06–1.52)**	1.23 (1.00–1.50)	1.30 (1.00–1.67)	1.21 (0.97–1.49)	1.21 (1.00–1.46)
2501–3500 g	**1.11 (1.04–1.18)**	**1.11 (1.04–1.18)**	**1.15 (1.08–1.23)**	1.06 (0.98–1.16)	**1.10 (1.02–1.18)**	**1.11 (1.04–1.18)**
3501–4500 g	1	1	1	1	1	1
>4500 g	0.99 (0.85–1.14)	0.97 (0.84–1.13)	1.03 (0.88–1.20)	0.87 (0.70–1.09)	0.94 (0.79–1.11)	0.95 (0.81–1.10)
Birth weight in relation to gestational age						
Not small for gestational age	1	1	1	1	1	1
Small for gestational age	**1.53 (1.33–1.76)**	**1.50 (1.30–1.72)**	**1.49 (1.28–1.73)**	**1.44 (1.18–1.75)**	**1.57 (1.34–1.84)**	**1.43 (1.24–1.66)**
Not large for gestational age	1	1	1	1	1	1
Large for gestational age	1 (0.86–1.17)	1.01 (0.86–1.17)	1.04 (0.89–1.22)	0.97 (0.78–1.21)	0.96 (0.80–1.14)	1.02 (0.87–1.19)
Apgar score after 5 min						
Normal, score ⩾7	1	1	1	1	1	1
Abnormal, score <7	1.08 (0.82–1.41)	1.08 (0.83–1.42)	1.14 (0.86–1.51)	1.12 (0.78–1.62)	1.12 (0.83–1.52)	1.13 (0.87–1.48)
Head circumference (cm)						
Small head circumference (<10th centile/gestational week)	**1.30 (1.13–1.50)**	**1.27 (1.10–1.47)**	**1.23 (1.05–1.44)**	**1.27 (1.05–1.54)**	**1.27 (1.08–1.49)**	**1.26 (1.09–1.45)**
Normal head circumference	1	1	1	1	1	1
Large head circumference (>90th centile/gestational week)	0.94 (0.84–1.05)	0.91 (0.81–1.01)	0.97 (0.81–1.16)	0.98 (0.84–1.15)	0.95 (0.84–1.08)	0.93 (0.83–1.04)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; HR, hazard ratio; OCD, obsessive-compulsive disorder; TD/CTD, Tourette's disorder/chronic tic disorder. [a]Organic brain disorder and epilepsy. [b]Schizophrenia and bipolar disorder. [c]Data available from 1982. [d]Additionally adjusted for gestational age, both linear and quadratic terms. Significant predictors are highlighted in bold.

spurious and explained by both familial factors and ADHD comorbidity. A dose–response relationship was also found, whereby the higher the number of perinatal events, the higher the risk for TD/CTD. These findings are important for the understanding of the etiology of TD/CTD and will hopefully inform future gene by environment interaction and epigenetic studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the *Molecular Psychiatry* website (http://www.nature.com/mp)