# Prenatal Maternal Smoking and Increased Risk for Tourette Syndrome and Chronic Tic Disorders

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**Objective:** We assessed the role of prenatal maternal smoking in risk for Tourette syndrome and chronic tic disorder (TS/CT) and pediatric-onset obsessive-compulsive disorder (OCD).

**Method:** In an analysis of 73,073 singleton pregnancies from the Danish National Birth Cohort, we calculated incidence rates (IR) per 1,000 person-year for TS/CT and OCD. We then determined crude and adjusted hazard ratios and 95% CIs associated with prenatal maternal smoking, considering smoking as a dichotomous (yes/no) variable or a stratified variable (no smoking, light smoking, and heavy smoking [≥10 cigarettes/day]). Additional analyses examined the effect of maternal smoking on risk for TS/CT with other comorbid psychiatric conditions.

**Results:** In final adjusted analyses, heavy smoking was associated with a 66% increased risk for TS/CT (adjusted hazard ratio = 1.66, 95% CI = 1.17–2.35). In addition, heavy smoking was associated with a 2-fold increased risk for TS/CT with comorbid attention-deficit/hyperactivity disorder (ADHD), and both light and heavy smoking were associated with a more than 2-fold increased risk for TS/CT with any non-ADHD psychiatric comorbidity. Our parallel analyses of pediatric-onset OCD were likely underpowered but showed similar relationships.

**Conclusion:** Prenatal maternal smoking was associated with increased risk for TS/CT as well as TS/CT with comorbid psychiatric conditions, even after adjustment for several important variables, including maternal psychiatric history, socioeconomic status, and partner smoking. Our findings point to a pathway linking prenatal tobacco exposure and altered brain development to TS/CT.

**Key words:** chronic tic disorder, obsessive-compulsive disorder, prenatal, smoking, Tourette syndrome

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Tourette syndrome (TS) and chronic tic disorder (CT) are related pediatric-onset, neuropsychiatric disorders and frequently co-occur with obsessive-compulsive disorder (OCD) in individuals and within families.[1-4] There is substantial evidence for a genetic contribution to the etiology of both TS/CT and OCD.[5] Twin and family studies provide heritability estimates of 30% to 60% for each disorder[6-11]; these reports are supported by a recent study considering inherited common genetic variation that estimated heritability at 58% for TS and 37% for OCD with substantial shared risk between the disorders.[12] How environment contributes to risk for TS/CT and OCD is less well established, but various factors such as birth complications, maternal mood, maternal autoimmune disease, and perinatal smoking have been suggested as putative risks.[6-9,13-20]

Prenatal maternal smoking has been associated with several neuropsychiatric disorders including attention-deficit/hyperactivity disorder (ADHD),[21] schizophrenia,[22] and autism spectrum disorder (ASD),[23] although the precise nature of the risk relationship remains to be determined. Previous literature on the role of prenatal maternal smoking in TS/CT and OCD offers mixed results. Some studies identify prenatal maternal smoking as a risk factor for TS/CT[14,24] (or tic severity[25]), whereas other studies report no association[16,26]; smoking has been more consistently identified as a risk factor for TS with comorbid ADHD.[16,24,27] Studies of maternal prenatal smoking in OCD risk are very limited, with both positive[25] and negative findings.[17,28] Many prior studies exploring environmental risk factors for TS/CT and OCD, including prenatal maternal smoking, use retrospective data collection and/or specialty clinic samples, rendering them susceptible to recall and ascertainment biases and unclear generalizability. With a few exceptions, the sample sizes are relatively small, likely contributing to variable results among studies.

The Danish National Birth Cohort (DNBC) is a prospective cohort study of approximately 100,000 women enrolled early in pregnancy from 1996 to 2002, with planned follow-up for decades.[29] The DNBC includes detailed quantitative information on lifestyle, health, and health behaviors, including prenatal smoking behavior and related covariates, with prospectively obtained data, minimizing biases. The aim of our study was to use DNBC data to assess the role of prenatal maternal smoking in risk for TS/CT and pediatric-onset OCD. We also investigated whether prenatal maternal smoking was differentially associated with risk for

This article is discussed in an editorial by Drs. James F. Leckman and Thomas V. Fernandez on page 751.

Supplemental material cited in this article is available online.

TS/CT with comorbid ADHD or other comorbid psychiatric diagnoses.

## METHOD

The Danish Data Protection Agency, the DNBC Steering Committee, and the Mount Sinai institutional review board approved this study.

### Participants and Exposures

We ascertained data regarding all participants in the DNBC[29] and their offspring (up to age 15 years). Information about smoking and other exposures during pregnancy was extracted from 3 research interviews, conducted on average at the 17th and 32nd weeks of gestation, and 6 months after birth (referencing the last part of the pregnancy). For a dichotomous (yes/no) assessment of prenatal smoking, women who answered "yes" to at least 1 of the following questions were considered positive for prenatal maternal smoking: Did you smoke during this pregnancy (first interview); Do you smoke now (first and second interviews); Have you smoked since the last interview (second interview); and, Did you smoke during the last part of the pregnancy (third interview). Interviewers rated 99% of the responses to smoking-related questions as trustworthy.

To compare light and heavy prenatal smoking, maternal smoking was a priori categorized as a 3-level variable (no smoking, light smoking [<10 cigarettes/day], and heavy smoking [≥10 cigarettes/day]), calculated as the average number of cigarettes smoked across the entire pregnancy as assessed at each of the 3 interviews.

Of note, of 55,817 participants with 0 average smoking during pregnancy, a small number (1,923; 3.4%) reported smoking at some point during pregnancy while responding "None" when asked about the number of cigarettes smoked at each interval. This was interpreted to reflect prior, occasional cigarettes but not current smoking. In the analyses of maternal smoking as a dichotomous variable, these individuals were classified as smokers. However, in the analyses of maternal smoking as a variable with 3 categories (nonsmoker, light smoker, and heavy smoker), this group was categorized as nonsmokers. To ensure that this did not skew results, we performed a sensitivity analysis on data related to smoking dose, reconsidering this latter group as light smokers rather than nonsmokers, and observed similar results.

### Outcomes

Information on psychiatric diagnoses in the offspring was obtained by linkage to the Danish Psychiatric Central Register (DPCR)[30] and the Danish National Hospital Register (LPR).[31] The *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) has been used in Denmark since 1994.[32] The outcomes of interest were TS/CT (*ICD-10* codes F95.1, F95.2) and OCD (*ICD-10* codes F42.0, F42.1, F42.2). In addition, we considered the broader category of tic disorders, including transient and unspecified tic disorders (TS/CT spectrum: *ICD-10* codes F95.0, F95.1, F95.2, F95.8, F95.9) and the broader category of OCD, including individuals with obsessive-compulsive behaviors who do not meet full criteria for OCD (OCD spectrum: *ICD-10* codes F42.0, F42.1, F42.2, F42.8, F42.9). Because TS/CT and OCD are related disorders with likely overlapping risk factors, we also considered TS/CT and OCD cases combined. We investigated further the association between prenatal smoking and TS/CT with comorbid ADHD (*ICD-10* codes F90.0, F90.1, F90.8, F90.9) or TS/CT with other comorbid psychiatric diagnoses (*ICD-10* codes F00-F99 excluding participants who had ADHD).

### Statistical Analyses

We calculated incidence rates per 1,000 person-year for each diagnostic category, then calculated crude hazard ratios (HR) and adjusted hazard ratios (aHR) and 95% CI using Cox proportional hazard models, with child's age as the time scale (censor date: October 7, 2013). To account for prevalence trends over time, we adjusted for birth year in all analyses. Proportional hazard assumptions were tested using Schoenfeld residuals. We adjusted for possible confounders using multiple approaches. In addition to the crude model (model 1), we ran 5 adjusted models with increasing adjustment for confounders/covariates (models 2–6, with model 3 as our primary analysis).

In model 2, we adjusted for sex of the child, parity, birth year, maternal age (15–24, 25–29, 30–34, and ≥35 years), and maternal psychiatric history. In model 3, we adjusted for socioeconomic

**FIGURE 1** Incidence of Tourette syndrome (TS), chronic tic disorder (CT), obsessive-compulsive disorder (OCD), and related disorders in children as a function of maternal prenatal smoking. Note: (A) Nonsmokers versus smokers. (B) Nonsmokers versus light smokers (<10 cigarettes per day) or heavy smokers (≥10 cigarettes per day). *$p < .05$.

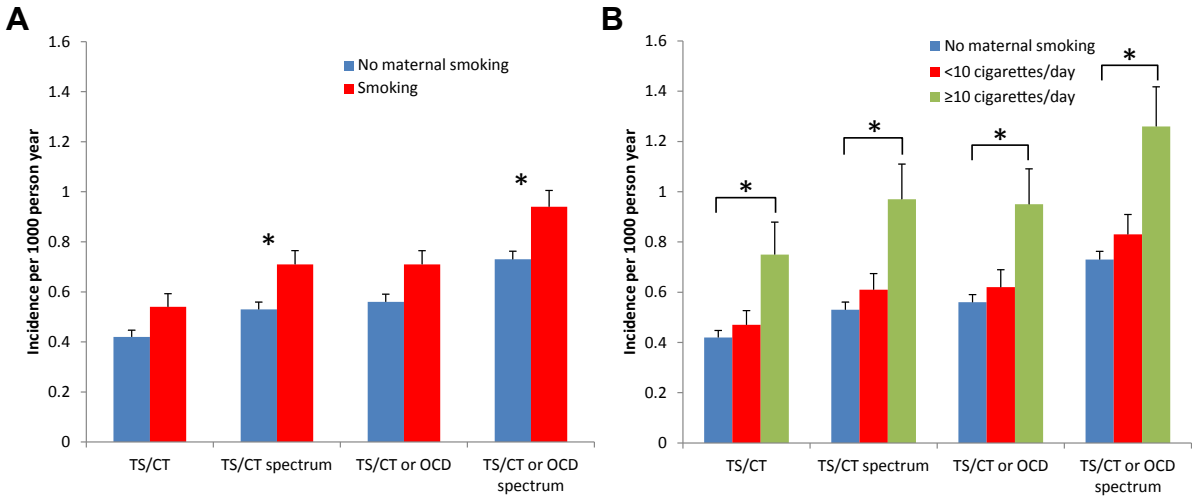

**TABLE 1** Crude and Adjusted Hazard Ratios (95% CIs) for the Association Between Smoking During Pregnancy and Tourette Syndrome (TS)/Chronic Tic Disorder (CT) or Obsessive-Compulsive Disorder (OCD)

| Model[a] | TS/CT | TS/CT Spectrum | TS/CT or OCD | TS/CT or OCD Spectrum |
|---|---|---|---|---|
| Model 1 | | | | |
| Any smoking | 1.29 (1.05–1.58) | 1.33 (1.11–1.59) | 1.25 (1.04–1.49) | 1.29 (1.10–1.50) |
| <10 cigs/d | 1.09 (0.84–1.40) | 1.12 (0.90–1.41) | 1.10 (0.88–1.38) | 1.14 (0.94–1.38) |
| ≥10 cigs/d | 1.79 (1.32–2.43) | 1.83 (1.40–2.40) | 1.67 (1.27–2.19) | 1.73 (1.37–2.19) |
| Model 2 | | | | |
| Any smoking | 1.16 (0.93–1.43) | 1.20 (1.00–1.45) | 1.13 (0.94–1.36) | 1.16 (0.99–1.36) |
| <10 cigs/d | 0.99 (0.76–1.29) | 1.03 (0.82–1.29) | 1.01 (0.81–1.27) | 1.04 (0.86–1.26) |
| ≥10 cigs/d | 1.55 (1.13–2.13) | 1.59 (1.20–2.10) | 1.45 (1.10–1.92) | 1.50 (1.17–1.90) |
| Model 3 | | | | |
| Any smoking | 1.19 (0.95–1.49) | 1.23 (1.01–1.50) | 1.20 (0.98–1.46) | 1.22 (1.02–1.45) |
| <10 cigs/d | 1.02 (0.78–1.33) | 1.06 (0.83–1.34) | 1.07 (0.85–1.35) | 1.09 (0.89–1.33) |
| ≥10 cigs/d | 1.69 (1.19–2.39) | 1.71 (1.27–2.32) | 1.64 (1.21–2.22) | 1.66 (1.28–2.15) |
| Model 4 | | | | |
| Any smoking | 1.18 (0.93–1.50) | 1.19 (0.97–1.47) | 1.21 (0.98–1.49) | 1.19 (1.00–1.42) |
| <10 cigs/d | 1.02 (0.78–1.34) | 1.02 (0.81–1.31) | 1.08 (0.86–1.37) | 1.07 (0.87–1.32) |
| ≥10 cigs/d | 1.69 (1.17–2.44) | 1.65 (1.20–2.27) | 1.67 (1.21–2.30) | 1.62 (1.24–2.13) |
| Model 5 | | | | |
| Any smoking | 1.18 (0.93–1.50) | 1.19 (0.96–1.47) | 1.21 (0.98–1.48) | 1.19 (0.99–1.42) |
| <10 cigs/d | 1.02 (0.78–1.34) | 1.03 (0.81–1.31) | 1.08 (0.85–1.37) | 1.07 (0.87–1.31) |
| ≥10 cigs/d | 1.68 (1.16–2.44) | 1.64 (1.19–2.27) | 1.65 (1.20–2.28) | 1.60 (1.22–2.11) |
| Model 6 | | | | |
| Any smoking | 1.19 (0.94–1.51) | 1.19 (0.97–1.47) | 1.22 (0.99–1.49) | 1.19 (1.00–1.43) |
| <10 cigs/d | 1.03 (0.78–1.35) | 1.03 (0.81–1.32) | 1.09 (0.86–1.39) | 1.07 (0.87–1.32) |
| ≥10 cigs/d | 1.71 (1.18–2.48) | 1.65 (1.20–2.28) | 1.66 (1.20–2.29) | 1.62 (1.23–2.13) |

*Note: Reference group = no smoking.*

[a]*Model 1 is adjusted for birth year only; model 2 is adjusted for birth year, sex, maternal age, parity, and maternal psychiatric disorders; model 3 is adjusted for all the variables in model 2 plus socioeconomic status, consumption of beer, wine, spirits, and coffee, smoking hashish, and binge drinking; model 4 is adjusted for all the variables in model 3 plus partner smoking; model 5 is adjusted for all the variables in model 4 plus gestational age and birth weight as categorical variables; model 6 is adjusted for all the variables in model 4 plus gestational age and birth weight as continuous variables.*

status[27] (SES; low, middle, high), alcohol consumption (beer [<1, 1–3, >3 drinks per week], wine [<1, 1–3, >3 drinks per week], or spirits [any drinking]), binge drinking, smoking hashish, and coffee intake (<1 cup, 1–3 cups, >3 cups per day) in addition to covariates in model 2. Approximately 4% of the women had missing data and were classified according to their father's SES. Birth weight was obtained by linkage to the Danish Medical Birth Registry[33]; maternal age was obtained by linkage to the Danish Civil Registration System[34]; maternal psychiatric history was obtained by linkage to the DPCR and LPR; and the remaining variables were extracted from DNBC interview data.

After identifying the association between maternal smoking and phenotype, we examined additional models. First, to fully explore the specific role of maternal smoking, we adjusted for the effect of partner smoking (model 4). Because of the potential involvement of gestational age (<37, 37–40, and >40 weeks) and birth weight (<2,500, 2,500–3,999, and ≥4,000 g) in the causal pathway, we adjusted for these variables both as continuous and categorical variables (models 5 and 6).

Finally, we carried out post hoc exploratory analyses and grouped families into 4 categories related to prenatal parental smoking (maternal only, partner only, both maternal and partner, and neither maternal nor partner).

In follow-up analyses, we used logistic regression to predict a propensity score (PS) for smoking as the dependent variable and then adjusted for the PS as a continuous and as a categorical variable (consisting of quartiles) in the Cox model. The covariates included in the PS analysis were sex of the child, birth weight, gestational age, maternal prepregnancy body mass index (BMI), parity, birth year, maternal age, maternal psychiatric history, parental smoking status, SES, alcohol consumption (beer, wine, or spirits), binge drinking, smoking hashish, and caffeine (cola and coffee) intake.

Only cases with all available covariate data were included in the analyses. Because a few (6.2%) mothers contributed ≥2 children to the birth cohort, we used cluster-adjusted standard errors to calculate the 95% CIs. A two-tailed $p$ value of $< .05$ was considered statistically significant. Statistical analyses were performed using STATA 14.1 software (StataCorp, College Station, TX).

## RESULTS

### Cohort Characteristics

There were 90,977 pregnancies with data on smoking, yielding 92,765 live-born children, 89,189 of whom were singleton births and the focus of the current study. Of the children, 49% (n = 43,521) were female. The median duration of follow-up was 13 years. By October 2013, a total of 906 children (1.0%) were diagnosed with the outcomes of interest: 667 children with a TS/CT spectrum diagnosis (531 with TS/CT) and, because of the young age of the

cohort, a smaller number (n = 294) with an OCD spectrum diagnosis (209 with OCD) (see Tables S1 and S2, available online). Prenatal maternal smoking was present during 26% of all pregnancies (n = 24,045), 33% of pregnancies with a child with TS/CT (n = 175), and 34% of pregnancies with a child with TS/CT spectrum (n = 227). Maternal heavy smoking was present in nearly 8% of all pregnancies (n = 6,836) and 12% of pregnancies with children with TS/CT (n = 65) and TS/CT spectrum (n = 84). Approximately 82% of all pregnancies with live-born children (n = 73,073) had complete data on covariates of interest. The distribution of variables based on smoking status is presented in Table S3, available online. The percentages of pregnancies with prenatal maternal smoking (26%, n = 19,179) or offspring with an outcome of interest (1.0%, n = 736) remained unchanged after exclusion of pregnancies with missing covariate data.

*Effect of Prenatal Maternal Smoking on Risk for TS/CT and OCD.* Prenatal maternal smoking was associated with increased IR for TS/CT (0.42 [95% CI = 0.38–0.47] versus 0.54 [95% CI = 0.46–0.64] for no smoking and smoking, respectively) and TS/CT spectrum (0.53 [95% CI = 0.48–0.59] versus 0.70 [95% CI = 0.61–0.82]) (Figure 1A). Furthermore, light smoking was associated with an IR of 0.46 (95% CI = 0.37–0.58) for TS/CT and 0.60 (95% CI = 0.49–0.73) for TS/CT spectrum, whereas heavy smoking was associated with an IR of 0.76 (95% CI = 0.58–1.00) for TS/CT and 0.97 (95% CI = 0.76–1.24) for TS/CT spectrum (Figure 1B). The IR for OCD was 0.17 (95% CI = 014–0.20) versus 0.19 (95% CI = 0.14–0.25) for no smoking versus smoking, respectively, and the IR for OCD spectrum was 0.24 (95% CI = 0.21–0.28) versus 0.28 (95% CI = 0.23–0.36) for no smoking versus smoking, respectively (see Figure S1, available online). Combining all cases of TS/CT and OCD or TS/CT spectrum and OCD spectrum showed similar patterns as each alone (Figure 1). Sensitivity analyses did not alter the results (see Table S4, available online).

Our primary analysis was based on model 3 (adjusting for birth year, sex, maternal age, parity, maternal psychiatric disorders, SES, consumption of beer, wine, spirits, and coffee, binge drinking, and consumption of hashish) (Table 1). Based on this model, heavy smoking was significantly associated with an approximately 65% higher risk for TS/CT (aHR = 1.69, 95% CI = 1.19–2.39) and TS/CT spectrum (aHR = 1.69, 95% CI = 1.25–2.29). Analysis of light smoking in TS/CT found an aHR of 1.02 (95% CI = 0.78–1.33) and an aHR of 1.05 (95% CI = 0.83–1.33) for TS/CT spectrum. Analyses combining cases of TS/CT and OCD produced results that were similar to those for TS/CT alone, and analyses under additional models (models 1, 2, 4, 5, and 6) also produced similar results. In adjusted analyses under all models, prenatal maternal smoking did not show a significant effect on risk for OCD, whether categorized as a dichotomous variable or stratified by light versus heavy smoking (see Table S5, available online), although the trends were similar when comparing TS/CT and OCD.

*Effect of Prenatal Maternal Smoking on Risk for TS/CT With Comorbidities.* In previous studies, maternal smoking has been associated with TS/CT and comorbid ADHD. In our cohort, 36% of children with TS/CT had comorbid ADHD, and prenatal maternal smoking was associated with an increased IR for TS/CT with comorbid ADHD (0.13, 95% CI = 0.11–0.16 for nonsmokers versus 0.21, 95% CI = 0.16–0.28 for smokers) (Figure 2). In adjusted analyses under model 3, heavy prenatal maternal smoking was associated with a 2-fold increased risk for TS/CT with comorbid ADHD (aHR = 1.94, 95% CI = 1.14–3.29), whereas an analysis of risk for TS/CT and comorbid ADHD in children whose mothers were light smokers found an aHR of 0.95 (95% CI = 0.60–1.50) (Table 2). To determine whether prenatal maternal smoking increased risk for TS/CT with any psychiatric comorbidity, we focused on the 30% of individuals who did not have ADHD but had a non-ADHD comorbid psychiatric diagnosis. We observed that prenatal

**FIGURE 2** Incidence of complex Tourette syndrome (TS) and chronic tic disorder (CT) in children as a function of maternal prenatal smoking. Note: (A) Nonsmokers versus smokers. (B) Nonsmokers versus light smokers (<10 cigarettes per day) or heavy smokers (≥10 cigarettes per day). *$p < .05$.

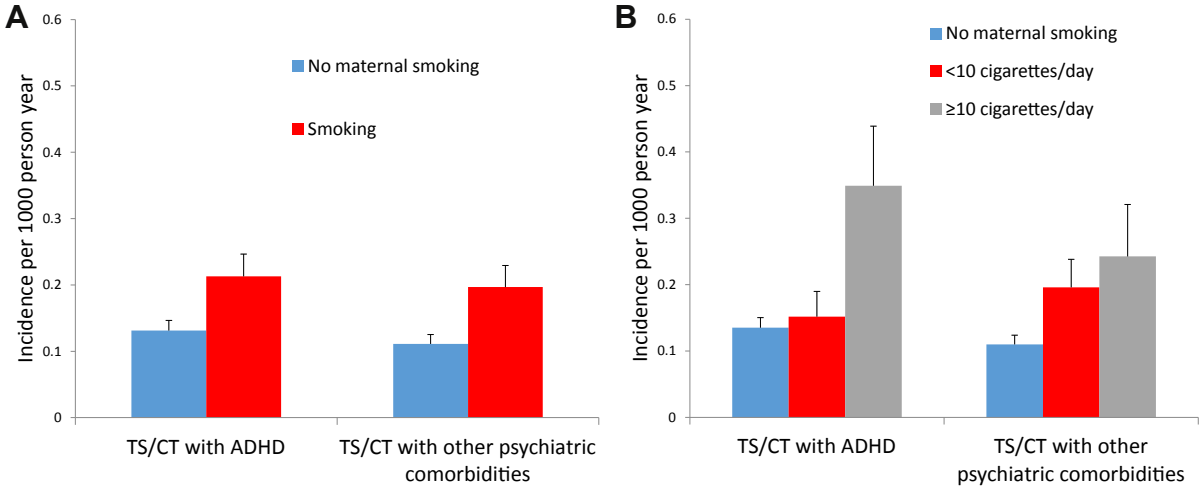

**TABLE 2** Crude and Adjusted Hazard Ratios (95% CIs) for the Association Between Smoking During Pregnancy and Tourette Syndrome (TS)/Chronic Tic Disorder (CT) With Psychiatric Comorbidities

| Model[a] | TS/CT With ADHD | TS/CT With Other Comorbidities[b] |
|---|---|---|
| Model 1 | | |
| Any smoking | 1.62 (1.15–2.27) | 1.76 (1.22–2.53) |
| <10 cigs/d | 1.12 (0.72–1.75) | 1.77 (1.17–2.69) |
| ≥10 cigs/d | 2.57 (1.63–4.07) | 2.17 (1.23–3.84) |
| Model 2 | | |
| Any smoking | 1.42 (1.01–2.01) | 1.55 (1.04–2.30) |
| <10 cigs/d | 1.01 (0.65–1.57) | 1.60 (1.03–2.48) |
| ≥10 cigs/d | 2.15 (1.33–3.45) | 1.82 (1.00–3.32) |
| Model 3 | | |
| Any smoking | 1.31 (0.90–1.90) | 1.79 (1.19–2.71) |
| <10 cigs/d | 0.95 (0.60–1.50) | 1.81 (1.16–2.80) |
| ≥10 cigs/d | 1.94 (1.14–3.29) | 2.50 (1.30–4.83) |
| Model 4 | | |
| Any smoking | 1.20 (0.82–1.78) | 1.94 (1.25–2.99) |
| <10 cigs/d | 0.87 (0.54–1.40) | 1.97 (1.27–3.07) |
| ≥10 cigs/d | 1.73 (1.00–3.01) | 2.84 (1.37–5.88) |
| Model 5 | | |
| Any smoking | 1.24 (0.84–1.83) | 1.93 (1.25–2.99) |
| <10 cigs/d | 0.89 (0.56–1.43) | 1.97 (1.27–3.08) |
| ≥10 cigs/d | 1.77 (1.02–3.08) | 2.84 (1.36–5.94) |
| Model 6 | | |
| Any smoking | 1.22 (0.83–1.80) | 1.95 (1.27–3.02) |
| <10 cigs/d | 0.89 (0.56–1.42) | 1.99 (1.28–3.11) |
| ≥10 cigs/d | 1.80 (1.04–3.12) | 2.95 (1.42–6.14) |

*Note: Reference group = no smoking. ADHD = attention-deficit/hyperactivity disorder.*

[a]*Model 1 is adjusted for birth year only; model 2 is adjusted for birth year, sex, maternal age, parity, and maternal psychiatric disorders; model 3 is adjusted for all the variables in model 2 plus socioeconomic status, consumption of beer, wine, spirits, and coffee, smoking hashish, and binge drinking; model 4 is adjusted for all the variables in model 3 plus partner smoking; model 5 is adjusted for all the variables in model 4 plus gestational age and birth weight as categorical variables; model 6 is adjusted for all the variables in model 4 plus gestational age and birth weight as continuous variables.*

[b]*Excluding participants with ADHD.*

maternal smoking increased risk for TS/CT with *any* non-ADHD psychiatric comorbidity, with an IR of 0.20 (95% CI = 0.15–0.26) in the presence of prenatal maternal smoking, compared to an IR of 0.11 (95% CI = 0.09–0.14) in the absence of prenatal maternal smoking. Adjusted analyses demonstrated that both light smoking (aHR = 1.81, 95% CI = 1.16–2.80) and heavy smoking (aHR = 2.50, 95% CI = 1.30–4.83) increased risk for TS/CT with any non-ADHD psychiatric comorbidity. Similar findings were observed under all models.

PS-adjusted analysis (using either continuous or categorical PS) yielded results similar to those of the above models, although the aHR for the association between heavy smoking and TS/CT with any non-ADHD psychiatric comorbidity was as high as 3.70 to 4.25 (see Tables S5 and S6, available online).

## DISCUSSION

The DNBC is a unique and powerful resource for relating maternal factors with subsequent medical and health outcomes. The prospectively collected quantitative data in the DNBC have shown a relation between prenatal maternal smoking and ADHD,[21] low birth weight,[35] and childhood obesity.[36] In our study, heavy maternal prenatal smoking was associated with an increased risk for TS/CT (and tic disorders more broadly) in the offspring, with a strong association with complex presentations of TS/CT, that is, TS/CT with comorbid psychiatric diagnosis. Importantly, both multivariable and PS-adjusted Cox models showed that the observed associations could not be attributed to many potential confounders such as SES, maternal psychiatric history, maternal use of alcohol, caffeine, or hashish during pregnancy, or partner smoking. Maternal light smoking was not associated with an increased risk for TS/CT in the offspring, consistent with a dose-dependent relationship between exposure and risk.

To further investigate whether maternal or partner smoking has differential effects on risk, in exploratory analyses (see Table S7, available online), cohort families were divided into 4 groups based on whether maternal (M) smoking or partner (P) smoking was present (+) or absent (−). This resulted in smaller groups and thus reduced power; however, the point estimates for risk were higher (1.3) for M+P− families compared with M-P+ families (1.0), suggesting an important and unique role for maternal smoking in risk for TS/CT and related disorders. A previous DNBC study associated ADHD and both maternal and paternal prenatal smoking.[21] Although exploratory, our results for TS/CT with comorbid ADHD are consistent with those results.

Significantly, although prenatal maternal smoking has been linked to low birth weight and preterm birth,[35,37,38] our adjusted analyses indicate that the association between prenatal maternal smoking and TS/CT is unlikely to be mediated by the effect of smoking on birth weight or gestational age and appears to have a more direct role in increasing TS/CT risk.

We observed similar trends with pediatric-onset OCD compared to TS/CT; however, the smaller number of OCD cases resulted in lower power to determine significant findings. As pediatric-onset and adult-onset OCD may have different pathophysiology, symptomatology, and course,[39] examining maternal smoking and both pediatric-onset and adult-onset OCD risk in larger cohorts would be of interest.

Our study extends previous research in 2 important ways. First, our study is the largest to date to investigate the association between prenatal maternal smoking and childhood risk for TS/CT and OCD, and to suggest a dose–response relationship in the association of prenatal maternal smoking with tic disorders. Our finding that heavy maternal smoking is associated with elevated TS/CT risk contrasts with a previous population-based study (based on

122 TS/CT cases, using maternal self-report questionnaires) that found no step-wise association between smoking dosage and TS/CT risk,[26] and a previous registry-based study that found no association between prenatal maternal smoking and TS,[16] although smoking behavior was not stratified by quantity smoked.

Second, our study confirms previous work that prenatal maternal smoking (particularly heavy smoking) increases risk for TS with comorbid ADHD.[13,16,24,27] Importantly, however, we show that the risk relationship is not limited to ADHD but, rather, that prenatal maternal smoking increases risk for complex presentations of TS/CT (TS/CT plus any comorbid psychiatric disorder).

Interestingly, recent studies with a genetically sensitive design suggest that the association between maternal smoking and some neuropsychiatric disorders (e.g., ADHD and ASD) might reflect shared risk mechanisms rather than a causal relationship.[40,41] It is possible that the observed association between maternal smoking and complex TS/CT represents, at least partially, a shared inheritance. Although we and others adjust for confounding effects of maternal psychiatric disorders, risk for residual and/or unrecognized effects cannot be ruled out.[42]

Several mechanisms might explain a possible direct association between prenatal maternal smoking and higher risk for TS/CT, both with and without comorbid psychiatric diagnoses. Prenatal nicotine exposure affects several aspects of fetal brain maturation, including neuronal migration, proliferation, and differentiation.[43] Exposure of the fetal brain to nicotine alters the development of multiple neurotransmitter systems including dopamine, the most consistently altered neurotransmitter in studies of TS/CT.[44,45] In addition, prenatal exposure to smoking might cause subtle structural changes in the striatum, thalamus, thalamocortical fibers, and cortex.[46-48] Abnormalities in these brain circuits have been implicated in the pathophysiology of TS/CT and its common comorbidities, including OCD, ADHD, and ASD.[45,49-54] Immune dysregulation, which has also been linked to risk for TS/CT, may be another mechanism through which maternal smoking affects fetal brain development.[18,19,55]

Key strengths of our birth cohort study include detailed prospective data collection and large sample size. We were able to consider the effect of smoking dosage, as well as important potential confounders, on risk for illness in a robustly designed study.

Our study also has several limitations. First, exposure was determined using maternal self-report, albeit in a prospective and contemporaneous interview format (and responses to smoking-related questions were rated as highly trustworthy). Recent molecular analyses of neonatal blood spots provide strong support for the validity of maternal self-report of smoking (J. Mill, Buxbaum, Schendel, Parner, and Reichenberg, unpublished, 2016). Regarding diagnostic outcomes used in this study, the Danish Psychiatric Central Register and the Danish National Hospital Register include health care–seeking individuals and may not capture those with milder presentations.

Second, although we adjusted for many confounding factors, we did not have access to paternal psychiatric history through the DNBC, a factor that could affect our analyses; however, a previous study has shown that paternal psychiatric history is unlikely to affect the association between maternal smoking and TS/CT.[16] In addition, although we were able to adjust for low birth weight and preterm birth, we could not adjust for other birth complications that have been previously suggested to be associated with maternal smoking as well as with risk for TS/CT.[15,26] Similarly, less severe maternal psychiatric disorders (including milder mood and anxiety disorders) may go unrecorded in some cases.

Third, although we had an 18% rate for missing data, distribution of exposures and outcomes did not change after exclusion of missing data, and thus they appear unlikely to threaten the external validity of our study.

Finally, it is important to note that diagnoses of TS/CT and OCD have yet to be fully validated in Danish registries, although the validity of tic disorders and OCD in similar systems, such as the Swedish national registries, is strong.[56]

In conclusion, our results show that heavy prenatal maternal smoking is associated with elevated risk for TS/CT as well as for TS/CT with comorbid psychiatric disorders. These findings may point to a biological pathway that links prenatal tobacco exposure and altered brain development. This possibility can be further investigated in epidemiological studies that simultaneously address the roles of genetic background, social environment, and in utero tobacco exposure. &

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