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). *$p < .05$.