

Prenatal and Perinatal Morbidity in Children with Tourette Syndrome and Attention-Deficit Hyperactivity Disorder

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ABSTRACT: *Objective:* Tourette syndrome (TS) and attention-deficit hyperactivity disorder (ADHD) are frequently seen in combination, though the cause of comorbidity is uncertain. Low birth weight is a known risk factor for ADHD. The objective of the study was to assess the association between pre- and perinatal morbidity and the comorbid diagnosis of ADHD in children with TS. *Method:* A nested case-control study of children evaluated for TS at a subspecialty clinic was performed. Cases were defined as children with TS and ADHD; controls had TS without ADHD. Exposure to pre- and perinatal morbidity was assessed using demographic information booklets completed by parents before the diagnostic interview. *Results:* Three hundred fifty-three children were included, 181 cases and 172 controls. Children with TS and ADHD had a greater odds of exposure to low birth weight status, prematurity, breathing problems, and maternal smoking compared with children with TS only. A multivariable logistic regression model found adjusted odds ratios for the comorbid diagnosis of TS and ADHD of 2.74 (95% CI 1.03–7.29, $p = .04$) in children born low birth weight, and of 2.43 (95% CI 1.23–4.82, $p = .01$) for children exposed to maternal smoking. *Conclusion:* In children with TS, there is a greater odds of comorbid ADHD in children born with low birth weight or with exposure to maternal smoking. The commonality of risk factors for ADHD only and tic-related ADHD supports a common underlying neurobiology. Women with fetuses at risk for TS should avoid smoking and preventable causes of low birth weight to minimize the risk of comorbid ADHD.

(*J Dev Behav Pediatr* 30:115–121, 2009) **Index terms:** Tourette syndrome, attention deficit hyperactivity disorder, perinatal morbidity, case control study.

Tourette syndrome (TS) is a childhood onset neuropsychiatric disorder, consisting of multiple motor and one or more vocal tics persisting for greater than 1 year.¹ TS seems to be an inherited disorder, though the exact gene or mode of inheritance is yet to be determined.² Attention-deficit hyperactivity disorder (ADHD) is a disruptive behavioral disorder with onset in childhood. The core features of ADHD include an inability to maintain focused attention, a lack of control over impulsive behavior, and a generalized behavioral overactivity. Symptom onset must occur before the age of 7, with impairment from the symptoms present in 2 or more settings.¹ There is evidence for both genetic and nonshared environmental influences for the development of ADHD.³

TS is frequently complicated by the presence of comorbid psychiatric disorders, of which ADHD is the most prevalent. Community-based studies have yielded rates of comorbid TS and ADHD of 38%,⁴ whereas clinic-based

studies yield higher rates of 60%.⁵ As these rates are much higher than expected due to chance alone, the reason for the association between these 2 disorders has been the subject of much debate and discussion in the medical literature.

The clinical implications of a comorbid diagnosis of ADHD in children with TS are significant. The risk for aggressive and delinquent behavior in children with TS is posed largely by the presence of ADHD,⁶ and the greatest independent predictor of psychosocial quality of life in children with TS is ADHD symptom severity.⁷ In contrast, the presence of a tic disorder has limited impact on ADHD outcome.⁸

Although studies have supported an association between prematurity, low birth weight and the development of ADHD, these factors do not seem to increase the risk of TS. Some studies have suggested an increased rate of maternal complications in patients with TS,^{9,10} but have not demonstrated an association between gestational age or birth weight and the diagnosis of TS. Longitudinal studies of low birth weight babies have not shown an increased risk for TS.¹¹ Small studies suggest that being a lower birth weight twin,¹² maternal stress, and nausea/vomiting during pregnancy¹³ are associated with increased tic severity but this has not been confirmed in a larger study, where only maternal smoking was significantly associated with tic severity.¹⁴ This is in contrast to a consistent literature docu-

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menting an association between prematurity, birth weight, and maternal smoking and ADHD.^{15,16}

Considering the evidence presented—the frequency of these disorders in the population alone and in combination, the uncertainty regarding the etiology of their comorbidity, the impact of comorbid ADHD on behavior and psychosocial quality of life, and the evidence supporting the association between pre- and perinatal factors and ADHD only, this study has relevance and importance. Evaluating the association between pre- and perinatal morbidity and a comorbid diagnosis of ADHD in children with TS will promote further understanding of the relationship between these 2 disorders, and provide the opportunity for interventions aimed at minimizing these risk factors in pregnant women at risk genetically for TS to prevent a comorbid ADHD outcome.

METHODS

This study was performed using a nested case-control study design. Cases and controls were selected and identified from the cohort of children seen at the Tourette Syndrome (TS) Neurodevelopmental Clinic at the Toronto Western Hospital. Children are routinely evaluated for the diagnosis of TS, attention-deficit hyperactivity disorder (ADHD), and obsessive compulsive disorder, as well as the presence of other neuropsychiatric comorbidities. Diagnosis is based on a structured diagnostic interview and fulfillment of DSM-IV-TR criteria.

All children referred to the clinic have a demographic information booklet completed by their parents before their initial diagnostic consultation. This booklet contains several questions regarding the history of the pregnancy and perinatal period. Information regarding the exposures of interest was collected by a retrospective review of the demographic information booklet. Information about the clinical diagnosis was taken from the patient's clinic chart. In addition, obsessive compulsive disorder status, other neuropsychiatric diagnoses, family history of ADHD, and birth weight and gestational age as elicited by the physician in the diagnostic assessment were obtained from the clinic chart records. Birth weight was obtained both from the demographic information booklet and from the consultation letters so the reproducibility of maternal reporting of birth weight could be assessed.

Patients included in the study were younger than 18 years of age at the time of their initial diagnostic consultation, and had a diagnosis of TS. All new case and control patients from the cohort seen from 2004 to 2006 who fulfilled inclusion criteria were included.

Patients for whom a demographic information booklet was not found or was incomplete were excluded from the study. Patients with a comorbid diagnosis of Autism, Asperger's syndrome, autistic spectrum disorder, or pervasive development disorder were excluded from the study. Patients without a clinical diagnosis of TS, or who did not complete the diagnostic interview were excluded from the study.

Cases were defined as children in the cohort fulfilling DSM IV-TR criteria for TS and ADHD. Controls were defined as children in the cohort with a DSM-IV-TR diagnosis of TS without ADHD. The primary exposure assessed was birth weight, and the primary outcome assessed was the diagnosis of comorbid TS + ADHD. The secondary exposures assessed were premature birth, small for gestational age status, breathing problems at birth, maternal hypertension, operative delivery, and prenatal street drug use. Small for gestational age status was determined by taking the birth weight and gestational age of the baby and comparing the value to a population-based Canadian reference¹⁷ for small for gestational age cutoffs (10th percentile).

Two group comparisons were assessed using the χ^2 test of independence for nominal data at the significance level of 0.05. Adjusted odds ratios were calculated with 95% confidence intervals. Although the primary exposure, birth weight, was recorded as a continuous variable, weight was then categorized as less than 2500 g or greater than 2500 g. Infants weighing less than 2500 g are defined as low birth weight according to the medical literature.¹⁸ The secondary exposures were recorded as dichotomous variables (yes/no), with the exception of gestational age, which was recorded in weeks as well as dichotomized into premature birth (less than 37 completed weeks of gestation) or term birth (greater than 37 weeks completed weeks of gestation).

Two-sample *t* tests were performed to assess for a difference in the mean birth weight in grams between case and controls groups, and to assess if there was a difference in the mean gestational age in weeks between case and control groups.

An adjusted odds ratio with 95% confidence interval was calculated for the diagnosis of comorbid TS + ADHD using multivariable logistic regression analyses. The selection of variables included in the model was based on univariate analysis of independent variables, and the clinical decision to adjust for potential confounders. Maternal smoking, alcohol use, gender, and family history of ADHD were included in the model as potential confounding variables. Collinearity between exposure variables was assessed for using the test for tetrachoric correlation. Variables with correlations greater than 0.8 were considered collinear and were not included in the same model.

To determine if a logistic regression model provided a good fit for the data, the Hosmer-Lemeshow goodness of fit test was used. The model was considered well calibrated and fitted the data well if the Hosmer-Lemeshow test statistic was not statistically significant ($p > .05$).

The sample size necessary to determine an association between our primary exposure, low birth weight, and outcome of comorbid TS + ADHD was calculated. A reference proportion of 6% was used for the rate of low birth weight babies (less than 2500 g) in the control population, based on data from Toronto Public Health on the incidence of low birth weight babies in the city of

Toronto.¹⁹ Choosing a meaningful difference in the proportion of low birth weight babies of 0.10 between the case and control populations, with a power of 0.8, and an alpha of 0.05 with 2 sides, it was determined that at least 153 subjects per group were needed.

The study was approved by the Research Ethics Board at the hospital and university level.

RESULTS

A total of 445 children was reviewed for the study. Of these 445 patients, 92 were excluded for failure to meet the inclusion criteria. Of the remaining 353 patients, 181 were cases (Tourette syndrome [TS] + attention-deficit hyperactivity disorder [ADHD]) and 172 were controls (TS). The average age at data collection was 9.9 years, with a range of 5 to 17 years, and a median age of 10. The sample was predominantly male (80.2%). Only 12.8% of the sample met diagnostic criteria for obsessive compulsive disorder at the time of their initial consultation. The rate of comorbid obsessive compulsive disorder is generally reported at 30% in clinic populations.⁵ The lower than expected rate of obsessive compulsive disorder comorbidity is due to the age of our sample at the time of diagnosis. Obsessive compulsive disorder symptoms typically peak at a later age than TS symptoms, usually between 12 and 13 years of age.²⁰ Characteristics of the study population are summarized in Table 1.

A total of 92 patients was excluded from the study. Thirty-eight patients were excluded because the demographic information booklet was incomplete or lost. The clinical characteristics of these patients did not differ from included patients with respect to demographic variables (mean age, 10.8 years; 82% male). Thirty-one patients were excluded because of a comorbid autistic spectrum disorder. Twenty patients were excluded because they did not have a diagnosis of TS, and 3 patients were excluded because they did not complete the diagnostic assessment.

Table 1 compares the demographic characteristics of case (TS + ADHD) versus control (TS) patients. There were no significant differences between case and control patients with respect to these variables with the exception of smoking. There was a greater proportion of

maternal smoking in the case group compared with the control group as assessed by the χ^2 test.

The child's birth weight was obtained and recorded by the study physician in the initial consultation letter (in addition to the birth weight recorded in the demographic information booklet) in 309 of the 353 (87%) study participants. The birth weight obtained and recorded by the study physician differed from the demographic information booklet birth weight recorded by the mother in 7 of the 309 (2%) participants. In none of these 7 cases was the margin of difference between values sufficient to affect placement of a child into or out of the low birth weight category. When the birth weight differed, the birth weight recorded by the mother in the demographic information booklet was used.

Using the χ^2 test, univariate odds ratios were calculated for the primary and secondary exposures of interest in the study. The odds of low birth weight status, premature birth, breathing problems at birth, and maternal smoking were all significantly higher in cases (comorbid TS + ADHD) compared with controls (TS without ADHD) (Table 2). The odds of exposure to small for gestational age status, maternal hypertension, operative delivery, prenatal street drugs, and maternal alcohol use were not significantly different between cases and controls. Looking specifically at girls ($n = 70$ subjects), only the odds of premature birth was significantly higher in cases than controls (OR 2.50, 95% CI 1.88–3.42).

A two-sample t test comparing the mean birth weight between case and control groups revealed that on average, children with TS + ADHD were 109.5 g lighter at birth than children with TS, however, this result was not statistically significant ($p = .09$).

The relationship between diagnosis and gestational age could not be examined using a two-sample t test, as the gestational age variable was not normally distributed. Therefore, the Wilcoxon two-sample test was used to assess if there was a difference in gestational age based on case or control status of the subject. This analysis revealed a significant difference in gestational age between groups by the two-sided t approximation ($p < .01$), with children with TS + ADHD born an average of 4.5 days earlier than children with TS only.

Table 1. Study Population Demographic Characteristics

	Total Sample ($n = 353$), n (%)	TS + ADHD ($n = 181$), n (%)	TS ($n = 172$), n (%)	p value (cases vs controls)
Mean age	9.93 \pm 2.80	10.0 \pm 2.8	9.9 \pm 2.8	NS
Male gender	283 (80.2)	151 (83.4)	132 (76.7)	NS
Comorbid OCD	45 (12.8)	22 (12.2)	23 (13.4)	NS
Other comorbid neuropsychiatric diagnosis (excluding ADHD and OCD)	37 (10.5)	20 (11.1)	17 (9.9)	NS
Family history of ADHD	42 (11.9)	27 (14.9)	15 (8.7)	NS
Maternal smoking	47 (13.3)	33 (18.2)	14 (8.1)	$p < .01$
Maternal alcohol exposure	65 (18.4)	31 (17.1)	34 (19.8)	NS

TS, Tourette syndrome; ADHD, attention-deficit hyperactivity disorder; OCD, obsessive compulsive disorder; NS, not significant.

Table 2. Unadjusted ORs for Primary and Secondary Exposures in Cases vs Controls

Exposure	n/N Cases	n/N Controls	OR	95% CI	<i>p</i>
Low birth weight (less than 2500 g)	20/181	6/172	3.44	1.34–8.77	<.01
Premature birth (less than 37 wks)	22/181	6/172	3.83	1.51–9.69	<.01
Small for gestational age (less than 10th percentile)	28/181	24/172	1.13	0.63–2.04	.69
Breathing problems at birth	25/181	10/172	2.60	1.21–5.58	.01
Maternal hypertension	12/181	11/172	1.04	0.44–2.42	.93
Operative delivery	64/181	57/172	1.10	0.71–1.71	.66
Prenatal street drug use	2/181	0/172	Incalculable		
Maternal smoking	33/181	14/172	2.51	1.30–4.89	<.01
Maternal alcohol use	31/181	34/172	0.83	0.49–1.44	.52

Adjusted odds ratio were calculated for the diagnosis of comorbid TS + ADHD according to the presence of the primary or secondary exposures, which were significant on univariate analysis (low birth weight, premature birth, and breathing problems at birth). Maternal smoking, maternal alcohol use, gender, and family history of ADHD were included in the model as possible confounders. A model combining low birth weight, premature birth, and breathing problems at birth could not be constructed due to significant collinearity between low birth weight status and premature birth (tetrachoric correlation 0.91). The decision was made, therefore, to omit premature birth from the multivariable model, and include low birth weight and breathing problems of birth. This decision was based on the use of low birth weight status as the primary exposure of interest in this study, and reinforced by the higher reproducibility of maternal reporting of birth weight in comparison with gestational age.²¹

According to the multivariable model (Table 3), both low birth weight and maternal smoking were associated with a significantly increased odds of comorbid TS + ADHD. The remaining covariates, breathing problems at birth, maternal alcohol use, gender, and family history of ADHD were not significantly associated with higher odds of a comorbid diagnosis of TS + ADHD. Of note,

Table 3. Adjusted ORs for Comorbid TS + ADHD According to Multivariable Logistic Regression Model

Variable	OR	95% CI	<i>p</i>
Low birth weight <2500 g	2.74	1.03–7.29	.04
Breathing problems at birth	1.95	0.87–4.37	.10
Maternal smoking	2.43	1.23–4.82	.01
Maternal alcohol	0.81	0.46–1.41	.45
Female gender	0.68	0.40–1.18	.17
Family history ADHD	1.75	0.88–3.48	.11

Likelihood ratio $Pr > \chi^2$ 0.0006.

Hosmer and Lemeshow Goodness of Fit Test $Pr > \chi^2$ 0.6813.

TS, Tourette syndrome, ADHD, attention-deficit hyperactivity disorder.

replacement of the low birth weight covariate with premature birth resulted in a similar model, with an odds ratio of comorbid TS + ADHD of 2.93 (95% CI 1.1–7.77, $p = .03$) for children born premature.

Goodness of fit was evaluated by the Hosmer-Lemeshow statistic (deciles of risk). The nonsignificant $\chi^2 = 3.12$, $df = 5$, $pr > \chi^2 = 0.6813$ suggests a good model.

DISCUSSION

This study is the first to examine as a primary objective the relationship between pre- and perinatal morbidity in children with comorbid Tourette syndrome (TS) + attention-deficit hyperactivity disorder (ADHD) compared with those with TS only. Our results confirm that similar to children with ADHD only, children with TS + ADHD have a higher odds of exposure to pre- and perinatal morbidity. The commonality of risk factors for the development of ADHD only and tic-related ADHD suggests a similar underlying neurobiological deficit in the origin of both ADHD only and tic-related ADHD.

Results of the univariate analysis revealed a significant relationship between case status and low birth weight, premature birth, breathing problems at birth, and maternal smoking. In comparison with case-control studies in patients with ADHD only, the odds ratios were quite similar. In a case-control study by Mick et al,²² the unadjusted OR for exposure to low birth weight status (less than 2500 g) was 3.27 (95% CI 1.18–9.01, $p = .016$) for children with ADHD compared with normal controls. A separate study by the same authors (2002) evaluated the association between maternal smoking and ADHD, and reported the odds for exposure was 2.63 (95% CI 1.44–4.8, $p = .0011$) in children with ADHD compared with normal controls. The study of the relationship between premature birth and hyperkinetic disorder (ADHD combined type) by Linnert et al¹⁶ revealed an odds ratio of 2.12 (95% CI 1.65–2.74, $p < .0001$) for prematurity (less than 37 weeks) in children with hyperkinetic disorder compared with controls.

Univariate analysis did not find an association between small for gestational age status, maternal hyper-

tension, operative delivery, prenatal street drug use or maternal alcohol use, and diagnosis of comorbid ADHD. More than 90% of the children who were classified as small for gestational age in this study were small for gestational age at term, and therefore were over 3000 g at birth (small for gestational age at 40 weeks is defined as birth weight less than 3079 g for boys). Although the proportion of children who were small for gestational age was slightly higher in cases than controls, it did not reach statistical significance.

Maternal alcohol use was not associated with comorbid ADHD in our sample. This is in contrast to other case-control studies, where there has been a documented association between daily alcohol intake or binge drinking and ADHD.²³ The failure to demonstrate an association in our study is most likely due to the fact that all the mothers in our study who had alcohol during pregnancy had only occasional exposure, with none of the 65 (18.4%) women who drank during pregnancy disclosing a history of drinking alcohol "often." Therefore, alcohol exposure was minimal in our group, or not honestly reported. The rate of alcohol consumption in our study is similar to reported population estimates for alcohol consumption in pregnant women.²⁴

There was no association between a history of operative delivery and comorbid ADHD. This likely reflects the tendency for operative delivery to occur more and more as a part of routine practice, rather than being reserved for births where there is concern regarding fetal demise or asphyxia. Thirty-four percent of the children in the sample were born by operative delivery.

A family history of ADHD was more common in children with TS + ADHD (14.9%), compared with children with TS alone (8.7%), though this was not statistically significant. This is in keeping with genetic studies of patients with comorbid TS and ADHD, which suggest that TS and ADHD are independently inherited. If a proband does not have ADHD, then the frequency of ADHD in the relatives is not increased.²⁵ Given the heritability of ADHD, the presence of a family history of ADHD was controlled for in the logistic regression model.

After controlling for all possible relevant variables, the only variables significantly increasing the odds of a diagnosis of comorbid TS + ADHD were low birth weight and cigarette smoking. When prematurity is substituted for low birth weight, this is also significant. In the study of the relationship between pre- and perinatal events and TS severity by Mathews et al¹⁴, a separate logistic regression model was created for the presence of comorbid ADHD as a secondary outcome. Significant predictor variables for this model included both birth weight and the number of prenatal problems, corroborating the findings of this study.

Why are children with low birth weight at increased risk of ADHD? This is most likely due to the documented effects of preterm birth on the developing nervous system. Brain development during the second and third

trimesters is a complex, orchestrated series of events. Although neuronal migration is largely completed by 25 weeks gestation, glial migration continues after this time, followed by axonal and dendritic spine elaboration, synapse formation, myelination, and growth in cortical connectivity.²⁶ During this time, preterm infants are exposed to factors that could potentially damage or interfere with this maturational program, such as infection, chronic hypoxia, periodic hypotension, and undernutrition. Neuroimaging studies of children born preterm have documented alterations in brain structure, which are correlated with neurodevelopmental outcome.^{27,28}

Peterson et al²⁷ studied whether regional brain volumes differ between term and preterm children, and performed a case-control study of 25 8-year-old preterm children and 39 matched term controls. At age 8 years, regional cortical volumes in preterm children were significantly smaller than in term controls. These abnormalities were centered in the sensorimotor cortex but also involved the adjacent premotor, parieto-occipital, subgenual, and mid-temporal regions, and the cerebellum. Subcortical gray matter in the basal ganglia, white matter in the posterior corpus callosum, and cortical gray matter in the amygdala and hippocampus were also reduced more than expected from the overall reduction in brain volume. Cerebrospinal fluid volumes in the occipital and temporal horns of the cerebral ventricles were markedly increased in the preterm children. The volumes of these brain regions in the preterm cohort correlated significantly with IQ measures, and also correlated significantly with gestational age at birth, 5 minute Apgar scores, and intraventricular hemorrhage within 6 hours of birth. These findings suggest that perinatal events produce long-term disturbances in cerebral development and that these disturbances in turn account for cognitive deficits in preterm infants.

Imaging studies of children with ADHD have also revealed changes in brain structure associated with the disorder. According to a meta-analysis of structural imaging studies in patients with ADHD by Valera et al,²⁹ there is evidence for global reductions in brain volume for ADHD subjects compared with control subjects, with a standardized mean difference of 0.408 ($p < .001$). The regions most frequently assessed and showing the largest differences included cerebellar regions, the splenium of the corpus callosum, total and right cerebral volume, and the right caudate. Several frontal regions, including the prefrontal cortex and deep frontal white matter, assessed in only 2 studies also showed large significant differences in volume. Similar to children born preterm, children with ADHD demonstrate reductions in brain volume which may account for their clinical symptoms.

Why are children exposed to maternal smoking at increased risk of ADHD? Nicotine is readily transferred to the fetal compartment throughout pregnancy, and fetuses of mothers who smoke are exposed to relatively higher nicotine concentrations than their mothers.³⁰

Nicotine acts on the brain by its action on nicotinic acetylcholine receptors. The premature activation of nicotinic acetylcholine receptors by exogenous nicotine in the fetus is expected to have long-term consequences because of the role of these receptors in brain development. Neuronal nicotinic acetylcholine receptors play a role in neuronal migration, pathfinding, and growth cone direction. The neural growth cone is responsible for the guidance of axons and dendrites during brain development.³¹ In utero exposure to nicotine could impair the function of nicotinic acetylcholine receptors in their role in neuronal pathfinding, leading to permanent abnormalities that alter brain function later in life.³² Nicotinic acetylcholine receptors are intimately involved in the regulation of catecholaminergic function in the brain, therefore, noradrenergic and dopaminergic synaptic transmissions are also affected adversely by fetal nicotine exposure. Hypoactivity in noradrenergic and dopaminergic projections after fetal exposure to nicotine has been demonstrated in animal models.³³ Abnormalities in noradrenergic and dopaminergic systems have been implicated in ADHD, with current treatments directed at modulation of dopamine and noradrenergic neurotransmission.³⁴

Although the results of this study support the commonality of risk factors for the development of ADHD in children with and without TS, it does not explain the higher than expected rate of comorbidity seen in the 2 disorders, as not all of the children in our sample with ADHD were exposed to low birth weight or maternal smoking. The data do support the additive model of comorbidity, which states that children with comorbid TS and ADHD have the additive combination of 2 separate disorders. According to this model, the co-occurrence may be related to shared or overlapping risk factors for the 2 disorders. There is evidence to support the presence of shared/overlapping risk factors for TS and ADHD, especially in light of the volume reductions in cortical and subcortical structures previously mentioned in children with ADHD. Imaging studies in patients with TS have also demonstrated reductions in regional specific brain volumes, with smaller caudate nucleus volumes compared with controls.³⁵ The finding of altered regional specific brain volumes in both disorders suggests that TS and ADHD independently and together may relate to an abnormality in the development of the central nervous system.

The finding of an association among low birth weight, maternal smoking, and a comorbid diagnosis of TS + ADHD provides the opportunity for physicians to take a role in helping to prevent cases of comorbid ADHD in patients with TS. Pregnant women with a fetus at risk for TS by family history should be counseled regarding the odds of an additional diagnosis of ADHD if her baby is exposed to tobacco in utero, or if the child is low birth weight. Although low birth weight status may not be a modifiable risk factor in many cases, smoking is a lifestyle factor that can be modified with proper counseling.

The effect of comorbid ADHD on health and quality of life⁷ should be underscored to stress the importance of preventative measures for this potential outcome.

There are potential sources of bias in the study. First, this study was performed in a tertiary care clinic. Tertiary care clinic populations are a selective sample, with different disease characteristics than community-based samples—typically more severe or complicated disease. A potential measurement bias was the recall of birth and pregnancy-related events as reported by parents. There is the potential for differential misclassification or recall bias, with parents with children in the control group having different recall of events than parents with children who are cases. In this study, both cases and controls are diseased (both have TS), and information was obtained by identical methods in each group, thus minimizing recall bias. With regard to the accuracy of information about birth and pregnancy-related events, there is evidence in the literature to support the reproducibility and validity of maternal recall of these events even 30 years after the birth of the child.²¹ Correlation coefficients are particularly high for birth weight, smoking during pregnancy, and history of operative delivery. Subjects in this study were 9.9 years old on average thus the recalled events were relatively recent.

In conclusion, this nested case-control study of 353 children with TS demonstrates a higher adjusted odds ratio for the comorbid diagnosis of ADHD in children with a history of low birth weight, and exposure to maternal smoking. The commonality of risk factors for ADHD only and tic-related ADHD supports a common underlying neurobiology. Women with fetuses at risk for TS should receive counseling to avoid smoking and preventable causes of low birth weight in an effort to minimize the odds of a comorbid diagnosis of ADHD.

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