

Association between pre- and perinatal exposures and Tourette syndrome or chronic tic disorder in the ALSPAC cohort†

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Background

Tourette syndrome and chronic tic disorder are heritable but aetiologically complex. Although environment plays a role in their development, existing studies of non-genetic risk factors are inconsistent.

Aims

To examine the association between pre- and perinatal exposures and Tourette syndrome/chronic tic disorder in the Avon Longitudinal Study of Parents and Children (ALSPAC) prospective longitudinal pre-birth cohort.

Method

Relationships between exposures and Tourette syndrome/chronic tic disorder were examined in 6090 children using logistic regression.

Results

Maternal alcohol and cannabis use, inadequate maternal

weight gain and parity were associated with Tourette syndrome or Tourette syndrome/chronic tic disorder. Other previously reported exposures, including birth weight and prenatal maternal smoking, were not associated with Tourette syndrome/chronic tic disorder.

Conclusions

This study supports previously reported relationships between Tourette syndrome/chronic tic disorder and prenatal alcohol exposure, and identifies additional previously unexplored potential prenatal risk factors.

Declaration of interest

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Tourette syndrome is a phenomenologically heterogeneous neuropsychiatric disorder comprised of multiple motor and vocal tics that begin in early childhood and persist for at least a year.¹ Chronic tic disorder is a highly related condition, with similar clinical and demographic characteristics, consisting of either only chronic motor or only vocal tics, but not both.¹ Tourette syndrome has a population prevalence of 0.3–0.8%, whereas chronic tic disorder has a population prevalence of 1–3% (summarised in Scharf *et al*).² Although varying widely in clinical presentation and impact, these disorders can cause significant physical and psychosocial morbidity, particularly in childhood, and in severe cases produce lifelong disability.³ Tourette syndrome and chronic tic disorder have a strong genetic component, and together these disorders have among the highest familial recurrence risks of all neurodevelopmental disorders.⁴ However, despite the high heritabilities, twin and family studies have consistently demonstrated a significant role for additional, non-genetic factors in the pathogenesis of Tourette syndrome and chronic tic disorder.^{4–9}

Although a number of studies have examined the potential contributions of various non-genetic factors in the development of Tourette syndrome, the results have been conflicting, and the potential biological mechanisms for the identified risk factors are unclear.^{7,10–14} Maternal prenatal smoking, complications during pregnancy, birth weight, gestational age, Apgar scores at 5 min after birth, number of prenatal visits, younger maternal age and older paternal age have all been reported to be associated with risk of Tourette syndrome.^{12,14–17} Low birth weight, maternal nausea and vomiting in the first trimester, maternal life stress and maternal smoking during pregnancy have also been associated with increased tic severity.^{5,10,11} Lastly, increased rates of co-occurring

obsessive–compulsive disorder (OCD) or attention-deficit hyperactivity disorder (ADHD) in Tourette syndrome have been reported to be associated with low birth weight, forceps delivery and either coffee, alcohol or tobacco use during pregnancy.^{10,13} Unfortunately, for the most part, the environmental risk factors identified have not been replicated, although some association between prenatal maternal smoking and Tourette syndrome, tic severity or comorbid conditions such as OCD or ADHD has been identified in multiple studies.^{10,13,14,18,19}

Although providing hints about potential environmental contributors to chronic tic disorder, most of the previously published studies have methodological limitations, including retrospective study designs,^{5,10–13,16–18,20} the absence of a control group of individuals without Tourette syndrome/chronic tic disorder,^{5,10–13} limited number of variables examined^{5,10–18,20} and/or ascertainment of cases from specialty clinics rather than from the general population.^{5,10–14,16,18,20} The aim of this work, the largest prospective study to date, was to (a) attempt to replicate the previous observational associations between tic disorders and non-genetic risk factors, and (b) examine a number of additional, previously unexplored, potential risk factors for tic disorders using the Avon Longitudinal Study of Parents and Children (ALSPAC). We hypothesised, based on the previous literature, that maternal prenatal smoking and alcohol use, excessive vomiting during pregnancy, complications of delivery (e.g. assisted delivery) and low birth weight or young gestational age at birth would be associated with Tourette syndrome and chronic tics in this population.

Method

Participants

The ALSPAC is an ongoing, prospective, population-based, pre-birth cohort study of all children born to 14 541 pregnant women

†See editorial, pp. 6–8, this issue.

resident in Avon, UK (representing 85% of the eligible population), with expected dates of delivery between 1 April 1991 and 31 December 1992.^{21,22} Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the local research ethics committees. The characteristics of the population-based ALSPAC sample and its generalisability have been previously reported^{21,22} and are summarised in the online supplement.

Outcome measures

Data were collected prospectively through maternal questionnaires, supplemented by obstetric and paediatric medical records that began at the time of enrolment and continued throughout pregnancy and at least yearly thereafter (see the online supplement). The primary outcome measures were diagnoses of Tourette syndrome or chronic tic disorder at age 13 or 14, based on DSM-IV-TR criteria¹ and were derived from the tic-related questions in the maternal questionnaires (summarised in Scharf *et al*).² Children with intellectual disability or autism were excluded from the sample. The final sample for this study consisted of 6090 children, with data available at ages 13–14, including 50 with Tourette syndrome, 72 with chronic tic disorder (for a total of 122 with either Tourette syndrome or chronic tic disorder) and 5968 with no tics (online Fig. DS1). To compensate for the relatively small sample sizes, two nested phenotypes were examined: Tourette syndrome and either Tourette syndrome or chronic tic disorder (Tourette syndrome/chronic tic disorder). Power calculations for representative predictor variables of interest are provided in the online supplement.

Predictor variables/exposures

Exposures of interest included prenatal and perinatal factors previously reported to be associated with either Tourette syndrome or tic severity in at least one previous study (confirmatory analyses), including parental age, maternal use of tobacco, alcohol or caffeine, and excessive nausea or vomiting during pregnancy. We also examined factors thought to be relevant to other related neurodevelopmental disorders such as ADHD (exploratory analyses), for example, gestational diabetes, maternal weight gain during pregnancy, and parity. For the confirmatory analyses, we examined the previously reported exposure (e.g. maternal nausea and vomiting) and the available related exposures (e.g. medication use for nausea/vomiting). Exposures were divided into five thematic categories: pre-existing parental fitness; early pregnancy exposures; toxic exposures; complications of pregnancy; and complications of delivery (see the online supplement for definitions of predictor variables). Pre-existing parental fitness included maternal and paternal age at child's birth, maternal baseline pre-pregnancy weight, pre-existing diabetes, maternal smoking before pregnancy, cannabis or alcohol use before pregnancy, and parity. Early pregnancy exposures included prior miscarriage or stillborn birth, hyperemesis of pregnancy, vomiting in the first trimester, and medications for vomiting in the first trimester. Toxic exposures were examined in the first, second and third trimesters separately, and included maternal influenza infection, substance use during pregnancy (nicotine, cannabis, alcohol, caffeine and illicit drugs) and partner smoking during and at the beginning of pregnancy. Complications of pregnancy included diabetes in pregnancy,²³ hypertensive disorder of pregnancy,^{24,25} vomiting or medications for vomiting in the second or third trimesters, placental weight (adjusted for birth weight), total maternal weight gain (both observed and predicted)²⁶ and twin or multiple births. Complications of delivery included method of delivery, Apgar scores of <7 at

5 min, inspired oxygen or mechanical ventilation at birth, resuscitation, pre-term labour or premature rupture of membranes, gestation of <37 or ≥42 weeks, and birth weight (in grams) were adjusted for gestational age. Maternal and paternal education and maternal marital status (ever married, and married at time of child's birth) were examined as potential confounders; as they were not significantly associated with Tourette syndrome/chronic tic disorder, they were not included as covariates in the analyses.

Analyses

Analyses were conducted in a step-wise process, using $P < 0.10$ for Tourette syndrome or Tourette syndrome/chronic tic disorder as the criterion for progression to the next step (online Fig. DS2). Variables with opposite direction of effects between Tourette syndrome and Tourette syndrome/chronic tic disorder were not retained for further analyses. The exception was maternal age, which was included in relevant multivariable models as a confounder. Univariable analyses were conducted using logistic regression, and any previously identified (confirmatory) predictor variables associated with Tourette syndrome or Tourette syndrome/chronic tic disorder at $P < 0.05$ were noted. Exploratory risk factors were only examined for association with Tourette syndrome or Tourette syndrome/chronic tic disorder after appropriate multivariable adjustment. In stage 2, all confirmatory or exploratory predictor variables that met the threshold criteria of $P < 0.10$ in univariable analysis were subjected to logistic regression including socioeconomic status (SES) as a covariate, as we have previously shown that low SES is associated with increased risk of Tourette syndrome/chronic tic disorder.²⁷ Additional covariates were also included as potential confounders (e.g. given the relationship between maternal age and substance use, maternal age was included in analyses of smoking, drug, or alcohol use).

As exposures within each thematic category might be related mechanistically (e.g. maternal vomiting may cause low weight gain during pregnancy), we examined the independent effects of each variable with $P < 0.10$ in the stage 2 analyses via multivariable regressions within their respective categories (e.g. maternal fitness, complications of pregnancy). For two co-linear variables, only the most strongly associated was included in the multivariable analyses. Finally, any variables or confounders that showed a trend for association ($P < 0.10$) in the category-specific multivariable models were examined in a final global model. Variables with $P < 0.05$ for either Tourette syndrome or Tourette syndrome/chronic tic disorder in the global model were interpreted as putative risk factors, with highest confidence placed in confirmatory variables, as well as exploratory variables with the same direction of effect for both nested phenotypes.

Results

Confirmatory analyses

Of the variables previously associated with increased Tourette syndrome/chronic tic disorder risk or severity, maternal age, paternal age, assisted delivery, maternal alcohol use in the last 2 months of pregnancy and a combined variable examining any maternal smoking, caffeine or alcohol use in the third trimester were associated with Tourette syndrome and/or Tourette syndrome/chronic tic disorder at $P < 0.05$ in unadjusted univariable analyses in the ALSPAC sample (see online Table DS1). Younger maternal and paternal ages were associated with increased odds of Tourette syndrome/chronic tic disorder ($P = 0.003$ and $P = 0.02$ respectively), but not with Tourette syndrome alone. Greater than two units of alcohol use per week

in the last 2 months of pregnancy was associated with an increased risk of Tourette syndrome alone ($P=0.03$) but not Tourette syndrome/chronic tic disorder, and any use of alcohol, tobacco or caffeine in the third trimester was associated with an increased risk of both Tourette syndrome and Tourette syndrome/chronic tic disorder ($P=0.05$ and $P=0.01$ respectively). Assisted delivery was associated with an increased risk of Tourette syndrome ($P=0.05$) but not Tourette syndrome/chronic tic disorder. No other previously reported risk factors were associated with Tourette syndrome/chronic tic disorder in the ALSPAC sample. Following adjustment for SES, only paternal age, maternal alcohol use in the last 2 months of pregnancy and maternal smoking, alcohol or caffeine use in the third trimester remained nominally associated with either Tourette syndrome or Tourette syndrome/chronic tic disorder (online Tables DS1 and DS2). In addition, although most associations decreased in strength after adjusting for SES, the association for medications for vomiting in the second trimester increased slightly (unadjusted odds ratio (OR) = 2.2; $P=0.07$; SES-adjusted OR = 2.31; $P=0.05$).

Exploratory risk factors

Four of the exploratory risk factors were nominally associated with either Tourette syndrome or Tourette syndrome/chronic tic disorder in the ALSPAC sample (Table 1). These risk factors included parity (for Tourette syndrome/chronic tic disorder), maternal cannabis use during pregnancy, particularly the last

2 months of pregnancy, for both Tourette syndrome and Tourette syndrome/chronic tic disorder, any illegal substance use in pregnancy (for Tourette syndrome) and less than adequate predicted weight gain during pregnancy. None of the other exploratory variables were associated with Tourette syndrome or with Tourette syndrome/chronic tic disorder.

Multivariable analyses

Individual variables with $P<0.10$ in SES-adjusted univariable analyses were examined jointly in multivariable models grouped into maternal fitness, complications of pregnancy and toxic exposures categories. Paternal age and maternal age were found to be co-linear, and therefore paternal age was excluded from subsequent models. Similarly, assisted delivery was not retained because the direction of association between this variable and Tourette syndrome and Tourette syndrome/chronic tic disorder were not consistent, suggesting that the identified trend for association was due to stochastic variation.

In the parental fitness category, only parity remained independently associated with Tourette syndrome/chronic tic disorder, with later births associated with lower risk (Table 2). For complications of pregnancy, less than adequate weight gain during pregnancy remained independently associated with Tourette syndrome and Tourette syndrome/chronic tic disorder. For toxic exposures, maternal alcohol and cannabis use in the last 2 months of pregnancy remained independently associated with

Table 1 Relationship of Tourette syndrome or chronic tic disorders to novel potential risk factors^a

Exposure	Tourette syndrome only				Tourette syndrome/chronic tic disorder				
	Unadjusted		Adjusted for SES		Unadjusted		Adjusted for SES		
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	
Maternal fitness									
Pre-pregnancy weight, kg	1.01 (0.98–1.04)	0.43			1.01 (0.99–1.02)	0.41			
Existing diabetes	0.37 (0.05–2.78)	0.34			0.46 (0.11–1.91)	0.29			
Maternal smoking before pregnancy	1.28 (0.68–2.38)	0.45	1.33 (0.69–2.57)	0.40	1.43 (0.97–2.13)	0.07	1.30 (0.85–1.99)	0.22	
Cannabis use before pregnancy	2.43 (0.86–6.84)	0.09	2.38 (0.83–6.81)	0.11	1.46 (0.64–3.73)	0.37	1.32 (0.56–3.08)	0.52	
Parity (second or later born v. first born)			0.60 (0.33–1.11)	0.10			0.62 (0.42–0.92)	0.02	
Early pregnancy exposures, prior miscarriage/stillborn	1.02 (0.51–2.05)	0.96			1.16 (0.75–1.79)	0.50			
Toxic exposures									
Influenza									
1st trimester	1.01 (0.36–2.82)	0.99			0.86 (0.41–1.77)	0.68			
2nd trimester	0.81 (0.19–3.35)	0.77			1.38 (0.67–2.86)	0.39			
3rd trimester	1.49 (0.46–4.84)	0.50			1.23 (0.54–2.84)	0.62			
Anytime in pregnancy	1.12 (0.52–2.39)	0.78			1.23 (0.76–1.97)	0.40			
Cannabis use in 1st trimester	4.74 (1.67–13.44)	0.003	4.68 (1.61–13.63)	0.005	1.87 (0.68–5.17)	0.23	1.68 (0.60–4.71)	0.32	
Cannabis use in last 2 months of pregnancy	6.37 (2.23–18.21)	0.001	6.00 (2.06–17.50)	0.001	3.11 (1.23–7.84)	0.016	2.82 (1.10–7.22)	0.03	
Any illegal drug use in pregnancy	4.28 (1.51–12.11)	0.006	4.20 (1.45–12.16)	0.01	2.10 (0.84–5.25)	0.11	1.93 (0.76–4.87)	0.17	
Partner smoked at start of pregnancy	1.50 (0.77–2.95)	0.24			1.24 (0.80–1.93)	0.33			
Pregnancy complications									
Diabetes in pregnancy	1.66 (0.51–5.38)	0.40			1.14 (0.46–2.81)	0.78			
Hypertensive disorder of pregnancy	0.98 (0.46–2.10)	0.96			1.01 (0.62–1.68)	0.95			
Placental weight (adjusted by birth weight), g	1.00 (1.00–1.00)	0.57			1.00 (0.99–1.00)	0.96			
Twin v. singleton	0.99 (0.14–7.26)	0.99			1.23 (0.39–3.92)	0.73			
Predicted weight gain^b									
Less than adequate	5.69 (1.99–16.25)	0.001	9.70 (2.71–34.73)	<0.0001	2.37 (1.22–4.60)	0.01	3.18 (1.52–6.65)	0.002	
More than adequate	1.98 (0.74–5.30)	0.17	2.95 (0.88–10.05)	0.09	1.27 (0.73–2.20)	0.40	1.54 (0.82–2.89)	0.18	
Complications of delivery									
Inspired oxygen	NA	NA			0.66 (0.09–4.82)	0.69			
Mechanical ventilation	NA	NA			1.35 (0.18–9.98)	0.77			
Resuscitation	0.28 (0.04–2.01)	0.21			1.15 (0.58–2.30)	0.69			
Preterm labour/PROM	NA	NA			1.64 (0.22–12.09)	0.63			

NA, no cases had the exposure; OR, odds ratio; PROM, premature rupture of membranes; SES, socioeconomic status.

a. Only variables where unadjusted P -value <0.10 were carried forward and adjusted. See online Table DS3 for numbers, means and percentage of cases and controls for each exposure.

b. Predicted using spline models and adjusted for gestational age.³⁴ Parity is defined as second born or later compared with first born as the reference category.

Table 2 Multivariable associations examining maternal fitness, pregnancy complications and potentially toxic exposures and Tourette syndrome/chronic tic disorder risk

	Tourette syndrome		Tourette syndrome/chronic tic disorder	
	OR (95% CI)	P	OR (95% CI)	P
Maternal fitness ^a				
Maternal age ^b	2.83 (0.81–9.95)	0.10	1.35 (0.47–3.86)	0.58
Parity ^c	0.65 (0.41–1.03)	0.07	0.72 (0.54–0.95)	0.02
Pregnancy complications ^d				
Less than adequate weight gain	4.55 (1.67–12.41)	<0.01	2.05 (1.05–4.00)	0.04
More than adequate weight gain	1.80 (0.72–4.47)	0.21	1.35 (0.81–2.29)	0.25
Medications for vomiting in 2nd trimester	1.13 (0.15–8.41)	0.91	2.13 (0.76–5.96)	0.15
Toxic exposures ^d				
Smoking in last 2 months of pregnancy	0.93 (0.48–1.80)	0.82	1.20 (0.82–1.77)	0.34
Alcohol use in last 2 months of pregnancy	1.57 (1.05–2.33)	0.03	1.24 (0.94–1.64)	0.12
Cannabis use in last 2 months of pregnancy	4.60 (1.28–16.62)	0.02	1.91 (0.56–6.49)	0.30

a. Mutually adjusted for other variables in the model and socioeconomic status level.
 b. Maternal age odds ratios (ORs) are denoted as change per 10 years of mother's age.
 c. Parity is defined as second born or later compared with first born as the reference category.
 d. Mutually adjusted for other variables in the model, maternal age and socioeconomic status level.

Tourette syndrome, but not with Tourette syndrome/chronic tic disorder. Maternal prenatal smoking, although not associated with Tourette syndrome or Tourette syndrome/chronic tic disorder in this sample, was included in the multivariable model because of the frequent association between smoking and alcohol use.²⁸

The final global model incorporated all of the pre- and perinatal variables that continued to show an association with Tourette syndrome or Tourette syndrome/chronic tic disorder in the multivariable analyses described above (Table 3). In this final model, which also included SES, maternal age and maternal smoking during pregnancy as confounders, only weight gain during pregnancy was consistently associated with both Tourette syndrome and Tourette syndrome/chronic tic disorder, with three- to sixfold increases in the odds of Tourette syndrome/chronic tic disorder or Tourette syndrome for less than adequate weight gain ($P=0.006$ for Tourette syndrome and $P=0.005$ for Tourette syndrome/chronic tic disorder). More than adequate weight gain also continued to show a trend for association with both outcome measures, with two- to threefold increases in risk for Tourette syndrome/chronic tic disorder and Tourette syndrome ($P=0.05$ and $P=0.08$ respectively). Similarly, alcohol and cannabis use in the last 2 months of pregnancy showed associations with Tourette syndrome (OR = 1.72, $P=0.01$ and OR = 4.30, $P=0.03$ respectively) and somewhat weaker associations with Tourette syndrome/chronic tic disorder in the same direction, whereas parity showed consistent association with both Tourette syndrome and Tourette syndrome/chronic tic disorder, although only the Tourette syndrome/chronic tic disorder association remained nominally significant in the final

model (OR = 0.57, $P=0.07$ for Tourette syndrome; OR = 0.66, $P=0.03$ for Tourette syndrome/chronic tic disorder).

Discussion

To our knowledge, this is the first comprehensive, large-scale, prospective study examining potential environmental risk factors for chronic tic disorder. Using an association threshold at $P<0.05$ for either Tourette syndrome or Tourette syndrome/chronic tic disorder in the global multivariable model and the same direction of effect for both nested phenotypes as our metric, the results of this study support an association between Tourette syndrome/chronic tic disorder and only one of the previously reported prenatal risk factors, alcohol use during pregnancy.^{10,15,17} We found no associations between Tourette syndrome/chronic tic disorder and the other prior candidate risk factors, most importantly, prenatal maternal smoking, low birth weight, gestational age and complications of delivery.^{5,7,10–13} We also found no consistent effect of parental age. Both younger maternal and paternal age were associated with Tourette syndrome/chronic tic disorder in the univariable analyses, but the direction of association changed when related variables (parity, maternal age and paternal age) were included in the multivariable analyses. This result, and the fact that parental age difference was not associated with Tourette syndrome/chronic tic disorder, suggests that the previous associations most likely reflect confounding and chance.

Of note, in our initial confirmatory analyses, five previously reported prenatal risk factors (maternal age, paternal age, assisted

Table 3 Multivariable associations examining all variables associated with Tourette syndrome or Tourette syndrome/chronic tic disorder in the parental fitness, complications of pregnancy and toxic exposures analyses^a

	Tourette syndrome		Tourette syndrome/chronic tics	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Maternal age	4.31 (0.86–21.67)	0.08	1.42 (0.31–6.43)	0.65
Parity	0.57 (0.31–1.05)	0.07	0.66 (0.45–0.97)	0.03
Less than adequate weight gain	6.66 (1.74–25.51)	<0.01	3.30 (1.43–7.65)	<0.01
More than adequate weight gain	3.03 (0.88–10.39)	0.08	2.03 (1.00–4.11)	0.05
Alcohol use in last 2 months of pregnancy	1.72 (1.13–2.62)	0.01	1.27 (0.95–1.69)	0.11
Smoking in last 2 months of pregnancy	0.99 (0.51–1.92)	0.97	1.25 (0.82–1.89)	0.30
Cannabis use last 2 months of pregnancy	4.30 (1.14–16.22)	0.03	2.01 (0.57–7.01)	0.28

a. All variables are mutually adjusted for one another and are adjusted for socioeconomic status. Smoking in the last 2 months of pregnancy is included in the model because of its strong association with alcohol and illicit drug use. Maternal age odds ratios are denoted as change per 10 years of mother's age. Parity is defined as second born or later compared with first born as the reference category.

delivery, maternal alcohol use, and maternal smoking, caffeine or alcohol use in the second trimester) were nominally associated with either Tourette syndrome or Tourette syndrome/chronic tic disorder in unadjusted univariable analyses. However, after adjustment for SES and other appropriate confounders, only maternal alcohol use in the last 2 months of pregnancy and maternal smoking, caffeine or alcohol use in the last trimester remained associated with Tourette syndrome or Tourette syndrome/chronic tic disorder. This finding suggests that the previously reported risk factors may have been confounded by unmeasured or incompletely measured variables, including SES. This highlights a major strength of the ALSPAC cohort, specifically the availability of extensive, detailed, prospectively collected, individual-level data to limit confounding.

We also identified three new potential prenatal risk factors for chronic tic disorders that to our knowledge have not been previously examined: cannabis use during pregnancy (independent of maternal alcohol and tobacco use), parity and inadequate weight gain during pregnancy (independent of the child's birth weight or gestational status). Of these, the strongest association was for inadequate weight gain during pregnancy, which was associated both with Tourette syndrome and with Tourette syndrome/chronic tic disorder in the final model.

In contrast to previous hypotheses (e.g. Mathews *et al*),¹⁰ the risk factors identified here do not fit easily into one mechanistic model (e.g. chronic hypoxia leading to basal ganglia damage *in utero*). Our findings, which remain strong even when variables from all three categories are simultaneously examined, suggest that there may be several types of environmental exposures that can interact with genetic susceptibility factors to increase the risk of chronic tic disorder. The mechanisms underlying these associations are not known, and some of the patterns observed in our study are not easily explained. For example, the associations between Tourette syndrome/chronic tic disorder, inadequate maternal weight gain and parity (being the first born child)²⁹ may suggest a less-than-optimal intra-uterine environment for the developing fetus, although the lack of association between Tourette syndrome/chronic tic disorder, birth weight and younger gestational age at birth stand somewhat in contradiction to this hypothesis.

The associations between prenatal maternal cannabis and alcohol use appear to be more straightforward, and may represent direct toxic effects on the developing fetal brain, such as is seen in fetal alcohol syndrome.³⁰ Although phenotypically distinct from Tourette syndrome, both fetal alcohol syndrome and Tourette syndrome are neurodevelopmental disorders that manifest in early childhood, and what is understood of the mechanisms behind the development of fetal alcohol syndrome³⁰ may serve as a starting point for the investigation of how toxic exposures such as alcohol and cannabis might lead to the development of chronic tic disorder as well.

Several of the risk factors identified here have also been suggested as risk factors for other neurodevelopmental disorders such as autism and ADHD.^{15,31,32} This is not surprising, given the high degree of phenotypic overlap between these disorders and the emerging evidence for shared aetiologies across neurodevelopmental disorders.³³ The aetiology of tic disorders and of other neurodevelopmental disorders is clearly complex, with both shared and unique environmental and genetic factors contributing to their development.

Limitations

The primary limitation of this study relates to sample size. Although it is the largest study reported to date examining potential environmental risk factors for chronic tic disorders, the number of children identified in the ALSPAC cohort with

Tourette syndrome or chronic tic disorder was fairly low. This is likely due to the low prevalence of these disorders in the general population and is an inherent limitation of population-based studies. The small number of cases leads to a relative lack of power, which may prevent the identification of true Tourette syndrome/chronic tic disorder risk factors that are uncommon in the study population (e.g. twin or premature births). We have compensated for this to the extent possible by examining two nested phenotypes, Tourette syndrome and Tourette syndrome/chronic tic disorder, and focusing on variables that showed the same direction of effect for both. This relative lack of power is counterbalanced by the many other advantages of this population-based cohort, most notably the prospective data collection, the comprehensiveness of the environmental risk variables available for study, and the depth, complexity and precision of the data (e.g. the use of multiple informants as well as the availability of medical and education records). This advantage has allowed us to definitively exclude proposed risk factors such as low birth weight from having a moderate or large effect on Tourette syndrome/chronic tic disorder risk, at least in the ALSPAC sample, as this was precisely determined from obstetric records for all children in the study.

The small sample size also does not allow us to differentiate between false positives and differential association between Tourette syndrome (the more extreme phenotype) and Tourette syndrome/chronic tic disorder (less extreme). Some of the putative risk factors in the global model had stronger associations with Tourette syndrome than with Tourette syndrome/chronic tic disorder (e.g. maternal alcohol and cannabis use), whereas for others (e.g. parity), the effect was stronger for Tourette syndrome/chronic tic disorder than for Tourette syndrome. However, the directions of effect for Tourette syndrome and Tourette syndrome/chronic tic disorder were consistent for all of these variables, suggesting that the associations are less likely to be due to chance. Similarly, we cannot exclude the possibility that our associations may reflect residual confounding despite our best attempts to adjust for potential confounders. This is an inevitable limitation of observational analyses.

Implications

This study suggests several potentially modifiable environmental risk factors for Tourette syndrome and chronic tic disorder. One previously reported risk factor, alcohol use in the third trimester of pregnancy, remained significant in the final adjusted model and could thus be considered a replicated prenatal risk factor for Tourette syndrome and chronic tic disorder. Others are novel and require replication in other cohorts. As parallel efforts to identify Tourette syndrome susceptibility genes in large cohorts are also underway, a logical next step would be to examine the interaction between environmental factors such as prenatal maternal alcohol use and future definitive Tourette syndrome genetic susceptibility alleles. With the extensive environmental and phenotypic data, along with genetic data, the ALSPAC cohort provides an excellent opportunity for examinations of gene \times environment interactions such as these in the future.

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