Parental Smoking During Pregnancy and ADHD in Children: The Danish National Birth Cohort

WHAT'S KNOWN ON THIS SUBJECT: Prenatal maternal smoking has been associated with attention-deficit/hyperactivity disorder in children, but the causal nature of this association is unclear. Controlling for the association with paternal smoking has been inconsistent.

WHAT THIS STUDY ADDS: Women who used nicotine replacement also had children with a higher risk of attention-deficit/hyperactivity disorder. Mother's smoking behavior appears more important than father's, suggesting a possible causal effect of nicotine exposure or factors related to maternal nicotine dependence.

abstract

FREE

BACKGROUND: Prenatal maternal smoking has been associated with attention-deficit/hyperactivity disorder (ADHD) in children, but the causal nature of this association is still under scrutiny. We examined the association with maternal smoking and nicotine replacement use during pregnancy, using association with paternal smoking as a marker of potential genetic or social confounding.

METHODS: We included 84 803 singletons who participated in the Danish National Birth Cohort. Information on parental smoking was reported by the mothers during pregnancy. Children with ADHD were identified from the Danish Psychiatric Central Register, the Danish National Patient Register, and the Register of Medicinal Product Statistics by the *International Classification of Diseases, 10th Revision* diagnosis or medication. We also used hyperactivity/inattention score of the parent-reported Strengths and Difficulties Questionnaire, included in the 7-year follow-up of the National Birth Cohort.

RESULTS: Maternal and paternal smoking during pregnancy were associated with an elevated risk of ADHD defined by hospital diagnosis, medication, and hyperactivity/inattention score, but the association was stronger for maternal smoking than for paternal smoking. Compared with children born to nonsmoking mothers and smoking fathers, children born of smoking mothers and nonsmoking fathers had a higher risk of ADHD (adjusted hazard ratio = 1.26; 95% confidence interval, 1.03 to 1.53). We also saw a higher risk of ADHD in children of mothers who used nicotine replacement during pregnancy.

CONCLUSIONS: Our findings indicate that the association between prenatal maternal smoking and ADHD may overestimate a causal link, but nicotine exposure or related factors may still play a causal role. *Pediatrics* 2014;134:e382–e388

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KEY WORDS

attention-deficit/hyperactivity disorder (ADHD), maternal smoking, paternal smoking, Strengths and Difficulties Questionnaire (SDQ)

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
CI—confidence interval
DNBC—Danish National Birth Cohort
HR—hazard ratio
ICD-10—*International Classification of Diseases, 10th Revision*
SDQ—Strengths and Difficulties Questionnaire

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Prenatal maternal smoking has been associated with attention-deficit/hyperactivity disorder (ADHD) in children in a number of studies,[1–6] but whether the association is causal is still under debate. It is biologically plausible that nicotine from cigarette smoke could affect the fetal brain (intrauterine effect), because increased locomotor activity and cognitive impairment have been related to in utero nicotine exposure in animal models.[1,7,8] On the other hand, maternal smoking may be a marker of genetic or shared family environmental factors that cause the association. ADHD has a high level of heritability,[9] and smoking is more prevalent in families with ADHD.[10,11]

It is an epidemiologic challenge to disentangle the intrauterine effect from the influence of genetic or shared family environmental factors. One approach is to compare the magnitudes of associations with maternal and paternal smoking during pregnancy. If the mother smokes as a result of her ADHD, this would lead to genetic confounding, and we would expect a similar association with the father. If prenatal tobacco smoke is a causal factor, we would expect a larger effect of maternal smoking compared with paternal smoking, because paternal smoking leads to much less fetal exposure, depending on how carefully mothers avoid passive smoking. Previous studies using this design reported conflicting results.[12–14] Langley et al[14] reported that the association of ADHD symptoms in children with exposure to paternal smoking during pregnancy was similar to that with maternal smoking and also present in the absence of maternal smoking, suggesting a genetic effect rather than causal effect. Two other studies found no association of ADHD with paternal smoking.[12,13]

Using data from the Danish National Birth Cohort (DNBC),[15] we examined the associations of ADHD with maternal and paternal smoking during pregnancy. Additionally, we investigated the association between use of nicotine replacement during pregnancy and ADHD. If tobacco smoke is causally related to the occurrence of ADHD in fetal life, we predicted maternal smoking to be a stronger risk factor than paternal smoking. If nicotine is the culprit for this association, it will also be present among nicotine substitute users.

METHODS

Study Population

The DNBC (http://www.bsmb.com) recruited women early in pregnancy through their general practitioners (between 1996 and 2002). They were invited to participate in 4 computer-assisted telephone interviews.[15] When the child was 7 years old, a follow-up questionnaire about child health and development, including the parent-reported Strengths and Difficulties Questionnaire (SDQ),[16] was filled out by the primary caregiver, either through the Internet or on paper. We first linked all live-born singletons to the Danish National Patient Register,[17] the Danish Psychiatric Central Register,[18] and the Register of Medicinal Product Statistics,[19] and identified children with ADHD diagnosis or medication. We also used the 5 hyperactivity/inattention items of the SDQ for children who participated in the 7-year follow-up.

We included in the study only those who participated in the first interview, where parental smoking status during early pregnancy was reported by the pregnant women. We restricted our analysis to live-born singletons. There were 92 891 pregnancies in the first interview of the DNBC. We excluded unsuccessful pregnancies (n = 4055), pregnancies where mother emigrated (n = 38) or died (n = 1), pregnancies with unknown birth outcomes (n = 27), pregnancies resulting in twins or triplets (n = 1962), and births with missing birth dates (n = 87) or with missing information on maternal or paternal smoking (n = 1918). This left a total of 84 803 singletons in the analysis of prenatal exposure to parental smoking and child ADHD diagnosis or medication. Of these, 50 870 children also participated in the 7-year follow-up with complete data on the hyperactivity/inattention items of the SDQ.

Exposure Assessment

In the first interview (around 16 weeks' gestation), the participating pregnant women were asked whether they had smoked during pregnancy, and if so, whether they still smoked at the time of the interview and how many cigarettes they smoked on average per day or week. The women also reported whether they used nicotine substitutes (chewing gum, patches, or sprays) during pregnancy. Women who reported smoking at the time of the interview were classified as smokers, regardless of their use of nicotine substitutes. Women who reported no current smoking but reported use of nicotine substitutes at the time of the interview were classified as nicotine users. Women who had smoked but quit smoking without use of nicotine substitutes at the time of the interview were classified as smoking quitters. The women were also asked whether her husband or partner smoked, but the question did not mention whether he smoked inside the home. Consequently, we categorized parental smoking status into 8 groups, as stated in Table 1. Children of nonsmoking parents were used as reference group.

Outcome Measures

ADHD Diagnosis or Medication

We used a combination of ADHD medication and hospital diagnosis (the *International Classification of Diseases, 10th Revision* [ICD-10]) to identify children with ADHD. In the Danish National

TABLE 1 Number and Percentage of Children With ADHD by Parental Smoking Status

Mother	Father	Number of Children	With ADHD	
			n	%
Smoker	Smoker	8771	368	4.2
Nicotine replacement user	Smoker	240	7	2.9
Smoking quitter	Smoker	3199	113	3.5
Nonsmoker	Smoker	14 004	360	2.6
Smoker	Nonsmoker	4776	164	3.4
Nicotine replacement user	Nonsmoker	574	22	3.8
Smoking quitter	Nonsmoker	4167	83	2.0
Nonsmoker	Nonsmoker	49 072	892	1.8
Total		84 803	2009	2.4

Patient Register and the Danish Psychiatric Central Register,[17,18] we identified children with diagnosis of hyperkinetic disorder from outpatient and inpatient hospital contacts (ICD-10 code F90). Diagnosing hyperkinetic disorder is based on a more strict definition than the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria of ADHD and includes ADHD cases with all 3 core symptoms (inattention, hyperactivity, and impulsivity). These registers hold information on all inpatient hospital admissions since 1969 and include outpatient hospital visits since 1995. Diagnostic information for hyperkinetic disorder is based on the Danish version of the ICD-10 from 1995 onward. Children were defined as having ADHD if they had outpatient contact or inpatient hospital admission because of hyperkinetic disorder after the age of 5. The Danish National Patient Register was updated to October 10, 2010 and the Danish Psychiatric Central Register to August 1, 2011.

Information on ADHD medication was obtained from the Register of Medicinal Product Statistics.[19] All Danish residents are provided tax-supported health care by the National Health Service, which refunds part of the costs of most prescribed drugs. Children were included if they had 2 or more prescriptions of N06BA04 (central stimulating drugs only, methylphenidate), N06BA09 (noradrenalin reuptake inhibitors, atomoxetine), or N06BA07 (modafinil) in the register after the age of 5. The Register of Medicinal Product Statistics included prescriptions redeemed until December 31, 2011.

Parent-Rated Hyperactivity/Inattention Score

We used the 5 items of the hyperactive/inattention scale of the parent-rated SDQ. The SDQ is developed to assess emotions, behaviors, and peer relationships in young children and adolescents (http://www.sdqinfo.com). The questionnaire consists of 25 questions, and the items are rated on a 3-point Likert scale (not true, somewhat true, and certainly true). It contains 5 scales (emotional symptoms, conduct problems, hyperactivity/inattention, peer problems, and prosocial behavior) with 5 items each. The psychometric properties of the SDQ have generally been found to be satisfactory.[20–23] In the study, we used only the hyperactivity/inattention score.

Statistical Analysis

We used Cox regression to examine the associations between parental smoking and child ADHD. All children were followed from 5 years of age until a diagnosis of ADHD, an ADHD prescription, death, emigration, or the end of follow-up (December 31, 2011), whichever came first. The information on death and emigration was obtained from the Civil Registration System, which was updated to October 18, 2010.

We used linear regression to examine the associations between parental smoking status and hyperactivity/inattention scores among children who participated in the DNBC 7-year follow-up.

Potential confounders included in the Cox or linear regression models were maternal age at birth of the child (<25, 25–34, 35+ years), alcohol intake during pregnancy (0, 1, 2+ units per week in the early part of pregnancy), parental socio-occupational status (high, middle, low), parental psychopathology (yes, no), parity (0, 1, 2+), and child's gender (male, female). Because a few (6.6%) women contributed 2 children to the cohorts, we used a robust variance estimator to calculate the 95% confidence intervals (CIs). We also checked whether the associations were different for boys and girls by adding an interaction term between exposure and gender and using the Wald test. In addition, we compared the effect estimates of parental smoking on birth weight to illustrate our study design, because here the causal intrauterine effect of maternal smoking is well documented.[24,25] We used Stata/IC 11.2 for Windows (Stata Corp, College Station, TX) for all analyses. The study was approved by the Danish Data Protection Agency and the DNBC Steering Committee.

RESULTS

Children With ADHD Diagnosis or Medication

Of the 84 803 children, 2009 (2.4%) received an ADHD diagnosis or ADHD medication during the follow-up period (Table 1).

Characteristics of the Study Population

The characteristics of the study population are shown in Table 2. Parents who smoked (mother, father, or both)

were more likely to have lower socioeconomic status and to have mental problems than nonsmoking parents.

Parental Smoking During Pregnancy and ADHD Diagnosis or Medication

Both maternal and paternal smoking were associated with an elevated risk of ADHD diagnosis or medication in children, but the association was stronger for maternal smoking (Table 3). Compared with children born to nonsmoking mothers and smoking fathers, children born to smoking mothers and nonsmoking fathers had a higher risk of ADHD (adjusted hazard ratio [HR] = 1.26; 95% CI, 1.03 to 1.53). These associations were not significantly different between boys and girls (Wald test P = .31).

Mother's use of nicotine replacement during pregnancy was also associated with a higher risk of ADHD in the children, although the CI included unity for nicotine replacement using mothers and smoking fathers. For mothers who quit smoking during early pregnancy and did not use any nicotine replacement, we found a significant association for those who had smoking partners (Table 3).

TABLE 2 Characteristics of the Study Population According to Parental Smoking Status

	Nonsmoking Mother and Nonsmoking Father		Smoking Mother and Nonsmoking Father		Nonsmoking Mother and Smoking Father		Others[a]	
	n	%	*n*	%	*n*	%	*N*	%
Maternal age								
<25	3298	6.7	554	11.6	1348	9.6	2620	15.5
25–34	38 465	78.4	3423	71.7	10 534	75.2	12 194	71.9
35+	7309	14.9	799	16.7	2122	15.2	2137	12.6
Parity								
0	22 429	45.7	1961	41.1	6342	45.3	8851	52.2
1	18 782	38.3	1857	38.9	5377	38.4	5541	32.7
2+	7837	16.0	954	20.0	2271	16.2	2546	15.0
Missing	24	0.0	4	0.1	14	0.1	13	0.1
Alcohol intake								
0	26 775	54.6	2576	53.9	7892	56.4	9586	56.6
1	15 485	31.6	1343	28.1	4165	29.7	4738	28.0
2+	6812	13.9	856	17.9	1946	13.9	2627	15.5
Missing	0	0.0	1	0.0	1	0.0	0	0.0
Maternal socioeconomic status								
High	29 069	59.2	1718	36.0	7041	50.3	6985	41.2
Middle	16 778	34.2	2293	48.0	5586	39.9	7356	43.4
Low	3148	6.4	753	15.8	1341	9.6	2552	15.1
Missing	77	0.2	12	0.3	36	0.3	58	0.3
Paternal socioeconomic status								
High	25 700	52.4	1622	34.0	5683	40.6	5990	35.3
Middle	17 627	35.9	2103	44.0	5682	40.6	7200	42.5
Low	4336	8.8	870	18.2	2178	15.6	3114	18.4
Missing	1409	2.9	181	3.8	461	3.3	647	3.8
Maternal psychopathology								
No	48 250	98.3	4607	96.5	13 708	97.9	16 299	96.2
Yes	822	1.7	169	3.5	296	2.1	652	3.8
Paternal psychopathology								
No	48 404	98.6	4650	97.4	13 547	96.7	16 184	95.5
Yes	464	0.9	73	1.5	345	2.5	567	3.3
Missing	204	0.4	53	1.1	112	0.8	200	1.2
Gender of child								
Female	23 894	48.7	2309	48.3	6803	48.6	8300	49.0
Male	25 178	51.3	2467	51.7	7201	51.4	8651	51.0

[a] Including smoking mother and smoking father, nicotine replacement use mother and smoking father, smoking quit mother and smoking father, nicotine replacement use mother and nonsmoking father, and smoking quit mother and nonsmoking father.

Parental Smoking During Pregnancy and Hyperactivity/Inattention Score

When we used hyperactivity/inattention scores as the outcome, we found similar results as in Table 3, and all the risk estimates became statistically significant (Table 4). Children of smoking mothers and nonsmoking fathers had a higher hyperactivity/inattention score than children of smoking fathers and nonsmoking mothers (adjusted regression coefficient β = 0.28; 95% CI, 0.18 to 0.38).

Parental Smoking During Pregnancy and Birth Weight

As a check of model assumption, linear regression demonstrated that maternal smoking but not paternal smoking was associated with child birth weight (Table 5). Furthermore, when mother quit smoking or used nicotine substitutes during pregnancy, the children had a birth weight similar to those of children of nonsmoking parents.

DISCUSSION

In this large cohort of children followed up to 8 to 14 years of age, we found that both maternal and paternal smoking during pregnancy were associated with an elevated risk for ADHD, based on hospital diagnosis, medication, and hyperactivity/inattention scores. The association was consistently stronger for maternal smoking than for paternal smoking and was also found for mother's use of nicotine replacement during pregnancy. These results suggest a causal effect of smoking (and nicotine) during fetal life or other factors related to maternal nicotine dependence. The findings for paternal smoking could reflect an effect of passive smoking but may also be a result of social or genetic confounding.

TABLE 3 HRs for ADHD in Children According to Parental Smoking During Pregnancy, Using Children of Nonsmoking Parents as Reference

Mother	Father	
	Smoker	Nonsmoker
	HR (95% CI)	HR (95% CI)
Smoker	1.83 (1.60 to 2.10)	1.63 (1.36 to 1.94)
Nicotine replacement user	1.28 (0.57 to 2.89)	2.28 (1.48 to 3.51)
Smoking quitter	1.70 (1.38 to 2.10)	1.08 (0.85 to 1.36)
Nonsmoker	1.29 (1.14 to 1.47)	Reference

Cox regression, adjusted for maternal age, parity, alcohol intake during pregnancy, parental socioeconomic status, parental psychopathology, and child's gender.

We found that paternal smoking, independent of maternal smoking, was associated with a slightly elevated risk of ADHD in children, in agreement with 1[14] but not 2 other studies.[12,13] Psychological assessment in children of younger age (3- and 4-year-olds)[12,13] and small sample size[13] may have contributed to the findings of no association with paternal smoking in these studies, because 1 of the studies also reported no significant association between ADHD and maternal smoking.[12] On the other hand, these 2 studies suggested an intrauterine effect of maternal smoking on ADHD or conduct/externalizing problems.[12,13]

Using registered data in Finland and sibling-matched analyses, we previously reported a weak association between maternal smoking during pregnancy and ADHD in children (HR = 1.20; 95% CI, 0.97 to 1.49),[26] but the sample size was small (N = 880 pairs). Data also indicated that women who were able to change smoking habits between pregnancies smoked less than women who were not able to change. In addition, it is also possible that a diagnosis given to a child may influence the threshold for diagnosing another child in the family.

Our findings suggest that maternal smoking is more important than paternal smoking and that nicotine may play a role. Women who continue to smoke after getting pregnant or who use nicotine replacements are probably very dependent on nicotine and are likely to differ from other pregnant women in a number of ways. The stronger association in women smoking or using nicotine replacements in pregnancy suggests that nicotine affects ADHD development or that maternal genes in combination with other family factors may increase the risk of ADHD.

Possible effects of environmental and genetic factors on ADHD-like symptoms have been studied in animal models. In general, in utero nicotine exposure has increased locomotor activity in mice, rats, and other species.[1,8] Animals prenatally exposed to nicotine also display cognitive impairment, which is consistent with the cognitive deficits found in children with ADHD. Nicotine is readily transferred to the fetal compartment, and the fetuses are exposed to higher nicotine concentrations than their mothers.[27] Nicotine acts primarily through its action on nicotinic acetylcholine receptors. Abnormalities in cell proliferation and differentiation, disturbances in neuronal pathfinding, and disruptions in the development of the cholinergic and catecholaminergic systems have all been reported in animal models with in utero exposure to nicotine. The resulting permanent alterations may lead to functional deficits, such as maladaptive behavior later in life.[1]

Although twin studies suggested an average heritability of 70% to 80% for ADHD, identification of genes that confer susceptibility to ADHD has been less convincing. Targeted genes (eg, DAT1, DRD4) from classic genetic studies and newly identified genes (eg, GRM5, GRM7) from genome-wide association studies contribute all with very small effects.[28] Studies on gene–environment interactions or epigenetic changes are much needed.[29–31]

It is well known that maternal smoking during pregnancy is a causal risk factor for fetal growth restriction.[24,32,33] In line with this understanding, we found that maternal smoking, not paternal smoking, was strongly correlated with birth weight. We found that children of women who used nicotine replacement during pregnancy had birth weight similar to those born of nonsmokers or smoking quitters, consistent with a previous report.[34] In addition, regardless of father's smoking status, children of women who quit smoking in pregnancy had a slightly higher birth weight than children of nonsmoking mothers, perhaps reflecting that these

TABLE 4 Regression Coefficients for Hyperactivity/Inattention Score in Children According to Parental Smoking During Pregnancy, Using Children of Nonsmoking Parents as Reference

Mother	Father	
	Smoker	Nonsmoker
	β (95% CI)	β (95% CI)
Smoker	0.54 (0.46 to 0.61)	0.44 (0.35 to 0.53)
Nicotine replacement user	0.39 (0.06 to 0.73)	0.45 (0.20 to 0.70)
Smoking quitter	0.30 (0.20 to 0.40)	0.16 (0.07 to 0.25)
Nonsmoker	0.16 (0.11 to 0.21)	Reference

Linear regression, adjusted for maternal age, parity, alcohol intake during pregnancy, parental socioeconomic status, parental psychopathology, and child's gender.

TABLE 5 Regression Coefficients for Birth Wt (g) in Children According to Parental Smoking During Pregnancy, Using Children of Nonsmoking Parents as Reference

Mother	Father	
	Smoker	Nonsmoker
	β (95% CI)	β (95% CI)
Smoker	−248.3 (−262.0 to −234.5)	−209.6 (−227.1 to −192.0)
Nicotine replacement user	−18.7 (−95.1 to 57.7)	−15.8 (−63.8 to 32.2)
Smoking quitter	−0.4 (−21.0 to 20.3)	28.8 (11.3 to 46.2)
Nonsmoker	−11.1 (−21.8 to −0.3)	Reference

Linear regression, adjusted for maternal age, parity, alcohol intake during pregnancy, parental socioeconomic status, parental psychopathology, and child's gender.

mothers are more aware of the health of their children and therefore may also have a more healthful diet.

Our study had several strengths. First, we followed a large number of children up to the age of 14. Second, we used several sources to define the outcome (ie, ADHD diagnosis, ADHD medication, and hyperactivity/inattention score from the SDQ). None of these outcomes are perfect, but they have different bias profiles. Children in hospital care reflect the severe types, whereas those on medication are diagnosed by child psychiatrists and less selected. SDQ scoring bypasses diagnostic variation in catchment, because all were offered the screening questionnaire. Third, in the analysis we were able to adjust for several potential confounders including parental psychopathology and socioeconomic status.

Our study also had limitations. First, information on parental smoking was self-reported. Second, the number of mothers using nicotine replacement was small, resulting in unstable estimates with wide CIs. Third, the response rate for the 7-year follow-up including the SDQ was moderate. Nonresponse may cause selection bias for results on the hyperactivity/inattention scale if related to both parental smoking status and behavioral outcomes in children. Using ADHD diagnosis and medication in the entire cohort showed similar results.

In conclusion, our findings suggest that exposure to prenatal tobacco smoke, possibly nicotine, may have a prenatal programming effect on the risk of ADHD in children. Alternatively, our findings may reflect confounding by family factors more linked to maternal than paternal smoking, which could be both genetic and postpartum caring factors.

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