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BRIEF REPORT

Brief Report: Maternal Smoking During Pregnancy and Autism Spectrum Disorders

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Abstract Prenatal exposure to tobacco smoke is suggested as a potential risk factor for autism spectrum disorders (ASD). Previous epidemiological studies of this topic have yielded mixed findings. We performed a case–control study of 3,958 ASD cases and 38,983 controls nested in a large register-based cohort in Sweden. ASD case status was measured using a multisource case ascertainment system. In adjusted results, we found that maternal smoking during pregnancy is not associated with increased risk of ASD regardless of presence or absence of comorbid intellectual disability. Apparent associations were attributable to confounding by sociodemographic characteristics of parents such as education, income, and occupation.

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Introduction

One suggested environmental risk factor for autism spectrum disorders (ASD) is maternal smoking during pregnancy (Newschaffer et al. 2007), which is recognized for detrimental effects on fetal and childhood development. Prenatal exposure to tobacco smoke is associated with neurobehavioral outcomes, including attention-deficit/hyperactivity disorder (Milberger et al. 1996); behavioral difficulties such as externalizing behaviors and problems with peers (Cornelius et al. 2011); and poor intellectual performance (Eskenazi and Castorina 1999). There is some support that these associations may be causal, given the teratogenic chemicals in tobacco smoke, including heavy metals, benzene, and nicotine (Shea and Steiner 2008). Furthermore, prenatal exposure to tobacco smoke is an important risk factor for obstetric complications that may influence neurodevelopment, such as preterm birth and fetal growth restriction (Cnattingius 2004).

Several population-based studies have examined whether prenatal exposure to tobacco smoke is associated with ASD but findings are inconsistent. In a Swedish study, maternal smoking at first prenatal visit was associated with 1.4 times the odds (95% confidence interval (CI): 1.1, 1.8) of ASD diagnosis as ascertained from inpatient records (Hultman et al. 2002). In contrast, studies from Denmark (Larsson 2005), the U.S. (Kalkbrenner 2010), and Canada (Burstyn et al. 2010) found no associations. Some limitations hinder interpretation of these studies. For example, the Nordic studies relied on inpatient case ascertainment while none of the above studies examined if a dose–response relation exists

between maternal smoking and ASD risk. In addition, no studies have examined whether associations differ by ASD degree of functioning.

Although a link between prenatal tobacco smoke exposure and ASD is biologically plausible, an alternative explanation is confounding by familial characteristics. For example, lower socioeconomic status is associated with higher likelihood of maternal smoking (Lu et al. 2001) and differential ASD incidence (Fountain et al. 2010). Here, we examine the association of maternal smoking during pregnancy and ASD, adjusted for potential confounders, in a large population-based Swedish cohort.

Methods

Study Population

The Stockholm Youth Cohort (SYC) is a longitudinal register-based study consisting of all individuals aged 4–17 years (i.e., born 1984–2003) who were ever residents in Stockholm County at any time between 2001 and 2007 (total $N = 479{,}212$). Using the identification number assigned to all persons in Sweden (Ludvigsson et al. 2009), individuals were linked to national and regional data registers (Table 1). For the present analysis, exclusion criteria excluded all children who had not resided in Stockholm County for at least 4 years ($N = 34{,}285$) and adopted children ($N = 5{,}636$). After exclusion, the study population from which our case–control sample is drawn consisted of 439,291 individuals.

ASD Diagnosis

In Stockholm County, free developmental assessments are carried out at regular intervals from 1 to 60 months. The screenings are conducted by a pediatrician or nurse and includes assessment of social, motor, language, and cognitive development. One aim of this screening is to provide referral of children with suspected ASD to specialist services for diagnosis. ASD diagnoses in Stockholm County are made by specialists in child neuropediatric or mental health services. Regional guidelines mandate that diagnoses are made from structured evaluations covering details of the child's social, medical and developmental history by parental report, observation of the child in naturalistic settings, and a neuropsychiatric assessment including cognitive testing (using standardized tools relevant to the child's age and developmental level) (Axén 2010).

ASD case status as of December 31, 2007 was ascertained using national and regional data registers. We implemented a case ascertainment procedure that covers all potential pathways to ASD care and diagnosis in Stockholm, using regional registers administered by the Stockholm County Council and national registers (Table 1).

Table 1 National and regional data registers used for the present study

Register	Description
National registers	
Medical birth register	Contains data from over 99% of all births in Sweden extracted from standardized prenatal, obstetric, and neonatal records, and include medical and social variables such as medications, family situations, type of delivery, and maternal and child diagnoses. The recording and preservation of birth records is enforced by law.
National patient register	Contains data on admission and discharge diagnoses for all hospitalizations since 1973. Psychiatric diagnoses are recorded according to ICD 7–10.
Multi-generation register	Contains family information data on the Swedish population. All persons born in Sweden since 1932 are linked with first-degree biological relatives using this register.
Integrated database for labor market research	Contains sociodemographic data including country of birth, family income, education, and occupation.
Regional registers	
Clinical database for child and adolescent psychiatry in Stockholm	Child and Adolescent Psychiatry of the Stockholm County Council is the primary provider of ASD diagnostic assessments in Stockholm County. This register contains DSM-IV codes at the group level for all mental health services utilization in Stockholm County since 2001
Stockholm County Council VAL	The VAL is an administrative register containing records of all publicly financed inpatient and outpatient health services in Stockholm County since 1990. Diagnoses are recorded using ICD-9/10 codes. Is complete since 1996 and 2006 for inpatient and outpatient care, respectively.
Habilitation services register	This register does not provide formal diagnoses but categorizes recipients of habilitation services as autism with or without intellectual disability. Habilitation services are free for all children with an ASD diagnosis in Stockholm County

ASD status was determined through ICD-9 (299), ICD-10 (F84), and DSM-IV (299) classifications in the National Patient Register and the Stockholm County Council VAL (meaning "choice") database, Clinical Database for Child and Adolescent Psychiatry, and Habilitations Services Register. Presence of intellectual disability was determined through use of ICD-9 (317–319), ICD-10 (F70-79), and DSM-IV (317–319) classifications, and supplemented using the Habilitation Services Register, which categorizes service recipients as having autism with or without intellectual disability.

Previous studies have validated the diagnostic accuracy of mental health and ASD diagnoses recorded in Swedish inpatient registers (Hultman et al. 2010) and in Denmark where an almost identical system of healthcare and registers exists. In addition, we cross-validated the SYC cases against a national population-based study of twins (the Child and Adolescent Twin study in Sweden-CATSS) (Lichtenstein et al. 2010). We identified 27 ASD cases among the twins in the SYC and 23 (85.2% [95% CI 66.2–95.8%]) of these had an ASD confirmed in CATSS, while 1.0% [95% CI 0.7–1.4%] of non-case twins in the SYC received an ASD diagnosis in CATSS.

The study outcomes were three ASD classifications: any ASD, ASD without recorded comorbid intellectual disability (HFA or high-functioning autism), and ASD with recorded comorbid intellectual disability (LFA or low-functioning autism, IQ < 70 by Swedish and international convention). The use of these classifications as study outcomes was based on literature proposing the categories of HFA and LFA as key subcategorizations and as phenotypes with potentially distinct etiologies (Szatmari et al. 2007).

Maternal Smoking During Pregnancy

Information on maternal smoking was extracted from the Medical Birth Register, which contains data on maternal, perinatal, and infant factors for over 99% of all births in Sweden since 1973 (Cnattingius et al. 1990). Self-reported information on smoking is recorded by midwives at the first prenatal visit approximately 8–12 weeks after conception under three categories: non-smoker, 1–9 cigarettes daily, and $\geq$10 cigarettes daily. The data are validated and data quality is considered high (Cnattingius et al. 1990; National Board on Health and Welfare 2003).

Other Covariates

Sociodemographic data were extracted from the Integrated Database for Labor Market Research for the year before birth of child or as close as possible to this when information was unavailable. Occupational class (the higher of the mother or father) was categorized as: unskilled manual worker, skilled manual worker, lower level non-manual employee, intermediate level non-manual employee, high level non-manual employee, self-employed, and unclassified (those without a formal occupation). The higher of years of paternal or maternal educational attainment was categorized as: $\leq$9 years, 10–12 years, and $\geq$12 years of education. Family income was calculated after deductions of taxes and is adjusted for family size. To account for inflation, family income was categorized by quintiles according to birth year. Maternal origin of birth was categorized as Sweden, other parts of Europe, Africa, the Americas, and Asia/Oceania.

Statistical Methods

In this case–control study, we investigated the associations of maternal smoking with ASD. Cases and controls were individually matched 1:10 on birth year (to account for trends in ASD diagnostic incidence) and sex. Conditional logistic regression models adjusted for covariates a priori identified by the literature or in preliminary analyses as predictive of ASD. Maternal smoking at first prenatal visit was parameterized as binary (any smoking vs. none) and categorical (1 to 9 cigarettes daily vs. none, and $\geq$10 cigarettes daily vs. none). **Model 1** adjusted for maternal age, paternal age, and parity. **Model 2** included Model 1 covariates, and parental education, parental occupational class, family income, and maternal origin of birth. To ensure comparability of models with different levels of adjustment, analytical samples consist of children with complete covariate data. Approximately 14% of the sample was excluded for missing data. After exclusion for missing covariate data, 3,958 ASD cases and 38,983 controls were included in the analysis. Analyses were performed using IBM SPSS Statistics, version 19.

Results

Any ASD

Overall, 19.8% of ASD cases and 18.4% of controls were exposed to maternal smoking during pregnancy (Table 2). Significant differences in parental age, parity, education, income, occupation, and maternal region of birth were also noted.

In unadjusted analyses, maternal smoking was associated with higher odds of any ASD (OR = 1.10, 95% CI: 1.01, 1.20), compared with no smoking (Fig. 1). A dose–response trend was present, with increasing ORs observed for higher levels of smoking (1–9 cigarettes daily: OR = 1.05, 95% CI: 0.95, 1.17; $\geq$10 cigarettes daily: OR = 1.18, 95% CI: 1.04, 1.33). These associations remained after adjustment for

Table 2 Selected characteristics of autism cases and associated controls in the Stockholm Youth Cohort, born in 1984–2003

Characteristic	Cases ($N = 3,958$)	Controls ($N = 38,983$)	P value
Maternal smoking at first prenatal visit (%)			
Do not smoke	80.2	81.7	0.030
Any smoking	19.8	18.4	
1–9 cigarettes/day	11.6	11.2	
≥10 cigarettes/day	8.2	7.2	
Male (%)	73.0	72.8	0.750
Maternal age at delivery, years (%)			
<20	1.9	1.9	0.000
20–24	16.6	15.6	
25–29	32.1	33.0	
30–34	29.0	32.5	
35–39	16.6	14.4	
≥ 40	3.8	2.6	
Paternal age at delivery, years (%)			
<25	9.6	8.5	0.000
25–29	24.2	26.0	
30–34	30.8	32.6	
35–39	21.0	20.6	
40–49	12.6	11.1	
≥50	1.7	1.2	
Parity (%)			
1	47.7	44.4	0.000
2	33.1	35.9	
3	13.1	14.1	
≥4	6.1	5.7	
Highest level of parental/maternal education at birth, years (%)			
≤9	7.4	7.3	0.001
10–12	46.6	43.9	
≥12	46.0	48.8	
Household income, quintiles (%)			
Q1 (lowest)	16.6	15.3	0.000
Q2	24.2	20.6	
Q3	22.8	21.5	
Q4	19.1	21.3	
Q5 (highest)	17.3	21.3	
Occupational class (%)			
Unskilled manual worker	17.8	13.7	0.000
Skilled manual worker	15.8	14.2	
Non-manual employee—lower	13.8	15.0	
Non-manual employee—intermediate	17.8	20.9	
Non-manual employee—higher	17.8	19.1	
Self-employed	3.7	4.9	
Unclassified	13.3	12.2	
Region of birth of mother (%)			
Sweden	77.8	78.6	0.000
Europe, other	9.2	8.5	
Americas	3.2	2.3	
Africa	3.1	2.1	
Asia/Oceania	6.8	8.6	

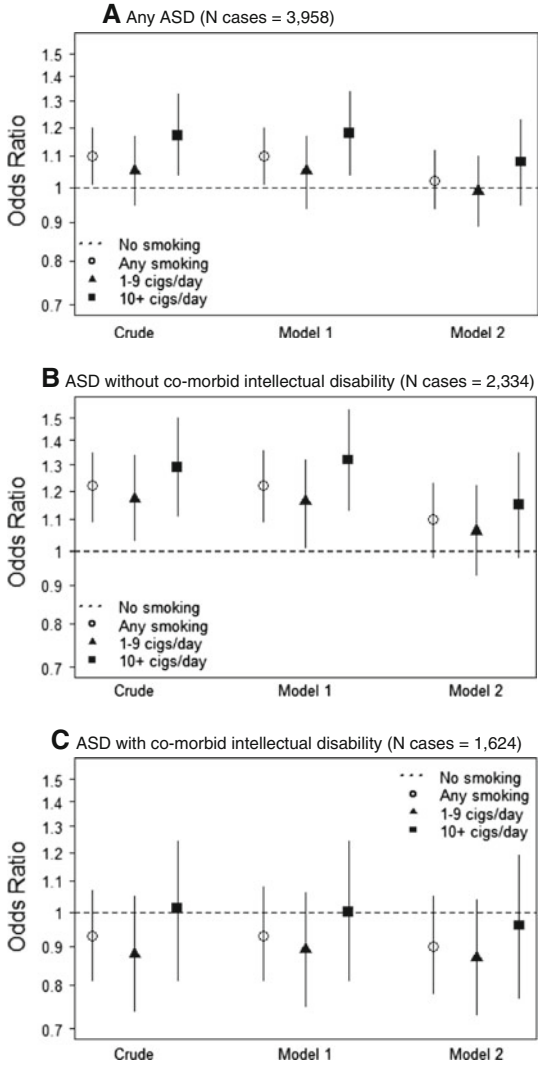

Fig. 1 Odds ratios and 95% confidence intervals for the association of maternal smoking at first prenatal visit and autism spectrum disorders (ASD) in the Stockholm Youth Cohort, 1984–2003. *Crude*: logistic regression model matched on birth year and gender. *Model 1*: logistic regression model matched on birth year and gender and adjusted for maternal age, paternal age, and parity. *Model 2*: logistic regression model matched on birth year and gender and adjusted for maternal age, paternal age, parity, maternal/paternal education, maternal/paternal occupational class, family income, maternal origin of birth. Estimates are based on the following number of ASD cases exposed to maternal smoking during pregnancy: any smoking—783 cases; 1–9 cigarettes daily—459 cases; 10+ cigarettes daily—324 cases

maternal age, paternal age, and parity in Model 1. However, after additional adjustment in Model 2 for sociodemographic covariates, the associations between maternal smoking and ASD were no longer statistically significant.

ASD with or Without Intellectual Disability

Maternal smoking was significantly associated with increased odds of HFA in an unadjusted model and Model 1(OR = 1.22, 95% CI: 1.09, 1.36). These associations exhibited a dose–response trend for higher levels of smoking. However, associations of smoking and HFA were no longer statistically significant after additional adjustment in Model 2. Maternal smoking during pregnancy was not associated with odds of LFA in either unadjusted or adjusted models.

Discussion

In this population-based study in Stockholm County, we found no evidence that maternal smoking during pregnancy increases risk of ASD. In unadjusted analyses, there was an increased risk of any ASD and HFA in children with prenatal exposure to maternal smoking. These associations remained after adjustment for parental age and parity, but disappeared after adjustment for parental education, occupation, and income. This indicates that the apparent relationship of maternal smoking and ASD may be attributable to confounding by sociodemographic factors.

The null findings are consistent with other studies that controlled for sociodemographic factors (Burstyn et al. 2010; Kalkbrenner et al. 2010) and fit the ecological evidence regarding trends in diagnosis and smoking habits. Smoking practices of Swedish pregnant women have declined steadily over time, from 31% in 1993 to 13% in 2000 (Cnattingius 2004) while ASD incidence has increased (Gillberg et al. 2006). In contrast, a previous Swedish register study reported an increased risk of ASD with fetal exposure to tobacco smoke (Hultman et al. 2002). That study, however, did not adjust for familial characteristics other than the mother's origin of birth, and furthermore was based solely on inpatient records for case ascertainment.

To examine whether calendar trends in ASD diagnosis and maternal smoking influenced results, we repeated all analyses stratified by birth year (1984–1993 and 1994–2003). We did not find evidence that calendar trends influenced our results although stratified estimates had less precision due to smaller sample size. For example, the fully adjusted associations of any smoking with any ASD were as follows: for 1984–1993 births, an OR of 0.97 (95% CI: 0.87, 1.09) and for 1994–2003 births, an OR of 1.08 (95% CI: 0.93, 1.26).

Strengths and Limitations

Limitations include potential misclassification of maternal smoking or ASD status that may lead to incorrect estimates of associations. Maternal smoking was defined according to self-report at the first prenatal visit and not throughout pregnancy. These data are collected prospectively and therefore are not sensitive to recall bias. Furthermore, self-reported data have been validated against serum cotinine levels and found to be reasonably accurate, although underreporting of smoking exists (George et al. 2006). Non-differential exposure misclassification nevertheless may be present, since 20–40% of pregnant smokers discontinue smoking during pregnancy, thereby attenuating results toward the null (Cnattingius 2004). In addition, we did not have information on paternal smoking during pregnancy. This opens the possibility that not adjusting for paternal smoking may attenuate associations between maternal smoking and ASD. The biological importance of paternal smoking during pregnancy and ASD is unknown, although studies of children's cognitive development suggest that effects of paternal smoking are much less, if any, compared with maternal smoking (Julvez et al. 2007). Further investigation are warranted regarding trimester-specific associations of maternal smoking, as well as the relative and joint contributions of maternal and paternal smoking to risk of ASD.

Outcome misclassification may be possible due to reliance on administrative data. However, our multi-source case ascertainment system that exhausts all pathways to ASD care in Stockholm County is likely to have captured most cases, since the free child development assessments as well as free habilitation services ensures that a majority of cases with suspected ASD would already have been identified. Previous Nordic studies of maternal smoking and ASD (Hultman et al. 2002; Larsson 2005) were limited by the lack of outpatient ASD data included in the national registers. Strengths of the present study include the large sample size, the prospective collection of exposure data based on mandatory reporting, and the multi-source case ascertainment system. We used a theory-driven approach of dichotomizing ASD into high and low functioning autism but were unable to study subtypes of autism according to current nosology. The DSM V working group however, suggests all these categories to be subsumed in one ASD diagnosis with and without comorbid disorders such as intellectual disability, which guided our approach.

Conclusion

The present study indicates that maternal smoking during pregnancy is not associated with increased risk of ASD,

and that apparent associations are attributable to confounding by familial sociodemographic factors such as parental education, income, and occupation.

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