



Research report

Is maternal smoking during pregnancy associated with bipolar disorder in offspring?



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ABSTRACT

Background: Prenatal smoking exposure affects fetal growth and development and is associated with increased risk of various neurodevelopmental disorders. Only one previous study has examined the association between maternal smoking during pregnancy and the risk of bipolar disorder (BPD).

Methods: In this nested case control study derived from all singleton live births in Finland between January 1st 1987 and December 31st 1998, we identified 724 children diagnosed and/or treated with BPD until 2008 and 1419 matched controls from four nationwide registers. Conditional logistic regression was used to examine the association between maternal smoking during pregnancy and BPD adjusting for potential confounding due to parental psychiatric history, maternal age and education level.

Results: 18.5% of offspring were exposed to maternal smoking during pregnancy. In the unadjusted analysis, smoking during pregnancy was associated with a 1.41-fold (95% CI 1.12–1.79, $P=0.004$) increased risk of BPD. In the final model adjusting for potential covariates, the risk was 1.14-fold (95% CI 0.88–1.49, $P=0.323$).

Limitations: The limitations of this study include: hospital based clinical diagnosis for case ascertainment, inclusion of early onset BPD cases, and lack of information on alcohol or other substance abuse during pregnancy.

Conclusion: This study demonstrated that, in this sample, an increased risk of BPD among offspring of mothers who smoked during pregnancy is most likely due to confounding by familial background factors. Future studies including information on serological measures of smoking exposure in pregnancy e.g. cotinine are warranted to further clarify this association.

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1. Introduction

Prenatal smoking exposure affects fetal growth and development and is associated with adverse perinatal events, (Hofhuis et al., 2003) high blood pressure and diabetes (Blake et al., 2000; Montgomery and Ekblom, 2002). Furthermore, maternal smoking is associated with increased risk of attention-deficit/hyperactivity disorder (ADHD) (Button et al., 2005), conduct disorder (Fergusson et al., 1998) and autism spectrum disorder (ASD) (Hultman et al., 2002) as well as psychiatric morbidity (Ekblad et al., 2010).

Bipolar disorder (BPD) has a neurodevelopmental component, the development of which involves genetic and environmental factors (Berrettini, 2000). The existing literature on the risk associated with maternal smoking during pregnancy in development of mood disorders is limited with inconsistent findings. One previous study has investigated the association specifically for BPD and showed an increased risk (Talati et al., 2013). Another study showed it to be associated with an increased risk of mood disorders (Ekblad et al., 2010), while two studies did not find any association with anxiety or major depression (Fergusson et al., 1998; Weissman et al., 1999). Based on the inconsistent findings on mood disorders, and only one previous published study on BPD, we aim to examine the association between maternal smoking during pregnancy and the risk of BPD, in this large nationwide population based epidemiological study.

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2. Materials and methods

2.1. Study design

This study is based on the Finnish Prenatal study of Bipolar Disorders (FIPS-B) (Chudal et al., 2014). The sampling frame of this nested case-control study with a prevalent control design, includes all singleton live born children in Finland between January 1st 1987 and December 31st 1998 ($N=754,450$). The nested design is due to selection of cases and a sample of matched controls from a defined birth cohort. Ethical approval for the study was obtained from the Institutional Ethical Review Board at Turku University Hospital, Turku University, and the Institutional Review Board of the New York State Psychiatric Institute.

2.2. National register information

This study is based on data from four Finnish nationwide registers: the Finnish Medical Birth Register (FMBR), the Finnish Hospital Discharge Register (FHDR), the Finnish Central Population Register and the Register of Education at Statistics Finland. Detailed description of these registers and the study design of FIPS-B have already been reported elsewhere (Chudal et al., 2014). The FMBR, established in 1987, includes comprehensive data on the perinatal period for all newborns in Finland.

The Finnish public health care system consists of both primary health care and specialized health services. Patients are typically referred by a general practitioner to specialized mental health services where the assessment is led by a child, adolescent or adult psychiatrist, depending on the patient's age. The FHDR has all medical diagnoses in hospitals in Finland since 1969 and covers all inpatient wards, in somatic and psychiatric hospitals, local health centres, military wards, prison hospitals, and private hospitals. Since 1998, it also covers the outpatient care in public specialized hospital units. In Finland, diagnostic classification is based on the International Classification of Diseases (ICD); ICD-8 (World Health Organization, 1967) from 1968 to 1986, ICD-9 (World Health Organization, 1977) from 1987 to 1995 and ICD-10 (World Health Organization, 1992) from 1996 onwards. The Finnish Central Population Register is a computerized national register, maintained by the Population Register Centre and local register offices that contains basic information about Finnish citizens and foreign citizens residing permanently in Finland. The linkage between registers was made using the personal identity code (PIC), assigned to all residents of Finland since 1964.

2.3. Identification of study subjects

The cases include all singletons diagnosed with BPD ($N=724$) born between January 1, 1987 and December 31, 1998 and diagnosed and/or treated by December 31, 2008. They were identified from the FHDR using ICD diagnostic codes F31.x (ICD-10) and 2962A G, 2963A G, 2964A G, 2967A (ICD-9). The FMBR was established in 1987, therefore offspring born before 1987 were excluded.

Controls for this study ($N=1419$) were offspring who were without BPD, schizophrenia or diagnoses related to these disorders (ICD-10 diagnoses: F20–29, F30, F31, F34.0, F38.0, F39, F60.0 and F60.1); ICD-9 diagnoses (2962A G, 2963A G, 2964A G, 2967A BPD, 295, 297, 298, 3010A, 3012A and 3012C). The controls were selected among the remainder of the children born during the study years and were matched to cases on selected factors (sex, date of birth (± 30 days) and residence in Finland on the first date of diagnosis of the matched case). Two controls for each case were identified from the Finnish Central Population Register ($N=1448$). Among 1448 control children, 29 were excluded as they belonged to a twin pair resulting in 1419 controls in the final analyses.

2.4. Maternal smoking during pregnancy

Information about maternal smoking during pregnancy was obtained from FMBR. These data were collected by maternity clinic nurses during obstetric visits in the second trimester of pregnancy. This information between January 1st 1987 and September 30th 1990 was categorized as: non-smokers, smoking < 10 cigarettes per day, or > 10 cigarettes per day. From October 1st, 1990 to December 31st 1998, the information was available as: non-smokers, smoking only during the first trimester and smoking throughout pregnancy. Out of the total sample, smoking information was missing for 3.6% of cases and 4.7% of controls.

2.5. Covariates

The covariates initially considered in the analyses were: parental psychiatric history, maternal age and education level, place of birth and weight for gestational age (WGA). These covariates have been shown to be associated with maternal smoking (Matthews, 2001; Ventura et al., 2000; Jaakkola et al., 2001; Jaakkola and Gissler, 2004; Maughan et al., 2004) and BPD (Frans et al., 2008; Laursen et al., 2005; Chudal et al., 2014) in previous studies. Maternal age data obtained from the Medical Birth Register was classified as: < 20 , 20–24, 25–29, 30–34 and ≥ 35 years. Data from the FHDR was used to classify a father or mother as having a psychiatric history (Yes/No), if he/she had any mental disorder of F10–99, based on the ICD-10 classification, or corresponding diagnoses based on the ICD-9 (291–316) and the ICD-8 (291–308). Diagnoses related to mental retardation (ICD-10: F70–79, ICD-9: 317–319, ICD-8: 310–315) were excluded. Maternal educational level data obtained from Statistics Finland were classified into three categories: 1) university degree, 2) secondary school graduate and 3) basic education (comprehensive school). The birth municipality information for cases and controls obtained from the Population Register Centre was used to categorize birth-place into four categories (southern Finland, northern Finland, western Finland, and eastern Finland). The calculation of birth weight for gestational age [(small for gestational age (SGA)/appropriate for gestational age (AGA) and large for gestational age (LGA)] was done according to national sex-specific weight distributions standards at a given gestational age. The growth curves were derived from data on 75 061 singleton children, with a gestational age of 24–43 weeks, born between 1979 and 1983 in Helsinki University maternity hospitals in Uusimaa, Finland (Pihkala et al., 1989). WGA was categorized into three groups: SGA: < 2 standard deviations (SD) below the mean; AGA: between -2 SDs and $+2$ SDs and LGA: 2 SDs above the mean.

2.6. Statistical analyses

Initially, bivariate analyses were conducted (using Pearson's chi squared test for dichotomous variables with statistical significance at $p < 0.1$) to test the significance of association between covariates (maternal age, paternal psychiatric history, maternal psychiatric history, maternal education level, place of birth and weight for gestational age (WGA)) and maternal smoking among controls as well as between covariates and BPD (Appendix A: Supplementary material).

Conditional logistic regression models were used to examine the association between maternal smoking during pregnancy and BPD. Initially, smoking was examined as a binary variable (yes/no) for the total sample. Unadjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. Maternal smoking was then adjusted in sequential models for maternal age, educational level and maternal and paternal psychiatric history. In the final model, we calculated ORs adjusting for all the above mentioned covariates.

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