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Original article

Exposure to tobacco smoke in utero or during early childhood and risk of hypomania: Prospective birth cohort study

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ABSTRACT

Objectives: Using data from a prospective birth cohort, we aimed to test for an association between exposure to tobacco smoke in utero or during early development and the experience of hypomania assessed in young adulthood.
Methods: We used data on 2957 participants from a large birth cohort (Avon longitudinal study of parents and children [ALSPAC]). The primary outcome of interest was hypomania, and the secondary outcome was "hypomania plus previous psychotic experiences (PE)". Maternally-reported smoking during pregnancy, paternal smoking and exposure to environmental tobacco smoke (ETS) in childhood were the exposures of interest. Multivariable logistic regression was used and estimates of association were adjusted for socio-economic, lifestyle and obstetric factors.
Results: There was weak evidence of an association between exposure to maternal smoking in utero and lifetime hypomania. However, there was a strong association of maternal smoking during pregnancy within the sub-group of individuals with hypomania who had also experienced psychotic symptoms (OR = 3.45; 95% CI: 1.49–7.98; $P = 0.004$). There was no association between paternal smoking, or exposure to ETS during childhood, and hypomania outcomes.
Conclusions: Exposure to smoking in utero may be a risk factor for more severe forms of psychopathology on the mood-psychosis spectrum, rather than DSM-defined bipolar disorder.

1. Introduction

The adverse effects of smoking and exposure to environmental tobacco smoke (ETS) on a range of physical health outcomes are well documented [1,2]. Recent research suggests that exposure to ETS in utero can result in preterm birth, low birth weight and small gestational age [3–5] and exposure to smoking in utero has been linked to a range of adverse neuropsychiatric outcomes in offspring [6], including delayed intellectual development [7], neurodevelopmental impairment [8], attention deficit hyperactivity disorder (ADHD) [9], psychotic symptoms [10], schizophrenia [11,12], psychoactive substance use [13], and behavioural and emotional disorders [13].

It is established that nicotine, which easily crosses the placental membrane, can reach high concentrations in the fetal bloodstream, with deleterious effects on brain development [14], neurotransmitter function [15] and cognition [16]. One of the mechanisms of this may be via an action on nicotinic acetylcholine receptors, which influence the development of neural circuits, including those responsible for regulating mood [17]. Nicotine exposure in utero may also increase oxidative stress [18] and can cause epigenetic modifications [19].

To date, only two studies have assessed whether maternal smoking during pregnancy is a risk factor for the development of bipolar disorder (BD) in adulthood, with inconsistent results. In a nested case-control analysis of data from the Child health and development study (CHDS) in the United States, Talati et al. compared 79 individuals with bipolar disorder to 632 matched controls [17]. They identified a two-fold increase in risk for BD among offspring who had been exposed to maternal smoking during pregnancy, after adjusting for birth weight, maternal race, maternal alcohol use during pregnancy and maternal psychopathology. More recently, Chudal et al. used data from four Finnish population and health registers to compare rates of maternal smoking during pregnancy between 724 individuals with BD and 1419 matched controls [20]. After adjusting for parental

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psychiatric history, maternal age and maternal educational level, there was no association between maternal smoking during pregnancy and risk of BD.

In the current study, our primary aim was to assess the relationship between exposure to tobacco smoke in utero or during early childhood and risk of hypomania assessed in young adulthood, using prospective data from a large birth cohort. We aimed to extend previous work by adjusting for a range of potential confounders, including mother's age at delivery, maternal education level, maternal social class, marital status, low income, maternal history of depression, exposure to influenza in utero, use of cannabis, alcohol and illicit drugs during pregnancy, offspring sex, birth weight and gestation at delivery. Additionally, we take a broader view of the mood-psychosis spectrum by assessing the extent to which exposure to tobacco smoke in utero impacts on risk of psychotic experiences in the context of a concurrent history of hypomania.

2. Methods

2.1. Description of cohort and study sample

The ALSPAC birth cohort is comprised of all live births in the County of Avon, UK, with expected due dates between April 1991 and December 1992. The initial cohort comprised 14,062 live births, with 13,998 alive at 1 year (http://www.bristol.ac.uk/alspac/, accessed 19th March 2016). The ALSPAC website contains details of all data available in the data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/, accessed March 19th 2016). Ethical approval for this study was obtained from the ALSPAC Ethics and law committee and local research ethics committees.

From birth, parents completed regular questionnaires about all aspects of their child's health and development. From age 7, children attended assessment centres for tests and interviews annually. To date, ALSPAC data have been used in a wide range of studies in mental health [21,22]. In this study, we assess data on the 2957 LSPAC participants who completed an assessment of the primary outcome of interest, namely lifetime experience of hypomania, at age 22–23.

2.1.1. Sample selection

From the original ALSPAC cohort, 9359 young adults were invited to complete the "Your life now (at age 21+)" assessments, which included the Hypomania checklist (HCL-32) questionnaire. Participants could choose from paper or online versions. A total of 3447 participants returned the questionnaire (36.8% response rate), including 2957 with complete answers (representing our study sample).

2.2. Outcome measures

2.2.1. Primary outcome: lifetime hypomania assessed in young adulthood

Hypomania was defined using the HCL-32, assessed when participants were aged 22–23 years. The HCL-32 is a self-completed questionnaire for lifetime experience of manic features [23]. It asks individuals to consider a time when they were in a "high or hyper" state and respond to a number of statements about their emotions, thoughts and behaviours at this time. Examples of the 32 symptom statements are: "I think faster"; "I make more jokes or puns when I am talking"; and "I take more risks in my daily life". The HCL-32 also asks about the duration of episodes and any impact on family, social and work life [24,25]. Although initially developed as a screening instrument for use in people diagnosed with depressive disorders, it is also a sensitive screening tool for bipolar disorder type II within non-clinical settings, including samples of young adults [26,27].

We defined lifetime history of hypomania in line with previous approaches for studies of this nature, namely: a score of 14 or more out of 32 hypomanic features; plus at least one response of either "negative consequences" or "negative plus positive consequences"; plus a report that these mood changes caused a reaction in others; plus a duration of "2–3 days" or more. Overall, this definition of hypomania, which includes severity, impairment and duration criteria, is much more conservative than other studies using the HCL-32, which have tended to use only the threshold score of 14 for caseness [27,28]. We chose a duration criterion of 2–3 days or more because the 4-day threshold within DSM excludes many individuals with bipolar disorder type II [29,30] and because 2 days is the modal duration of hypomania for individuals with bipolar II disorder [31,32]. Based on previous work in non-clinical samples, we expected that between 5–10% of respondents might satisfy our criteria for hypomania [26,33].

2.2.2. Secondary outcome: hypomania with previous psychotic experiences (PE)

"Hypomania plus previous PE" was also studied as an outcome. PE were assessed using the semi-structured Psychosis-like symptoms interview (PLIKSi) administered at ages 12 and 18 [34]. The PLIKSi consists of 12 core questions covering hallucinations (visual and auditory); delusions (delusions of being spied on, persecution, thoughts being read, reference, control, grandiose ability and other unspecified delusions); and experiences of thought interference (thought broadcasting, insertion and withdrawal) over the past 6 months. Clinical cross-questioning and probing was used to establish the presence of symptoms, and coding of all items followed the glossary definitions and rating rules for Schedule for clinical assessment in neuropsychiatry (SCAN). PE were coded as present if one or more of the experiences was rated as "suspected or definitely present" by a trained psychologist. Unclear responses after probing were always "rated down", and symptoms only rated as definite when a credible example was provided. In our analysis, we included only symptoms that could not be directly attributed to falling asleep/waking or to fever and were reported either in the PLIKSi at age 12 or in the PLIKSi at age 18 [35,36].

2.3. Exposures of interest: maternal smoking during pregnancy, paternal smoking during pregnancy and exposure to ETS in early childhood

Exposure to smoking in utero throughout pregnancy was based on maternal responses to specific questions asking about number of cigarettes smoked. This was assessed at three time points: 8 weeks gestation, 18 weeks gestation, and 8 weeks post-partum. Paternal smoking during pregnancy was assessed at 8 weeks gestation. Exposure to ETS in early childhood was defined as active maternal and/or paternal smoking at 1 year 9 months since birth, 2 years 9 months and 3 years 11 months since birth.

2.4. Confounding variables

We identified a priori several potential maternal/paternal, socioeconomic and offspring confounding variables based on previous literature in this area: mother's age at delivery, maternal education level, maternal social class, marital status, low income, maternal history of depression, exposure to influenza, use of cannabis, alcohol and illicit drugs during pregnancy, offspring sex, birth weight and gestation at delivery [10,11].