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Research paper

Gestational influenza and risk of hypomania in young adulthood: prospective birth cohort study

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ABSTRACT

Background: Previous studies have suggested a possible link between exposure to influenza in utero and bipolar disorder in adulthood. Using data from a prospective birth cohort, we aimed to test for an association between exposure to gestational influenza and the experience of hypomania assessed in early adulthood.

Methods: We used data on 2957 participants from the Avon Longitudinal Study of Parents and Children (ALSPAC). The two main outcomes of interest were hypomania, assessed using the Hypomania Checklist (HCL-32) at age 22–23, and 'hypomania plus previous psychotic experiences (PE)'. Maternally-reported gestational influenza was the exposure of interest. Multivariable logistic regression was used and estimates of association were adjusted for a range of possible confounding factors, including maternal smoking in pregnancy.

Results: Relative to controls, rates of exposure to gestational influenza were higher for participants with hypomania (24.0%) and for participants with 'hypomania plus PE' (34.2%), but univariate and multivariable analyses of an association between gestational influenza and hypomania (with and without previous PE) were not significant.

Limitations: The response rate to those who were sent the HCL-32 questionnaire was 36.8%. As a result, some analyses may have been under-powered to detect a true effect. Influenza infection during pregnancy was self-reported by mothers.

Conclusions: In this prospective population study, gestational influenza was not identified as a clear risk factor for lifetime hypomania or for 'hypomania with PEs' in young adult offspring. It is possible that previous reports of an association between gestational influenza and bipolar disorder in adulthood have been confounded by factors such as maternal smoking during pregnancy.

1. Introduction

Bipolar disorder (BD) affects at least 2% of the global population and is characterised by episodes of depression alternating with episodes of mania or hypomania (Goodwin and Jamison, 2007). It is associated with significant psychological, social, occupational and physical health morbidity, as well as premature mortality due to suicide and cardiometabolic disease (Goodwin and Jamison, 2007; Walker et al., 2015). Our current understanding of the etiology of BD suggests that it occurs as a consequence of complex interactions between multiple genetic risk factors of small effect and non-genetic factors such as childhood trauma, adverse life events and substance misuse (Garno et al., 2005; Phillips and Kupfer, 2013). In recent years, autoimmunity and aberrant inflammatory processes have also been implicated in the pathophysiology of BD, alongside other mood and psychotic disorders such as major depression and schizophrenia (Berk et al., 2013; Dickerson et al., 2007; Frommberger et al., 1997; Harrison, 2013; Khandaker et al., 2015; Krishnadas and Cavanagh, 2012). One of the potential mechanisms of the association between neuroinflammation and psychiatric disorders might be infection in utero acting as a trigger for a cascade of abnormal immune responses during early development (Berk et al., 2013; Khandaker et al., 2012; Khandaker et al., 2013).

Recent work suggests that gestational influenza (infection occurring during pregnancy) may be a risk factor for BD in adult offspring, however, not all studies have found an association

Abbreviations: PE, Psychotic experiences

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(Simanek and Meier, 2015). Parboosing and colleagues conducted a nested case-control analysis of 92 BD cases and 722 controls within the Child Health and Development Study (CHDS) in the United States (Parboosing et al., 2013). They reported an association between self-reported gestational influenza and BD with and without psychotic symptoms, which appeared to be specific to influenza exposure during the third trimester. However, a subsequent analysis of the same sample, which this time used serologically-documented gestational influenza as the exposure of interest, did not find an association with BD in offspring, but did find that gestational influenza increased the risk of BD with psychotic features (Canetta et al., 2014). Alongside evidence that gestational influenza may be a risk factor for schizophrenia in offspring (Brown and Derkits, 2010), this suggests that prenatal exposure to influenza may be a non-specific risk factor for psychosis or severe psychopathology, rather than specific for a diagnostic grouping such as schizophrenia or BD.

Additionally, maternal smoking during pregnancy is known to be associated with psychotic experiences during adolescence (Zammit et al., 2009b) and schizophrenia in adulthood (Thapoulou et al., 2013). Although the CHDS studies cited above adjusted for factors such as maternal age, education and psychiatric history, neither study adjusted for maternal smoking during pregnancy.

Our study seeks to complement and extend the literature in this area by making use of comprehensive prospective data from the Avon Longitudinal Study of Parents and Children (ALSPAC) (Boyd et al., 2013). Specifically, we assess whether gestational influenza is a risk factor for lifetime hypomania assessed in young adulthood (with and without a history of psychotic experiences, PE), while taking account of a wider range of potential confounding factors than has been considered in previous studies of this research question.

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 consisted of 14,062 live births, with 13,998 alive at one year (http://www.bristol.ac.uk/alspac/). The study website contains details of all the data that are available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). Ethical approval for the 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 to participate in tests and interviews on an annual basis. To date, ALSPAC data have been used in a wide range of epidemiological studies in mental health (Fraser et al., 2013; Niarchou et al., 2015). In this study, we assess data on the 2957 ALSPAC participants who completed an assessment of the primary outcome of interest, namely lifetime experience of hypomania, at age 22–23.

2.2. 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 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).

2.3. Outcome measures

2.3.1. Primary outcome: lifetime hypomania assessed in young adulthood

Hypomania was defined using the Hypomania Checklist (HCL-32), assessed when participants were aged 22–23 years. The HCL-32 is a self-completed questionnaire for lifetime experience of manic features (Angst et al., 2005). It asks that people consider a time when they were in a "high or hyper" state and endorse 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 questionnaire also asks about the duration of such episodes and impact on family, social and work life (Carvalho et al., 2014; Court et al., 2014). Although initially developed as a screening instrument for use in people diagnosed with depressive disorders, it is also a sensitive screening tool in non-clinical settings, including samples of young (Meyer et al., 2007; Meyer et al., 2014).

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 more conservative than most other studies, which have tended to use only the threshold score of 14 (Hardoy et al., 2005; Meyer et al., 2014). 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 (Goldberg et al., 2009; Pini et al., 2005) and because two days is the modal duration of hypomania for individuals with bipolar II disorder (Angst and Cassano, 2005; Benazzi, 2001). Based on previous work in non-clinical samples, we expected that between 5 and 10% of respondents might satisfy our criteria for hypomania (Holtmann et al., 2009; Meyer et al., 2007).

2.3.2. 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 (Zammit et al., 2009a). 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 SCAN (Schedule for Clinical Assessment in Neuropsychiatry). 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 (Horwood et al., 2008; Zammit et al., 2013).

2.3.3. Exposure of interest: gestational influenza

Exposure to influenza in utero was based on maternal responses to specific questions about infection which were assessed at three time points: 18 weeks gestation, 32 weeks gestation, and 8 weeks post-partum. Respectively, the questions were: '*During*