Journal of Psychiatric Research 59 (2014) 132–139

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Exposure to stressful life events during pregnancy predicts psychotic experiences via behaviour problems in childhood

Kim S. Betts [a, *], Gail M. Williams [a], Jakob M. Najman [b], James Scott [c], Rosa Alati [d]

[a] School of Population Health, University of Queensland, Brisbane, Australia
[b] School of Social Science and Population Health, University of Queensland, Brisbane, Australia
[c] The University of Queensland Centre for Clinical Research and Metro North Mental Health, Royal Brisbane and Women's Hospital, Brisbane, Australia
[d] School of Public Health and Centre for Youth Substance Abuse Research, University of Queensland, Brisbane, Australia

ARTICLE INFO

Article history:
Received 17 February 2014
Received in revised form
3 August 2014
Accepted 6 August 2014

Keywords:
Psychotic experiences
Neurodevelopment
Prenatal stressful life events
Behavioural problems
Cognitive ability
Mediation

ABSTRACT

Background: Exposure to stressful life events during pregnancy has been associated with later schizophrenia in offspring. We explore how prenatal stress and neurodevelopmental abnormalities in childhood associate to increase the risk of later psychotic experiences.

Methods: Participants from the Mater University Study of Pregnancy (MUSP), an Australian based, prebirth cohort study were examined for lifetime DSM-IV positive psychotic experiences at 21 years by a semi-structured interview ($n = 2227$). Structural equation modelling suggested psychotic experiences were best represented with a bifactor model including a general psychosis factor and two group factors. We tested for an association between prenatal stressful life events with the psychotic experiences, and examined for potential moderation and mediation by behaviour problems and cognitive ability in childhood.

Results: Prenatal stressful life events predicted psychotic experiences indirectly via behaviour problems at child age five years, and this relationship was not confounded by maternal stressful life events at child age five. We found no statistical evidence for an interaction between prenatal stressful life events and behaviour problems or cognitive ability.

Conclusion: The measurable effect of prenatal stressful life events on later psychotic experiences in offspring manifested as behaviour problems by age 5. By identifying early abnormal behavioural development as an intermediary, this finding further confirms the role of prenatal stress to later psychotic disorders.

1. Objectives

Schizophrenia and other psychotic disorders are increasingly being understood as the severe and disabling end point of a continuous distribution of psychotic experiences present in the general population (Linscott and Van Os, 2010; Subramaniam et al., 2013). The neurodevelopmental model of schizophrenia posits that a number of environmental and genetic factors, either via accumulation or through more complex interactions, are responsible for an individual's movement along this continuum from transitory and relatively harmless psychotic experiences towards a clinical diagnosis (Rapoport et al., 2012; Van Os et al., 2009). The earliest environmental risk factors may interrupt normal brain development during fetal life, when the central nervous system is at a critical stage of formation, and are perhaps responsible for priming an individual toward an atypical trajectory of neurodevelopment increasing the risk of later schizophrenia (King et al., 2010; Meli et al., 2012; Meyer and Feldon, 2010). A number of epidemiological studies have shown that exposure to objective stressors during gestation, including death of a relative, military invasion and natural disasters, increase the risk for schizophrenia and other psychotic disorders in adult offspring (Khashan et al., 2008; Van Os and Selten, 1998; Selten et al., 1999; Malaspina et al., 2008). These findings are supported by animal studies which show that associations between induced prenatal stress in rats and offspring schizophrenia-like behaviour are accompanied by neuroendocrine abnormalities (Meyer and Feldon, 2010).

* Corresponding author. (Care of) Rosa Alati, School of Population Health, The University of Queensland, 4th floor, Public Health Building, Herston Rd, Herston QLD 4006, Australia. Tel.: +61 7 33655509.
E-mail addresses: kim.betts@uqconnect.edu.au (K.S. Betts), g.williams@sph.uq.edu.au (G.M. Williams), j.najman@uq.edu.au (J.M. Najman), james.scott@health.qld.gov.au (J. Scott), r.alati@sph.uq.edu.au (R. Alati).

http://dx.doi.org/10.1016/j.jpsychires.2014.08.001
0022-3956/

The neurodevelopmental model of schizophrenia is also consistent with findings that the condition is preceded by abnormalities in cognitive and motor development, and behavioural problems (Bearden et al., 2000; Woodberry et al., 2008; Walker et al., 1994; Welham et al., 2009). Previous studies have examined how these premorbid developmental abnormalities are associated with prenatal and perinatal environmental risk factors to increase later schizophrenia risk. However, evidence so far supports two separate interpretations of the resulting process, depending on whether the developmental abnormalities are viewed as the inevitable premorbid manifestation of a genetic predisposition to later schizophrenia, (Bearden et al., 2000; Cannon et al., 2002a), or if they are affected by prenatal environmental risk factors (Brown et al., 2001; Ellman et al., 2009).

With regard to the former, one study used delayed motor development as a proxy for a genetic predisposition to schizophrenia along with obstetric complications to implicate gene × environment interactions (Van Os et al., 2008) as playing a central role in the neurodevelopment of schizophrenia and related disorders (Clarke et al., 2011). Such an interaction is in line with the 'two-hits' hypothesis of schizophrenia, whereby an early environmental exposure can increase the risk of schizophrenia in those genetically susceptible, who may be identified by prodromal neurodevelopmental abnormalities, as is the case in the study by van Os (Van Os et al., 2008). Alternatively, studies supporting the latter view, see premorbid developmental abnormalities as part of the developmental sequelae resulting from prenatal exposures such as infection, which also increases the risk for schizophrenia, thus concluding that developmental abnormalities play a mediating role via which prenatal infection impacts schizophrenia risk (Brown et al., 2001; Ellman et al., 2009). With uncertainty remaining, further longitudinal studies are needed which can properly test both possibilities using statistical tests to assess possible mediating or moderating effects, as the findings will have important implications for our understanding of the neurodevelopmental model of schizophrenia (Khandaker et al., 2013), and are likely to inform preventative strategies.

To date, no study has investigated how prenatal stress and cognitive development or behaviour problems in childhood associate to predict later schizophrenia or psychotic illness. In this study we employ structural equation modelling to examine if the effect of prenatal stressful life events on psychosis experiences measured in early adulthood is moderated or mediated by behavioural problems or cognitive ability at child age five years. We use a latent factor of psychotic experiences as our outcome because a continuous outcome holds more statistical information than a binary diagnosis, giving us greater power to detect moderation and mediation effects. In addition, evidence suggests that 'psychosis' is better represented as a dimensional phenotype (Zammit et al., 2013; Ahmed et al., 2012; Subramaniam et al., 2013) rather than as categorical diagnoses, and subthreshold psychotic experiences are influenced by similar risk factors which predict schizophrenia including premorbid developmental abnormalities (Linscott and Van Os, 2010; Van Os et al., 2009; Blanchard et al., 2010; Kelleher et al., 2013). We also adjust for a number of important confounders including additional prenatal and perinatal risks for schizophrenia and maternal stressful life events at child age five years.

2. Materials and methods

2.1. Participants

Participants came from the Mater University Study of Pregnancy (MUSP), a prospective pre-birth cohort study following mothers and their children for over 20 years. A total of 7223 mothers attending their first clinic visit at Brisbane's Mater Misericordiae Hospital were recruited between 1981 and 1984, with subsequent follow-ups at birth, and child age 6 months, and 5, 14 and 21 years. Of the original 8556 pregnant mothers who were approached, 98 refused to participate, 710 delivered at another hospital, 59 had multiple births, 55 adopted out their child and 411 infants died during pregnancy or delivery. The MMH accounted for around 50% of all births in Brisbane during the catchment period and resulted in a sample skewed towards lower socio-economic position than the Brisbane average due to the exclusion of private patients attending the MMH, further information found elsewhere (Najman et al., 2005). At 21 years 2558 offspring completed the Composite International Diagnostic Interview (CIDI-Auto 2.1) (World Health Organization, 1997), providing the sample to examine the factor structure of psychosis. The final model included participants with values on all variables of interest ($n = 2227$). Informed consent from all participants was gained, all data was coded for confidentiality and ethics was approved for the cohort by the institution and funding body.

2.2. Experiences of positive psychosis

At the 21 year follow-up the lifetime version of the CIDI-Auto (World Health Organization, 1997) was administered by trained interviewers, including items assessing positive psychotic experiences (15 delusions and 6 hallucinations). Positive responses to delusions and hallucinations were probed to increase certainty that the experience was psychotic. As the prevalence of experiences was low, it was necessary to combine three pairs of 'like' delusions [(i) being secretly tested on ($n = 13$; 0.5%)/someone was plotting to hurt you ($n = 17$; 0.6%); (ii) thoughts were inserted into your mind ($n = 23$; 0.9%)/thoughts were taken from your mind ($n = 10$; 0.4%); (iii) felt under the control of an external force ($n = 13$; 0.5%)/felt strange forces working on you ($n = 21$; 0.8%)], and exclude two delusions [(i) convinced someone you never met was in love with you ($n = 5$; 0.2%); (ii) convinced your partner was cheating on you ($n = 17$; 0.6%)], to satisfy the requirements of the covariance matrix in the resulting structural equation model (Supplementary Table 1).

2.3. Prenatal and perinatal predictors

At the first clinic visit pregnant mothers were asked how many cigarettes they had smoked in the last week (none/1–19/20+) and completed the Delusions-States Symptoms Inventory (DSSI) (Bedford and Folds, 1977), measuring seven sympotms of depression and anxiety on separate scales, with 'casesness' on both scales defined at ≥4. The DSSI has been found to correlate well with the Edinburgh Postnatal Depression Scale (EPDS) and the Hospital Depression/Anxiety Scale (Bedford and Folds, 1978). At birth, mothers were asked about the experience of eight negative life events, drawn from the Social Readjustment Rating Scale (Holmes and Rahe, 1967), having occurred in the six months (thus inclusive of the second and third trimesters) prior to giving birth including; death/illness of someone close, health problems, serious disagreements with your partner, with someone else, financial problems, major employment change of partner, serious problems with housing or accommodation and serious problems with the law (45% of the sample had experienced 0 events, 28% experienced 1 event, 15% experienced 2 events, 7% experienced 3 events, and 5% experienced 4 or more events). At birth Apgar score (<7 at 1 min), forced induction of labour, pre-eclampsia, birth weight z-score adjusted for gestational age and gender (Betts et al., 2013) (continuous and lowest 10 percentile) were collected from obstetric records, and mothers' reported whether the baby required