Schizophrenia Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Maternal prenatal infection, early susceptibility to illness and adult psychotic experiences: A birth cohort study

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

[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. University of Queensland, Brisbane, Australia
[d] Metro North Mental Health, Royal Brisbane and Women's Hospital, Brisbane, Australia
[e] School of Public Health and Centre for Youth Substance Abuse Research, University of Queensland, Brisbane, Australia

ARTICLE INFO

Article history:
Received 27 December 2013
Received in revised form 9 March 2014
Accepted 2 April 2014
Available online xxxx

Keywords:
Psychotic experiences
Neurodevelopment
Prenatal infections
Infant illness susceptibility
Structural equation modelling
Moderation
Mediation

ABSTRACT

Background: Existing evidence has established that maternal infection during pregnancy and illness during early life are associated with later schizophrenia. No research has examined how the combination of these prenatal and postnatal exposures is linked to an increased risk to later schizophrenia and psychotic disorders.
Methods: Participants from the Mater University Study of Pregnancy (MUSP), an Australian based, pre-birth cohort study were examined for lifetime DSM-IV positive psychotic experiences at 21 years by a semi-structured interview. Structural equation modelling was used to derive a general factor of psychotic experiences at age 21. Next, we undertook a number of separate analyses to investigate how prenatal infections and infant illness susceptibility are related to positive psychotic experiences in early adulthood, allowing for tests of moderation and mediation between the two risk factors.
Results: After adjustment for important confounders, infant illness susceptibility was found to play a mediating role in the association between prenatal vaginal infection and later psychotic experiences. Whereby, infant illness susceptibility showed a direct association with psychotic experiences, while prenatal vaginal infection indirectly predicted psychotic experiences via infant illness susceptibility.
Conclusion: Our findings suggest that illness susceptibility in early infancy may be central to the relationship between prenatal vaginal infection and later psychotic experiences. Further research is needed to establish the mechanisms that link these prenatal and postnatal exposures with psychotic illness in later life.

1. Introduction

The neurodevelopmental model of schizophrenia suggests factors impacting during early neurodevelopment may influence the risk of later schizophrenia (Rapoport et al., 2012). Maternal prenatal infection is one such factor (Brown and Derkits, 2010), with genital/reproductive infection being one of the most prevalent groups of prenatal infections to be associated with schizophrenia (Brown et al., 2011), possibly contributing to 6% of schizophrenia cases (Brown and Derkits, 2010). A recent meta-analysis examining the effects of a range of prenatal infections on schizophrenia concluded that while existing evidence supports the association, there is a need for more sophisticated statistical models with the ability to properly account for mediating factors (Khandaker et al., 2013b). Another line of investigation has also found that early postnatal development may be a sensitive period during which a range of illnesses including infections (Khandaker et al., 2012) and atopic disorders (Pedersen et al., 2012; Khandaker et al., 2013a) increase the risk of later schizophrenia (Khandaker et al., 2012). However, research has not tested for interrelationships among these two exposures with schizophrenia or related disorders.

Aside from the possibility that prenatal infection and infant illness susceptibility may represent independent risk factors for schizophrenia, there are several ways in which the relationship between the two exposures may result in an increased risk of schizophrenia. Firstly, exposure to prenatal infection and infant illness susceptibility may have a cumulative effect on schizophrenia, whereas exposure to either but not both may not be sufficient to predict schizophrenia. A 'moderating' effect such as this could be considered consistent with the 'two hits' hypothesis of schizophrenia development, which views prenatal infection as a 'disease primer' leaving an individual susceptible to schizophrenia in the event of further environmental insults (Meyer, 2013).

Secondly, it is possible that prenatal infection indirectly increases the risk of adult schizophrenia via infant illness susceptibility. Such a 'mediating' effect may indicate that maternal prenatal infection was

* Corresponding author at: (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_g_scott@health.qld.gov.au (J. Scott), r.alati@sph.uq.edu.au (R. Alati).

http://dx.doi.org/10.1016/j.schres.2014.04.013
0920-9964/

transmitted to the fetus (Brown and Derkits, 2010) resulting in persistent or recurrent postnatal illness (Remington et al., 2010) which increases schizophrenia risk (Khandaker et al., 2012). Thirdly, it is possible that when testing for the effects of both exposures, only one will predict the outcome, revealing the period in which the developing brain is most sensitive to the risk of schizophrenia posed by exposure to illness and infection. Lastly, other potentially 'causal' risk factors of later schizophrenia may explain the effect attributed to either primary exposure. Prenatal smoking, pre-eclampsia, birth weight, preterm birth, induced labour, and fetal hypoxia appear to be associated with an increased risk of offspring schizophrenia and psychotic disorders (Cannon et al., 2002; Canon et al., 2002; Zammit et al., 2009; Nosarti et al., 2012; Eide et al., 2013; Stathopoulou et al., 2013), and have been linked to the exposures (King et al., 2010).

Lastly, there is agreement that the positive psychotic experiences, which are central to the diagnosis of schizophrenia and other psychotic disorders, exist as a dimensional phenotype (Ahmed et al., 2012; Subramaniam et al., 2013; Zammit et al., 2013) and represent a 'trait diathesis' which in extreme cases converts to schizophrenia and other psychotic diagnoses (Rapoport et al., 2012). Empirically, subthreshold psychotic experiences are influenced by similar risk factors which predict schizophrenia (van et al., 2009; Linscott and van, 2010), and are found to predict future psychosis (Fisher et al., 2013), which may necessitate clinical care (Yung et al., 2012). Previous studies based on the ALSPAC found a range of prenatal and perinatal risk factors, including prenatal infection, predicted an increased risk of psychotic experiences in children (Thomas et al., 2009; Zammit et al., 2009; Dorrington et al., 2013). In this study, we extend these findings by using structural equation modelling to assess how key prenatal and postnatal risk factors associate to predict the more serious psychotic experiences of later developmental stages (Kelleher et al., 2012). Specifically, we examine whether the impact of infant illness susceptibility on psychotic experiences in early adulthood is moderated by prenatal vaginal infection, or if the impact of prenatal vaginal infection on psychotic experiences is mediated via infant illness susceptibility.

2. 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 7,223 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, further information found elsewhere (Najman et al., 2005). At 21 years 2,558 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 ($n = 2{,}329$).

2.2. Positive psychotic experiences

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). Affirmative responses to delusions and hallucinations were probed to be surer the experience was psychotic. As the prevalence of experiences was low, it was necessary to combine three pairs of 'like' delusions (1) tested on/plotted against (being secretly tested on/someone was plotting to hurt you), (2) thought removal/insertion (thoughts were inserted into your mind/thoughts were taken from your mind), and (3) manipulated by external force (felt under the control of an external force/felt strange forces working on you), and exclude two delusions [(i) convinced someone you never met was in love with you; (ii) convinced your partner was cheating on you], resulting in a total of 16 psychotic experiences.

2.3. Risk factors

Vaginal infection was ascertained at birth when mothers reported if they had experienced vaginal infection/discharge over pregnancy (did not happen/ minor problem/ moderate problem/ major problem). Infant illness susceptibility was constructed as a single latent variable capturing the 'co-occurrence' of two indicator variables reported by mothers at infant age 6 months: (1) how many times medical attention had been sought for the infant (0/1/2/3–4/5+), and (2) four questions regarding the frequency (never/rarely/monthly/weekly/often) of health problems possibly resulting from infection (vomiting, diarrhoea/constipation, skin rashes, cold/cough/runny nose), which were summed.

Additional prenatal and perinatal risk factors which prior work indicate may play a causal role in the main hypothesis were ascertained at birth, including Apgar score (<7 at 1 minute), forced induction of labour, pre-eclampsia, and birth weight z-score adjusted for gestational age and gender (Betts et al., 2013), and if the baby required "specialist medical care" after delivery (did not happen/ minor problem/ moderate problem/ major problem). In addition, at the first clinic visit pregnant mothers were asked how many cigarettes they had smoked in the last week (none/1–19/20+).

2.4. Potential confounders

At the first clinic visit pregnant mothers were asked how often and how much alcohol they consumed since becoming pregnant (none/light/moderate/heavy). Maternal age, parity and level of education (incomplete high school/complete high school/undertaken tertiary education) were also collected at this time, while baby gender was taken at birth.

2.5. Statistical analysis

To examine the factor structure of the psychotic experiences we conducted Exploratory Factor Analysis (EFA) using the WLSMV estimator available in Mplus version 6, capable of handling the non-normality associated with categorical data. We then used the EFA results to undertake a number of Confirmatory Factor Analyses (CFA) (Chen et al., 2006). Model fit was assessed using the Root Mean Square Error of Approximation (RMSEA), the Comparative Fit Index (CFI), and the Tucker-Lewis Index (TLI), for which adequate fit is indicated by RMSEA < 0.06, CFI ≥ 0.95 and TLI ≥ 0.95 (Hu and Bentler, 1998).

Next we constructed the path analysis (regression) model. To avoid complicated model building strategies which may result from the inclusion of so many variables and pathways, we assessed each variable for inclusion using univariate analysis. Predictor variables were divided into risk factors and confounders (Table 2). Risk factors were included in the path analysis only if they predicted the outcome in univariate analysis, while confounders were included *a priori*. The remaining variables were then entered into the path analysis, connected by temporally appropriate pathways, before removing non-significant pathways by a systematic process (see supplementary text 1). Lastly, two separate analyses assessed whether: (1) the effect of infant illness susceptibility on psychotic experiences was moderated by prenatal vaginal infection; or (2) the effect of prenatal vaginal infection on psychotic experiences was mediated via infant illness susceptibility. A description of the statistical tests of moderation and mediation can be found in supplementary text 2.

We conducted a supplementary analysis to assess the psychopathological significance of our psychotic experiences factors by using them to predict common lifetime DSM-IV mental disorders also derived from the CIDI at age 21. Finally, we used multivariate logistic regression in Stata v.12 to compare those who had been lost to follow-up with

Please cite this article as: Betts, K.S., et al., Maternal prenatal infection, early susceptibility to illness and adult psychotic experiences: A birth cohort study, Schizophr. Res. (2014), http://dx.doi.org/10.1016/j.schres.2014.04.013