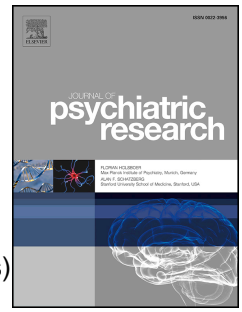
Accepted Manuscript



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

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PII: S0022-3956(14)00237-4

DOI: 10.1016/j.jpsychires.2014.08.001

Reference: PIAT 2440

To appear in: *Journal of Psychiatric Research*

Received Date: 17 February 2014

Revised Date: 3 August 2014

Accepted Date: 6 August 2014

Please cite this article as: Betts KS, Williams GM, Najman JM, Scott J, Alati R, Exposure to stressful life events during pregnancy predicts psychotic experiences via behaviour problems in childhood, *Journal of Psychiatric Research* (2014), doi: 10.1016/j.jpsychires.2014.08.001.

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Running head: prenatal stress, early behaviour problems and psychotic experiences

Abstract word count is 211 words.

Main text word count is 4,000 words.

There are 2 tables and 1 figure.

There is a supplementary section with 4 tables and 1 figure.

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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, pre-birth cohort study were examined for lifetime DSM-IV positive psychotic experiences at 21 years by a semi-structured interview (n = 2,227). 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.

Key words: Psychotic experiences, neurodevelopment, prenatal stressful life events, behavioural problems, cognitive ability, mediation

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).

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.

Materials and methods

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. Of the original 8,556 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 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 = 2,227). 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.

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).

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, 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, 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 minute), 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 "specialist medical care" (did not happen/ minor problem/ moderate problem/ major problem).

Childhood mediators

At 5 years mothers completed a shortened version of the Achenbach Child Behaviour Checklist (CBCL) (Achenbach, 1991) assessing 10 items each from the internalising and externalising scales, and 10 items from the social/attention/thought sub-scales. The most commonly occurring behaviours were included in the shortened version, and in this study we combined the items into a total behaviour problems scale (Alpha = 0.897), and dichotomised the scale defining 'cases' using a cut-off consistent with the percentage of cases identified by Achenbach in a community sample (Bor et al., 1997). Using a selected subsample of 76 parents at child age 5 years who completed the full version of the CBCL, the correlation between the full form and short form for total behaviour problems was found to be very high (r = 0.98) (Bor et al., 1997). Also at 5 years, children completed the Peabody Picture Vocabulary Test – Revised (PPVT-R), requiring them to indicate which one of four illustrations best represented a word expressed verbally by the examiner, resulting in a score measuring the subjects verbal ability (Jongsma, 1982). The PPVT-R has been validated against other standardised intelligence tests used on children (Childers et al., 1994, Dunn, 1981, Johnson et al., 1993).

Confounders

Maternal age, parity and level of education (incomplete high school/ completed high school/ undertaken tertiary education) were collected prenatally. In addition, mothers were asked how often and how much alcohol they consumed since becoming pregnant (none/ light/

moderate/ heavy), and offspring gender was recorded at birth. At the five year follow-up mothers again completed the Social Readjustment Rating Scale (Holmes and Rahe, 1967) (past six months) to give a stressful life events concurrent to child behaviour problems.

Statistical analysis

We explored the factor structure of the psychotic experiences with Exploratory Factor Analysis (EFA) using the Mplus version 6 default geomin rotation which is an oblique rotation method and is recommended in cases where a factor indicator may have a substantial loading on more than one factor (Browne, 2001, Muthén, 1998-2010), and using the Mplus weighted least squares with mean and variance adjustment (WLSMV) estimator which is appropriate for categorical data and shown to yield accurate test statistics, parameter estimates and standard errors under non-normal latent response distributions (Byrne, 2012). Next, we used Confirmatory Factor Analyses (CFA) guided by the EFA results, to test a range of structures including a single factor, multiple factors (correlated), and second-order and bifactor models (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). We took a systematic approach to our structural equation modelling, firstly assessing each variable for inclusion using univariate analysis. The risk factors were included in the full structural model only if they predicted the outcome in univariate analyses, while confounders were included *a priori*. In addition, we tested for the interaction of [(i) prenatal stressful life events × behaviour problems; (ii) prenatal stressful life events × cognitive ability], on the outcome. We used the continuous score of behaviour problems and cognitive ability in the interaction terms.

The final SEM was then constructed as follows: (i) temporally appropriate pathways were allowed between the risk factors, and the outcome was regressed on all of these factors; (ii) non-significant pathways were removed; (iii) every variable in the model was regressed on all confounding variables; (iv) non-significant pathways were removed before calculation of indirect parameter estimates of the effect of prenatal stressful life events on the outcome via behaviour problems. We used bootstrapping [1000 samples] to obtain bias corrected bootstrapped 95% confidence limits for the unstandardised indirect parameter estimates, which is preferable to the delta method (details of both methods can be found in MacKinnon et al. (2007)), resulting in the final model (estimates are probit regression parameters).

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. To address loss to follow-up, we used multivariate logistic regression in Stata v.12 to compare those who had been lost to follow-up with those used in the final analysis on a number of baseline variables to assess attrition bias on our results. In addition, from the multivariate logistic regression model we produced weights representing the inverse probability of each participant being included in the study. The final analysis was then replicated using these weights. We used inverse probability weighting instead of multiple imputation because missingness was likely to be associated with our outcome in addition to the risk factors (Lee and Carlin, 2012).

Results

The prevalence of individual life time delusions and hallucinations was very low in our sample, ranging between 1.1-3.7% and 1.3-8.8% respectively (see supplementary table 1), and 624 (24%) individuals had at least one psychotic symptom. This low prevalence reflects our method of psychotic experiences ascertainment by which positive responses were probed for truly psychotic content. In all, 36 people received a DSM-IV diagnosis of any psychotic disorder, including four with schizophrenia, four with delusional disorder, four with schizophreniform and 24 with brief psychotic disorder). The results of the measurement model revealed the positive experiences of psychosis were best represented by a bifactor model (shown in figure 1) which included a general psychosis factor, onto which all indicators loaded, and two group specific factors defined by paranoia/reference and thought interference (see supplementary section for a comprehensive summary).

Table 1 shows the results of the univariate analyses in which the risk factors and confounders were regressed on the three factors of the bifactor model. Of the risk factors, prenatal stressful life events and smoking, in addition to total behaviour problems and PPVT-R at age 5 years predicted the general factors of positive experiences of psychosis. Maternal stressful life events reported at child age 5 years was not associated with psychotic experiences. Of the confounding factors, gender and maternal education predicted psychotic experiences. Thus, all non-significant risk factors were dropped (in addition to PPVT-R which) from further analysis, while the confounders were retained, as according to the approach outlined in the methods section.

We found no statistical evidence for interaction [(i) prenatal stressful life events × behaviour problems $p = 0.863$; (ii) prenatal stressful life events × cognitive ability $p = 0.805$]. Risk factors not found to predict psychotic experiences including cognitive ability and maternal stressful life events during childhood were excluded from further analysis and the group specific factors of paranoia/reference and thought interference were not predicted.

The final model was then constructed following the steps given in the methods. Prenatal stressful life events did not predict psychotic experiences directly, but indirectly via childhood behaviour problems, producing an indirect effect via both the delta and bias corrected bootstrapping methods. In addition, after adjustment for confounders prenatal smoking no longer predicted psychotic experiences, due mostly to the addition of maternal education (see table 2 and figure 2).

Despite maternal stressful life events at child age 5 years not predicting the outcome in univariate analysis, we carried out a sensitivity analysis including it in the final model to be more certain the indirect effect was not confounded by this factor. We found stressful life events at 5 years did not predict the outcome and did not substantively change the direct or indirect parameters of interest (results available from corresponding author). The supplementary analysis revealed that the general factor of psychotic experiences strongly predicted all DSM-IV disorders tested (table 3), the paranoia/reference factor predicted social phobia, while the thought interference factor did not predict any disorders.

Results from the attrition analysis showed that mothers who were lost to follow-up were more likely to be younger, have previous children, less likely to have completed high school, more likely to smoke and to drink at low levels. In addition, mothers lost to follow-up had a small

increase in the number of stressful life events experienced during pregnancy. When we replicated our analysis using inverse probability weights, as a method to determine if our results had been biased by attrition, we found the results were virtually the same as those presented here (see supplementary tables 2 and 3).

Discussion

Using data from a prospective pre-birth cohort study, we found statistical evidence for mediation, suggesting that premorbid behavioural problems in childhood represent the early neurodevelopmental sequelae of exposure to prenatal stressful life events, later resulting in a greater risk of psychotic experiences as the subject ages. This interpretation is consistent with previous research into prenatal infections (Brown et al., 2001, Ellman et al., 2009). On the other hand, we found that prenatal stressful life events and premorbid behavioural problems were not related to later psychosis experiences in a manner consistent with the theory that abnormal development represents the early manifestation of a genetic susceptibility to schizophrenia, moderating the risk of prenatal stress. This does not support findings from a previous study where the risk of schizophrenia due to obstetric complications was moderated by delays in early motor development (Clarke et al., 2011). Support for mediation, along with our interpretation of the significance of developmental abnormalities to psychotic illness, is found in animal studies which inherently control for genetic variability and find that the increased post-adolescent schizophrenia-like behaviour in rats exposed to prenatal stress is preceded by cognitive, behaviour and loco-motor abnormalities (Meyer and Feldon, 2010). In summary, we elucidated an important factor in the pathway from prenatal stress to psychotic experiences, thus providing novel evidence in support of the neurodevelopmental model of schizophrenia and related disorders.

An important consideration of our results is that child behaviour problems predicted psychosis experiences regardless of the inclusion of prenatal stressful life events in our model. A previous MUSP study found that behaviour problems at age 5 and 14 years predicted an increased risk of delusions at age 21 (Scott et al., 2009), measured using the self-

reported Peter's Delusional Inventory (PDI) (Peters et al., 2004). Thus it may be that the risk of psychotic experiences due to behaviour problems, not explained by previous environmental exposures, is indicative of genetic susceptibility (Cannon et al., 2002a). It also remains possible that additional early-life environmental exposures are responsible for the abnormalities which precede schizophrenia, as has been found for prenatal infections (Brown et al., 2001, Ellman et al., 2009), but not for obstetric complications (Clarke et al., 2011, Bearden et al., 2000). Importantly, the R-square of the final model revealed the combination of behaviour problems and gender explained only 5% of the variance of the outcome, meaning other environmental or genetic factors need to be identified to better explain the occurrence of psychotic experiences.

Animal models indicate that increased maternal stress hormones, produced in response to prenatal stressors, cross the placenta and result in permanent changes in regions of the developing fetal brain associated with schizophrenia (King et al., 2010), and result in schizophrenia-like behaviours in adult rats which are preceded by several abnormalities detailed earlier (Meyer and Feldon, 2010). However, the majority of early environmental exposures and premorbid developmental abnormalities which have been studied are non-specific risk factors for a range of psychiatric outcomes in adults (Meyer and Feldon, 2010), suggesting that common pathways to general psychopathology may intersect with specific risk factors to produce particular psychiatric outcomes (Cannon et al., 2002a). A case-control study concluded that additional unknown genetic and/or environmental factors are necessary to make the prenatal brain susceptible to the increased premorbid cognitive abnormalities and psychotic disorders caused by prenatal influenza, as influenza did not influence cognitive ability in control subjects (Ellman et al., 2009). Genetic factors clearly play a role, and studies using a family history of schizophrenia as a proxy of genetic susceptibility find this

factor is a necessary condition for the increased risk of schizophrenia associated with selected prenatal and perinatal risk factors (Clarke et al., 2009, Keskinen et al., 2013, Cannon et al., 2002b). However, the importance of environmental exposures is supported by the aforementioned animal studies which inherently control for genetic variation (Meyer and Feldon, 2010), and human studies which show that early environmental risks can also interact with one another to increase the risk of psychotic disorders (Fineberg et al., 2013).

Our study had a number of strengths. A number of aspects of our design were intended to facilitate a causal interpretation insofar as is possible for non-experimental studies. These aspects included temporally appropriate relationships among prospectively measured factors, whose relationships have theoretical and empirical support, and strong estimates, including an indirect pathway based on the latest mediation methodology (MacKinnon et al., 2007). The direct effect of behaviour problems led to a change of 0.20 SD units of the outcome, while the indirect effect of prenatal life events led to a change of 0.03 SD units of the outcome indirectly via behaviour problems. Thus, roughly 13% of the effect of behaviour problems on the outcome was contributed by the indirect effect from prenatal life events. Our findings remained robust after adjustment for a range of confounding factors, including prenatal and perinatal risk factors and maternal stressful life events concurrent to child behaviour at 5 years. Finally, we extend the findings of a recent study which found that prenatal stressful life events did not predict psychotic experiences in children aged 12 years after accounting for prenatal depression and anxiety (Dorrington et al., 2013). These factors did not predict the outcome in our results, and the inconsistencies in our findings may reflect the different ages of the samples. Evidence shows that psychotic experiences are less transitory and take on increasing clinical significance as individuals age (Kelleher et al.,

2012), and thus the relationship between prenatal stress and psychotic experiences may become more evident in early adulthood than in childhood.

Our outcome measured the dimensional model of positive experiences of psychosis with an increased level of specification compared with previous risk factor studies which have predicted psychotic experiences. Firstly, epidemiological investigations into psychotic experiences have mostly relied on measurements ascertained via self-report or structured interview. These methods overestimate the prevalence of psychotic experiences in the population and underestimate their importance by not probing positive responses to confirm their psychotic nature (Zammit et al., 2013). We used psychotic experiences derived from a semi-structured interview, and as expected the majority of positive responses were in fact deemed non-psychotic after further probing. Further, 1.4% of our sample was diagnosed with any DSM-IV psychotic disorder, which is in line with prevalence estimates calculated in reviews (Jablensky, 2000, Saha et al., 2005). Secondly, the psychosis continuum is most often operationalised as a simple count of number of experiences (van Os et al., 2009), which ignores the complicated structure of the psychosis continuum. We used structural equation modelling to properly specify the multidimensional phenotype of psychosis, distinguishing between core symptomatic expression and unrelated variance. In doing so we found a structure closely representing the three principle dimensions of positive experiences of psychosis identified previously (Wigman et al., 2012, Wigman et al., 2011), and then imposed a general construct across the three highly correlated psychotic subdimensions (Reininghaus et al., 2013). Lastly, our general factor of positive experiences of psychosis was found to have strong psychopathological significance, and was strongly related to non-psychotic DSM-IV disorders also measured at 21 years.

Our study also had a number of limitations. Firstly, as the stressful life events may have occurred at any stage over the last 6 months of gestation, we were unable to provide information with regard to what period during pregnancy may be the most sensitive for an increased risk of later psychotic experiences. Recent studies find that stressful life events are most predictive of schizophrenia and affective disorders if exposure occurs in the first and second trimesters (Khashan et al., 2008, Khashan et al., 2011, Kleinhaus et al., 2013), while exposure in the third trimester may predict autism disorders (Class et al., 2013). Thus had we exposure information during trimester 1 we may have found a stronger relationship. Further, if we had been able to measure events occurring across the entire pregnancy and define the trimester in which the stressful life events had occurred, we may have found a more robust association. Secondly, we argued that the premorbid behavioural abnormalities which mediated the relationship between prenatal stress and later psychotic experiences represented pre-schizophrenia sequelae due to the environmental insult. However, as findings show premorbid behaviour to be present in the unaffected siblings of individuals with schizophrenia (Bearden et al., 2000), and much of the premorbid abnormalities are yet to be explained by preceding environmental exposures (Cannon et al., 2002a), genetic factors related to schizophrenia risk are likely to play a crucial role in the indirect relationship we found. That we could explore neither molecular nor proxy genetic factors is a major limitation in need of redress by future studies. Further, additional genetic and environmental factors not included in our study are needed to explain how non-specific risk factors (such as prenatal stressful life events and childhood behaviour problems) lead to psychotic illness instead leading to other psychiatric outcomes. Thirdly, unlike previous research which studied truly independent stressful events (Khashan et al., 2008, van Os and Selten, 1998, Selten et al., 1999, Malaspina et al., 2008), we used every day stressful life events which although measured objectively may be partly influenced by maternal or paternal personality

and temperament. As these factors are partly heritable and may impact offspring behaviour and psychotic experiences, this represents another pathway by which genetic factors may have confounded the relationship. Finally, our cohort was subject to considerable attrition, which was related to prenatal stressful life events. Despite this, results from our inverse probability analysis suggested attrition did not substantively change any parameter estimates in our model.

In conclusion, our findings suggest that the impact of prenatal stressful life events on later psychotic experiences is mediated via a broad measure of behavioural problems at age five. As we controlled for a number of important confounders and used prospective measures of risks and outcome, our results suggest the consequences of exposure to prenatal stress may appear early, manifesting as general behavioural problems, before resulting in increased risk of psychotic experiences. As both prenatal stressful life events and child behaviour problems are non-specific risks for a range of psychiatric disorders in adulthood, further studies should investigate what other conditions are necessary along this pathway to ultimately result in psychotic experiences. Lastly, further investigation into the clinical significance of psychotic experiences and how they relate to non-psychotic psychiatric disorders is necessary.

Funding and finance

Conflict of interest: All authors declare no conflicts of interest

Funding/Support: This study was funded by the National Health and Medical Research Council (NHMRC). R.A. is funded by a NHMRC Career Development Award Level 2 in Population Health (APP1012485).

Acknowledgements

Additional Contributions: The authors thank the MUSP team, MUSP participants, the Mater Misericordiae Hospital, and the Schools of Social Science, Population Health and Medicine (University of Queensland).

Ethical Standards: 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.

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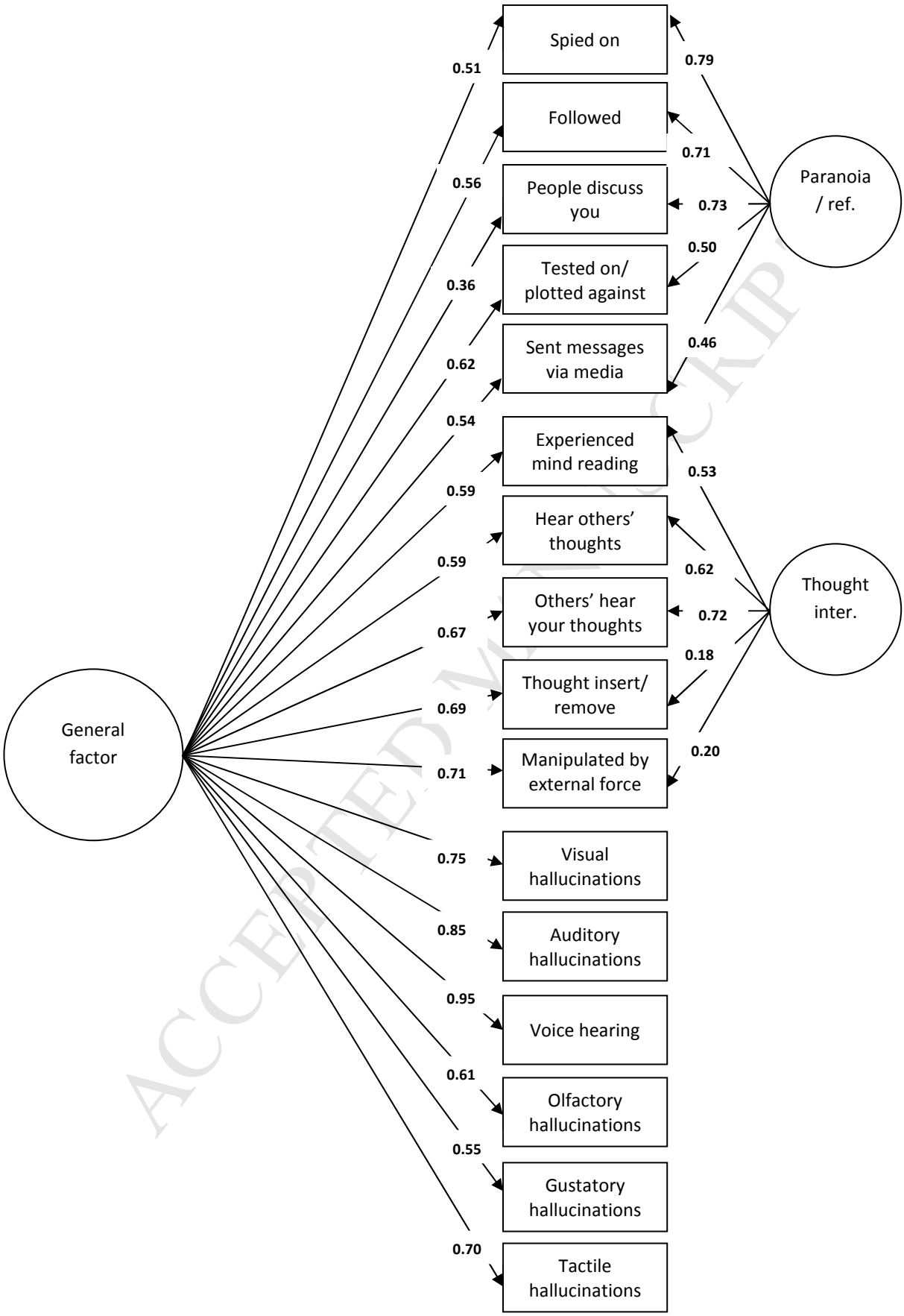

Figure 1: Bifactor model of lifetime positive psychotic experiences at age 21 years (standardised factor loadings).

Table 1: Univariate associations between the predictors, mediators and confounders with bifactor of psychotic experiences

Risk factors		**General psychotic experiences**				**Experiences of paranoia and reference**				**Experiences of thought interference**			
Prenatal/perinatal	*n*	USPE	SE	p-Value	SPE	USPE	SE	p-Value	SPE	USPE	SE	p-Value	SPE
stressful life events (prenatal)	2,542	0.06	0.03	**0.030**	**0.08**	0.04	0.05	0.921	0.05	-0.03	0.05	0.548	-0.03
smoking (prenatal)	2,533	0.14	0.05	**0.008**	**0.09**	0.02	0.10	0.871	0.01	-0.03	0.09	0.722	-0.03
maternal anxiety (prenatal)	2,519	0.02	0.02	0.481	0.02	-0.01	0.04	0.733	-0.02	-0.02	0.04	0.648	-0.03
maternal depression (prenatal)	2,523	0.00	0.03	0.895	-0.01	0.03	0.05	0.528	0.03	0.02	0.05	0.770	0.02
pre-eclampsia *(birth)*	2,558	-0.06	0.12	0.606	-0.06	0.00	0.23	0.987	0.00	0.16	0.22	0.473	0.16
bwt continuous (birth)	2,558	-0.03	0.03	0.410	-0.03	0.01	0.06	0.921	0.01	-0.05	0.07	0.471	-0.05
bwt ≤10 percentile (birth)	2,558	0.18	0.12	0.117	0.18	-0.08	0.22	0.718	-0.08	-0.10	0.02	0.654	-0.10
apgar score <7 (birth)	2,431	0.04	0.10	0.681	0.04	0.18	0.15	0.230	0.18	-0.07	0.16	0.657	-0.07
forced induction of labour (birth)	2,502	0.01	0.07	0.909	0.01	-0.18	0.13	0.161	-0.18	0.05	0.12	0.674	0.05
baby specialist medical attent. (birth)	2,523	0.06	0.05	0.234	0.04	-0.11	0.08	0.199	-0.07	-0.11	0.09	0.239	-0.07
negative life events (5 yrs)	2,160	0.05	0.03	0.063	0.07	0.03	0.05	0.580	0.04	-0.04	0.05	0.440	-0.05
total behaviour problems (5 yrs)	2,306	0.33	0.11	**0.003**	**0.10**	0.04	0.19	0.853	0.01	-0.34	0.21	0.100	-0.11
PPVT-R continuous score (5 yrs)	1,953	-0.01	0.00	**0.049**	**-0.08**	0.00	0.01	0.367	0.06	0.00	0.01	0.539	0.044
PPVT-R dichotomised (lowest 10%) (5 yrs)	1,953	0.07	0.12	0.539	0.07	0.06	0.19	0.287	0.06	-0.251	0.283	0.375	-0.25
Confounders													
maternal age (prenatal)	2,558	-0.01	0.01	0.237	-0.04	0.00	0.01	0.836	-0.01	0.00	0.01	0.836	-0.01
parity (prenatal)	2,558	0.01	0.03	0.669	0.02	-0.02	0.05	0.744	-0.02	-0.09	0.06	0.132	-0.11
maternal education (prenatal)	2,540	0.16	0.06	**0.004**	**0.10**	-0.01	0.09	0.889	-0.01	-0.28	0.11	0.010	-0.164
prenatal alcohol (prenatal)	2,540	0.02	0.05	0.712	0.01	-0.04	0.08	0.631	-0.02	0.05	0.09	0.590	0.03
offspring gender	2,558	0.23	0.07	**0.001**	**0.23**	-0.34	0.13	0.006	-0.34	-0.30	0.12	0.12	-0.30

Note: Estimates presented as Unstandardised Parameter Estimates (USPE), Standard Errors (SE) and p-Values, and Standardised Parameter Estimates (SPE).

Table 2: Structural equation model showing weighted least squares (WLSMV) estimates of the direct and indirect effect of prenatal maternal stress and smoking on offspring positive experiences of psychosis at age 21 (*n* = 2,227)

Outcome/mediator/prenatal risk	Predictor	USPE	SE	p-Value	SPE
Direct effects					
psychotic experiences (21 yrs)	total behaviour problems (5 yrs)	0.20	0.06	<0.001	0.19
total behaviour problems (5 yrs)	stressful life events (prenatal)	0.16	0.03	<0.001	0.19
	smoking (prenatal)	0.25	0.06	<0.001	0.15
stressful life events (prenatal)	parity	0.08	0.03	0.005	0.07
	maternal age (prenatal)	-0.04	0.01	<0.001	-0.14
smoking (prenatal)	parity	0.03	0.01	0.018	0.06
	maternal age (prenatal)	-0.02	0.00	<0.001	-0.16
	maternal education (prenatal)	0.16	0.02	<0.001	0.16
	maternal alcohol (prenatal)	0.16	0.02	<0.001	0.15
Indirect effects					
psychotic experiences. (21 yrs)	stressful life events (prenatal) *via behaviour problems (5 yrs)*	0.03	0.01	0.003	0.04

Note: Estimates presented as Unstandardised Parameter Estimates (USPE), Standard Errors (SE) and p-Values, and Standardised Parameter Estimates (SPE).
The bias corrected bootstrapping 95% confidence limits support the unstandardised indirect parameter estimates in the table [prenatal stressful life events USPE=0.03 (0.01, 0.07)].
Fit indices: CFI = 0.99; TLI = 0.98; RMSEA = 0.011; chi-square = 273.90; D.F = 212; p-value = 0.003.

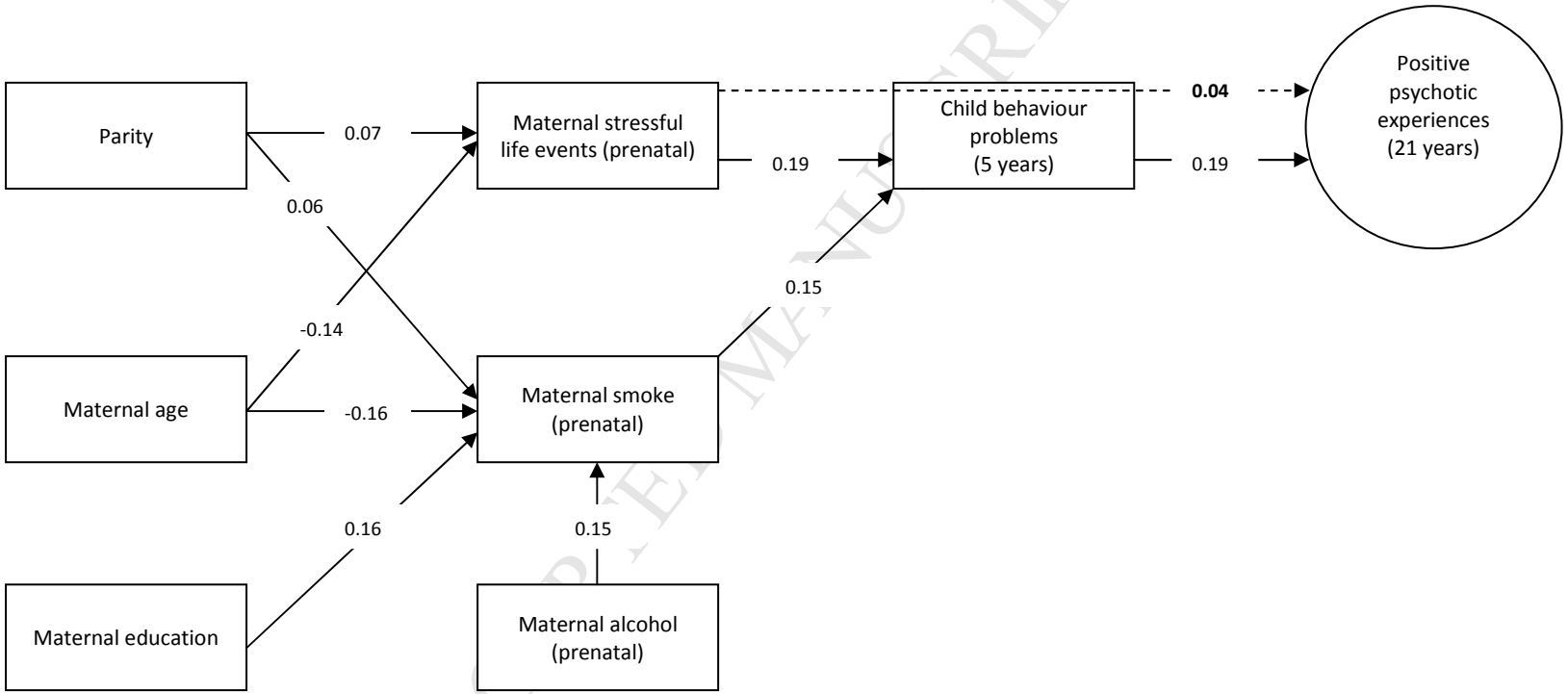

Figure 2: Structural equation model showing the effects of prenatal maternal stressful life events and smoking, and child behaviour problems on positive psychotic experiences in offspring at 21 years (n = 2,227). Showing standardised parameter estimates (all estimates are significant at $p < 0.05$ – see table 3 for standard errors and p-values).

The outcome is the general factor from the bifactor model. The dashed line represents the indirect estimates of prenatal stressful life events > child behaviour problems > psychotic experiences. Indirect estimates bolded.

Table 3: Univariate associations between the general and two specific factors of positive psychotic experiences with DSM-IV lifetime disorders at age 21 years [Parameter estimates are probit regressions using WLSMV estimation] (*n* = 2558)

	MDD			GAD			Mania			Social Phobia			PTSD		
Psychosis factors	USPE	SE	p-value	USPE	SE	p-value	USPE	SE	p-value	USPE	SE	p-value	USPE	SE	p-value
General factor	0.46	0.04	<0.001	0.43	0.06	<0.001	0.45	0.07	<0.001	0.33	0.05	<0.001	0.36	0.06	<0.001
Paranoia/reference	0.02	0.08	0.829	0.00	0.11	0.963	0.18	0.11	0.087	0.20	0.09	0.029	0.05	0.11	0.629
Thought interference	-0.04	0.07	0.578	-0.17	0.11	0.129	-0.13	0.16	0.418	0.01	0.09	0.934	-0.02	0.09	0.825

Note: Major Depressive Disorders (MDD), Generalised Anxiety Disorders (GAD), Post-traumatic Stress Disorders (PTSD).
Estimates presented as Unstandardised Parameter Estimates (USPE), Standard Errors (SE) and p-Values; Standardised Parameter Estimates (SPE) are not shown because they are equivalent to USPE

Acknowledgment

Attention Editors

Re: paper 'Exposure to stressful life events during pregnancy predicts psychotic experiences via behaviour problems in childhood'.

Additional Contributions: The authors thank the MUSP team, MUSP participants, the Mater Misericordiae Hospital, and the Schools of Social Science, Population Health and Medicine (University of Queensland).

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- Prenatal stress predicted later psychotic experiences via child behaviour problems.
- We used SEM to specify the multidimensional phenotype of psychosis.
- Our findings broadly support the neurodevelopmental model of schizophrenia.

Contributors

Attention Editors

Re: paper 'Exposure to stressful life events during pregnancy predicts psychotic experiences via behaviour problems in childhood'.

Authorship: KB devised the hypothesis, study design, conducted initial analysis and wrote the first draft of the manuscript. GMW provided statistical consultation and contributed to drafting the final version of the manuscript. JMN contributed to MUSP study design data collection and writing. JS and RA contributed to data interpretation and writing of the manuscript. All authors provided critical input and approved the final version of the manuscript.

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Funding Source

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This study was funded by the National Health and Medical Research Council (NHMRC). R.A. is funded by a NHMRC Career Development Award in Population Health (ID 519721). We acknowledge the support of the Australian Health Management (AHM) in the review and preparation of this manuscript.

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

Supplementary text 1: Results of factor analysis

Results from EFA revealed a three factor solution had superior fit (1 factor – CFI = 0.91, TLI = 0.91, RMSEA = 0.033; 2 factors – CFI = 0.96, TLI = 0.97, RMSEA = 0.021; 3 factors – CFI = 0.99, TLI = 0.99, RMSEA =0.010; 4 factors – identification problems), with the three highly correlated factors discriminating between delusions of paranoia and reference (F1), delusions of thought interference (bizarre/and non-bizarre) (F2), and hallucinations (F3). Using CFA we firstly replicated the 1 factor and correlated three factor models. Next, because (i) the unidimensional model indicated poor fit, (ii) the three factors in the multidimensional model were strongly correlated (F1 with F2 = 0.53; F1 with F3 = 0.59; F2 with F3 = 0.74), and (iii) we wanted to use risk factors to predict a 'general' positive psychotic experiences factor (if the data permitted), we then constructed a second-order and a bifactor model. The first-order and specific factors of hallucinations, in the second-order and bifactor models respectively, had non-significant residual variance, and in both cases when the hallucination items were instead loaded directly and solely onto the second-order or general factor the factor loadings were high and the residual variance of the items were also non-significant. Though largely equivalent we chose the bifactor model as it had superior fit and because it is the best solution when it is unclear if a unidimensional or multidimensional representation best fits the data (i.e., large factor loadings on the unidimensional model), because the general (overall) factor is retained while specific factors (in this case paranoia/reference and thought interference) can also be modelled separately [1] (see supplementary table 1 and figure 1).

Supplementary table 1: Standardised factor loadings (with standard errors) and fit indices for the 1 factor, 3 factor (correlated) and bifactor models of lifetime positive psychotic experiences at 21 years (*n* = 2,558)

Symptoms (DSM-IV)	Prevalence	1 Factor CFA	3 Factor CFA (correlated factors)			Bifactor model		
	% (*n*)	Factor 1	Factor 1	Factor 2	Factor 3	General factor	Specific factor 1	Specific factor 2
Delusions (paranoia/reference)								
spied on	1.8% (46)	0.79 (0.04)	0.89 (0.04)			0.51 (0.07)	0.79 (0.06)	
followed	2.0% (51)	0.79 (0.04)	0.91 (00.4)			0.56 (0.06)	0.71 (0.06)	
people discussing you	1.4% (37)	0.62 (0.06)	0.73 (0.06)			0.36 (0.08)	0.73 (0.08)	
tested on/plotted against	1.1% (28)	0.71 (0.05)	0.85 (0.06)			0.62 (0.07)	0.50 (0.08)	
sent messages via media	1.1% (28)	0.62 (0.06)	0.75 (0.07)			0.54 (0.08)	0.46 (0.11)	
Delusions (thought interference)								
experienced mind reading	1.6% (40)	0.73 (0.05)		0.79 (0.05)		0.59 (0.07)		0.53 (0.07)
hear others' thought	3.4% (86)	0.78 (0.03)		0.84 (0.03)		0.59 (0.05)		0.62 (0.07)
others' hear your thoughts	3.7% (95)	0.85 (0.03)		0.94 (0.03)		0.67 (0.05)		0.72 (0.08)
thought insertion/removal	1.3% (32)	0.68 (0.06)		0.77 (0.06)		0.69 (0.07)		0.18 (0.09)
manipulated by external force	1.3% (32)	0.68 (0.06)		0.78 (0.06)		0.71 (0.06)		0.20 (0.10)
Hallucinations								
visual hallucinations	7.7% (196)	0.70 (0.03)			0.75 (0.03)	0.75 (0.03)		
auditory hallucinations	4.3% (111)	0.81 (0.03)			0.85 (0.03)	0.85 (0.03)		
voice hearing	2.2% (55)	0.90 (0.03)			0.95 (0.03)	0.95 (0.03)		
olfactory hallucinations	4.1% (104)	0.57 (0.05)			0.62 (0.05)	0.61 (0.05)		
gustatory hallucinations	4.7% (120)	0.51 (0.05)			0.55 (0.05)	0.55 (0.05)		
tactile hallucination	8.8% (225)	0.65 (0.04)			0.70 (0.04)	0.70 (0.04)		
CFI; TLI		0.92; 0.91		0.99; 0.98			0.99; 0.99	
RMSEA		0.033		0.014			0.010	
Chi-square (free parameters)		395.76 (104)		151.68 (101)			116.94 (94)	

Note: The second-order model (not shown) was considered unsuitable as it had inferior fit (CFI = 0.98; TLI = 0.98, RMSEA = 0.016; chi-2 = 166.33; free parameters = 102) and the first order hallucinations factor had a non-significant residual variance (0.16; p = 0.274).
Parameters were derived using the WLSMV estimator and all factor loadings and factor variances were significant.

Supplementary table 2: Multivariate attrition analysis comparing those included in the analysis (*n* = 2,227) versus those lost to follow-up but with values on all baseline variables of interest (*n* = 4,822) [expressed in OR with 95% Confidence Intervals (CI)] (total *n* = 7,049)

Effect	OR (95% CI)	P-value	P for LRT
Offspring gender	*ref: male*		
Female	0.81 (0.73, 0.90)	<0.001	<0.001
Mother's age at birth	0.96 (0.95, 0.97)	<0.001	<0.001
Parity	1.13 (1.07, 1.19)	<0.001	<0.001
Prenatal stressful life events	**1.09 (1.05, 1.34)**	**<0.001**	**<0.001**
Maternal education	*ref: tertiary*		
high School	1.13 (0.98, 1.29)	0.086	
incomp. High School	1.36 (1.14, 1.62)	0.001	0.002
Maternal smoking	*ref: none*		
1-19	1.16 (1.03, 1.31)	0.013	
20+	1.32 (1.08, 1.61)	0.007	0.004
Maternal alcohol	*ref: none*		
low	0.83 (0.75, 0.93)	0.001	
moderate	1.12 (0.79, 1.58)	0.536	
high	1.21 (0.78, 1.88)	0.396	0.002

Note: Showing the odds of not being included in the study by baseline variables included in the final model

Supplementary table 3: Structural equation model showing weighted least squares (WLSMV) estimates of the direct and indirect effect of prenatal maternal stress and smoking on offspring positive psychotic experiences at age 21 (*n* = 2,227) [results based on inverse probability weights]

Outcome/mediator/prenatal risk	Predictor	USPE	SE	p-Value	SPE
Direct effects					
psychosis experiences (21 yrs)	total behaviour problems (5 yrs)	0.21	0.06	<0.001	0.20
total behaviour problems (5 yrs)	stressful life events (prenatal)	0.16	0.03	<0.001	0.19
	smoking (prenatal)	0.15	0.06	<0.001	0.14
stressful life events (prenatal)	parity	0.07	0.03	0.005	0.07
	maternal age (prenatal)	-0.03	0.01	<0.001	-0.14
smoking (prenatal)	parity	0.03	0.01	0.018	0.06
	maternal age (prenatal)	-0.02	0.00	<0.001	-0.15
	maternal education (prenatal)	0.16	0.02	<0.001	0.16
	maternal alcohol (prenatal)	0.15	0.02	<0.001	0.15
Indirect effects					
psychosis experiences (21 yrs)	stressful life events (prenatal) *via behaviour problems (5 yrs)*	0.03	0.01	0.002	0.04

Note: Estimates presented as Unstandardised Parameter Estimates (USPE), Standard Errors (SE) and p-Values, and Standardised Parameter Estimates (SPE).
The bias corrected bootstrapping 95% confidence limits support the unstandardised indirect parameter estimates in the table [prenatal negative life events USPE=0.03 (0.01, 0.07)].
Fit indices: CFI = 0.98; TLI = 0.98; RMSEA = 0.012; chi-square = 277.48; D.F = 212; p-value 0.002.