Author(s): S. Zammit*, D. Odd, J. Horwood, A. Thompson, K. Thomas, P. Menezes, D. Gunnell, C. Hollis, D. Wolke, G. Lewis and G. Harrison

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Investigating if adverse prenatal and perinatal events are associated with non-clinical psychotic symptoms at age 12 in the ALSPAC birth cohort

Stanley Zammit, David Odd, Jeremy Horwood, Andrew Thompson, Kate Thomas, Paulo Menezes, David Gunnell, Chris Hollis, Dieter Wolke, Glyn Lewis, Glynn Harrison

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Corresponding author*:* Dr Stanley Zammit, Department of Psychological Medicine, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, Wales, UK

Tel: +44(0)2920 743058 Fax: +44(0)2920 747839 email: zammits@Cardiff.ac.uk

ABSTRACT

Background: Non-clinical psychosis-like symptoms (PLIKS) occur in about 15% of the population. It is not clear whether adverse events during early development alter risk of developing PLIKS. We aimed to examine whether maternal infection, diabetes or pre-eclampsia during pregnancy, gestational age, perinatal cardio-pulmonary resuscitation or 5-minute Apgar score were associated with development of PLIKS during early adolescence.

Methods: This is a longitudinal study of 6,356 12-year old adolescents who completed a semi-structured interview for psychotic symptoms in the ALSPAC birth cohort. Prenatal and perinatal data were obtained from obstetric records and maternal questionnaires completed during pregnancy.

Results: Presence of definite PLIKS was associated with maternal infection during pregnancy (adjusted OR = 1.44, 95%CI 1.11, 1.86; p=0.006), maternal diabetes (adjusted OR = 3.43, 95%CI 1.14, 10.36; p=0.029), need for resuscitation (adjusted OR = 1.50, 95%CI 0.97, 2.31; p=0.065), and 5-minute Apgar score (adjusted OR per-unit decrease = 1.30, 95%CI 1.12, 1.50; p<0.001). None of these associations were mediated by childhood IQ-score. Most associations persisted, but were less strong, when including suspected as well as definite symptoms. There was no association between PLIKS and gestational age or pre-eclampsia.

Conclusions: Adverse events during early development may lead to an increased risk of developing PLIKS. Although the status of PLIKS in relation to clinical disorders such as schizophrenia is not clear, the similarity between these results and findings reported for schizophrenia indicates that future studies of PLIKS may help us

understand how psychotic experiences and clinical disorders develop throughout the life-course.

INTRODUCTION

About 15% of the population report experiencing delusions or hallucinations (Eaton *et al.*, 1991; Poulton *et al.*, 2000; van Os *et al.*, 2001; Johns *et al.*, 2004; Wiles *et al.*, 2006), although prevalence of clinical psychotic disorders is much lower (Kendler *et al.*, 1996; Perala *et al.*, 2007). It is not clear if these relatively common psychotic experiences represent an early expression of neurodevelopmental pathological processes that lead to schizophrenia, or whether they simply reflect common variation in the way individuals cognitively appraise, and describe, their surrounding environment, with little or no implications for health.

Although the body of evidence is not strong, results from the Dunedin (Poulton *et al.*, 2000) and NEMESIS (Hanssen *et al.*, 2005) cohorts suggest that people experiencing such symptoms may be at increased risk of developing clinically important psychotic disorders later in life. Studying PLIKS may increase our understanding of the development of psychotic experiences, and potentially help elucidate aetiological mechanisms underlying schizophrenia.

The neurodevelopmental model of schizophrenia postulates that neural insults from embryonic development through childhood and adolescence all play a causal role in the onset of this disorder. For example, maternal exposure to famine (Susser *et al.*, 1996; St Clair *et al.*, 2005) or to influenza (Brown *et al.*, 2004; Byrne *et al.*, 2007), as well as other prenatal and perinatal complications (see review by Cannon *et al.* 2002), have been associated with increased risk of schizophrenia in the offspring. A cross-sectional study of adolescents reported no association between psychotic

symptoms and composite measures of pregnancy and birth complications, as recalled by the mothers (Spauwen *et al.*, 2004). However there have been no longitudinal studies to date that we are aware of that have examined whether specific, adverse prenatal or perinatal events exposures are associated with development of non-clinical psychotic symptoms.

METHOD

Sample

This study examines data from 6356 children from the ALSPAC cohort who participated in the PLIKS semi-structured interview (PLIKSi) (Horwood *et al.*, 2008) at age 12 (data restricted to 1 child per nuclear family). The initial Avon Longitudinal Study of Parents and Children (ALSPAC) (www.alspac.bris.ac.uk) consisted of 14,062 children born to residents of the former Avon Health Authority area who had an expected date of delivery between 1st April 1991 and 31st December 1992. The cohort was set up to examine genetic and environmental determinants of health and development (Golding *et al.*, 2001). The parents have completed regular postal questionnaires about all aspects of their child's health and development since birth. The children have attended annual assessment clinics since age 7. Due to attrition and wave non-response, sample sizes in the analyses differ according to exposures and datasets examined (see Results & Tables).

Measures

Outcomes: The PLIKSi covers past 6-month occurrence of 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). For these 12 core items, 7 screening (stem) questions were derived from DISC-IV (Shaffer *et al.*, 2000) and 5 questions from SCAN version 2.0 (WHO, 1994) modified slightly after piloting (further detail available at http://www.bris.ac.uk/psychiatry/index.html (*address to be finalised*)). Coding of all items followed the glossary definitions and

rating rules for SCAN, and clinical cross-questioning and probing by psychologists trained in using the PLIKSi was used to establish the presence or absence of symptoms. Interviewers rated symptom as either not present, suspected or definitely present. Unclear responses after probing were always 'rated down', and symptoms only rated as definite when a credible example was provided. We included symptoms in our analyses only if they were not attributable to effects of sleep, fever or substance use, consistent with the approach of classification systems for diagnosis of functional psychotic disorders. The average kappa value for inter-rater reliability was 0.72.

We examined two primary PLIKS outcomes: a) presence of any suspected or definite symptoms, and b) a narrower outcome of definite symptoms only. As secondary analyses, we also examined associations with more frequently occurring symptoms (definite symptoms occurring ≥monthly), and with symptoms that may be more characteristic of schizophrenia (any suspected or definite 'bizarre' PLIKS). These symptoms, accorded greater weighting in both DSM-IV and ICD-10 criteria for schizophrenia, included either third person auditory hallucinations, delusions of control, or delusions of thought broadcast, insertion or withdrawal.

Exposures (a): In the main dataset we examined the following pregnancy-related exposures: i) maternal influenza or any other infections, ii) need for resuscitation, iii) 5-minute Apgar score, and iv) gestational age at birth.

Data on pre-natal exposure to influenza or other infections were obtained from self-report postal questionnaires completed by the mother at 18 and 32 weeks of pregnancy, and 2 months post-natally. We examined associations with these

exposures at any time during pregnancy, and also examined whether effects were different according to trimester of exposure.

Information on admission, resuscitation and perinatal well-being was retrieved from computerized records of all infants born in the two main maternity hospitals in the region (92% of the cohort). Our primary measure of hypoxia was resuscitation, defined as either positive pressure respiratory support (using a face mask or endotracheal tube) or cardiac compressions. Receipt of ambient oxygen alone was not considered to be a marker of clinical hypoxia, and these infants were included in the non-resuscitation group. As well as comparing infants who were or were not resuscitated, we also examined whether associations were stronger for children who received resuscitation and a) were admitted to a neonatal unit, and b) also developed signs of encephalopathy (defined as presence of seizures, jitteriness, a high-pitched cry, hypo- or hypertonia, or hyper-reflexia during admission). Data on 5-minute Apgar score was examined as a marker of perinatal well-being (scores ranging from 0 to 10, with 10 being the best outcome). Gestational age was analysed both as continuous (weeks) and categorical (pre-term (≤36 weeks), normal term (37-42 weeks), post-term (>42 weeks)) data.

Exposures (b): We also conducted a nested case-control study to examine whether maternal diabetes or pre-eclampsia were associated with PLIKS. Information on these two exposures was available only after manual retrieval and examination of obstetric records. As resources were limited this was done for all adolescents who reported PLIKS, and a random 20% of those without PLIKS on interview. Data was extracted blind to PLIKS status. We examined PLIKS associations with a) either a clinician

diagnosis of diabetes in the obstetric records or self-reported diabetes from a questionnaire at 12-weeks gestation, and b) poorly-controlled diabetes, defined as above but with additional presence of either birth weight >90th percentile, or presence of maternal glycosuria recorded on ≥3 antenatal visits. For pre-eclampsia, we examined associations with a) maternal pre-eclampsia (defined as systolic blood pressure ≥140mmHg or diastolic ≥90mmHg, with proteinuria (>trace), on ≥2 antenatal visits), and b) pre-eclampsia with intra-uterine growth restriction (IUGR) (as above but with additional presence of birth weight <10th percentile).

Confounders: Potential confounders were selected *a priori* on the basis of previous reports in the literature of their association with pregnancy or birth complications and with psychosis. In order to examine the potential confounding impact of multiple family risk factors a Family Adversity Index (FAI) was used (Bowen *et al.*, 2005). The FAI consists of 18 items taken from questionnaires that were administered during pregnancy. The index was based on a series of measures describing various aspects of family functioning covering early parenthood (maternal age <20 years at first child birth), housing adequacy, financial difficulties, parent educational qualifications, family size, social support, maternal relationship with partner, maternal affective disorder, parental substance abuse, and involvement with crime. If adversity was present this was rated as 1 and then totalled across the 18 items.

Other confounders adjusted for include urban/rural index at birth (urban/town, village/hamlet), maternal age, maternal use of prescribed medication (analgesics or hypnotics), maternal smoking during pregnancy, and maternal depression during pregnancy (Edinburgh Postnatal Depression Scale (Cox *et al.*, 1987)). For maternal diabetes we also adjusted for maternal body mass index (BMI).

We considered child total IQ score at age 8, from the Wechsler Intelligence Scale for Children (III) (Wechsler, 1991), as a potential mediator of any relationship between prenatal or perinatal exposures and development of PLIKS (i.e. lying on the causal pathway). We also considered birth weight (as a marker of chronic in-utero adversity) as a potential mediator for prenatal exposures, as lower birth weight was found to be associated with PLIKS at age 12 in this cohort (Thomas *et al*, submitted).

Ethical approval

Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

Statistical analysis

Logistic regression was used to calculate odds ratios and 95% confidence intervals for PLIKS given the prenatal and perinatal exposures. Examination of whether a non-linear relationship (within the logistic model) between weeks of gestation and PLIKS provided a better fit for the data was made by inclusion of quadratic terms and use of likelihood ratio tests (LRTs) to compare different models. All analyses, apart from those examining gestational age, were restricted to term births (>36 and <43 weeks gestation).

Missing data: Attrition is a problem common to all large-scale longitudinal studies (Plewis et al., 2004; Callaway et al., 2007). To examine if missing data may have biased our results we conducted sensitivity analyses using multiple imputations by chained equations (Raghunathan *et al.*, 2001; Royston, 2004). We used the *ice*

command in Stata (version 9) to impute confounder and outcome missing data. Approximately fifty variables relating to parental socio-demographic factors, and child emotional, social and behavioural characteristics were used to impute the missing data. Ten cycles of regression were carried out and 25 datasets imputed.

RESULTS

There were 734 children (11.6% of those interviewed; 95% CI 10.8%, 12.4%) rated as having suspected or definite PILKS not attributable to fever or sleep. Of these, 300 (4.7% of those interviewed) had definite symptoms. A summary of potential confounders in relation to the exposures examined is presented in Table 1.

Infection during pregnancy

There were 5379 women with data available for infection during pregnancy, confounders, and PLIKS data in their offspring. Of these, 2582 (48.0%) reported having had any infection, and 863 (16.0%) specifically reported having influenza. There was no evidence that having influenza anytime during pregnancy was associated more, or less, strongly than having other, non-influenza, infections (Table 2). We therefore present results here for any infection (influenza and non-influenza infections combined together).

Having any infection anytime during pregnancy was associated with any suspected or definite PLIKS in the offspring (adjusted OR = 1.31, 95% CI 1.10, 1.56; $p = 0.002$). This estimate was not substantially different when we examined definite PLIKS as the outcome (adjusted OR = 1.44, 95% CI 1.11, 1.86; $p = 0.006$). Further adjusting for birthweight or childhood IQ as possible mediators for this association had minimal effect on these results.

We also examined the effects of infection during specific trimesters. There were 658 women who had an infection only during their 1st trimester, 471 only during their 2nd

trimester, and 335 only during their 3rd trimester. Estimates of association with PLIKS were larger for early pregnancy exposure to infection (adjusted OR for 1st trimester only compared to no infection = 1.41, 95% CI 1.09, 1.83; 2nd trimester only = 1.36, 95% CI 1.01, 1.82; 3rd trimester only = 1.16, 95% CI 0.81, 1.66). However, the confidence intervals for these estimates overlapped substantially, and there was no statistical evidence of a greater risk of PLIKS with 1st trimester exposure compared to 3rd trimester (adjusted OR = 1.26, 95% CI 0.85, 1.87; $p = 0.441$).

Resuscitation

There were 5197 children with data available for PLIKS, confounders and resuscitation status. Of these, 390 (7.5%) received positive pressure ventilation or cardiac compressions. Infants who were resuscitated had an increased risk of developing any suspected or definite PLIKS (adjusted OR = 1.34, 95% CI 1.00, 1.81; $p = 0.053$). This estimate was not substantially different when we examined definite PLIKS as the outcome (adjusted OR = 1.50, 95% CI 0.97, 2.31; $p = 0.065$). Further adjusting for childhood IQ as a possible mediator for this association had minimal effect on these results.

Of the 390 infants resuscitated, 52 were additionally admitted to a neonatal unit, and 21 of these developed signs of encephalopathy. The estimates of association with any suspected or definite PLIKS were slightly larger for infants who were resuscitated and required admission to a neonatal unit irrespective of whether they developed encephalopathy (adjusted OR = 1.82, 95% CI 0.60, 5.48) or not (adjusted OR = 1.84, 95% CI 0.74, 4.54), compared to children who were resuscitated but did not require

admission (adjusted OR = 1.27, 95% CI 0.92, 1.76). However these estimates were based on small numbers of events and confidence intervals overlapped substantially.

5-minute Apgar score

There were 5262 children with PLIKS, Apgar score, and confounders data available, and of these 33 (0.6%) had a score of 6 or less. Decreasing Apgar score was moderately correlated with resuscitation (Spearman rho = 0.32, $p<0.001$). There was little evidence for any increased risk of any suspected or definite PLIKS as Apgar scores decreased (adjusted OR = 1.06, 95% CI 0.95, 1.15; $p = 0.292$). Evidence of association with reducing Apgar score was stronger when we examined definite PLIKS (adjusted OR = 1.30, 95% CI 1.12, 1.50; $p<0.001$).

Gestational age

Data on PLIKS, confounders, and gestational age in weeks was available for 6004 individuals (mean 39.5, sd 1.8, range 25 to 47). There were 301 children (5.0%) born preterm (<37 weeks), and 455 (7.6%) born post-term (>42 weeks). There was no association between gestational age and any suspected or definite PLIKS in the crude or adjusted analysis (adjusted OR = 1.01, 95% CI 0.96, 1.05; $p = 0.736$). There was no evidence to support a non-linear (quadratic) relationship with gestational age that might be present if an increased risk of PLIKS were present only at the extremes of gestational age (LRT $\chi^2 = 0.50$, df (1), $p = 0.478$). Compared to term births, neither preterm (adjusted OR = 0.96, 95% CI 0.66, 1.40) nor post-term (adjusted OR = 1.13, 95% CI 0.85, 1.52) birth was associated with risk of developing any suspected or definite PLIKS.

Nested sample: Diabetes during pregnancy

There were 1777 children in the nested case-control sample with data available on maternal diabetes, confounders, and PLIKS. Of these, 20 mothers (1.1%) had a diagnosis of diabetes during pregnancy, and 11 also had additional evidence of poor blood sugar control. Presence of maternal diabetes was associated with an increased risk of any suspected or definite PLIKS (adjusted OR = 2.68, 95% CI 1.08, 6.64; p = 0.034), with a slightly stronger association for definite PLIKS (Table 3). There was a suggestion that the association with any suspected or definite PLIKS was stronger where blood sugar control was poor (adjusted OR = 4.41, 95% CI 1.16, 16.81) as compared to good (OR = 1.56, 95% CI 0.41, 5.92). However the confidence intervals were very wide and overlapped substantially, whilst this difference was much less marked for definite PLIKS. Further adjustment for birthweight and IQ score made minimal difference to the results.

Nested sample: Pre-eclampsia during pregnancy

There were 1569 children in the nested case-control sample with data available on maternal pre-eclampsia, PLIKS and confounders. Of these, 33 (2.1%) had mothers with pre-eclampsia during pregnancy, and 5 of these had evidence of intra-uterine growth retardation (IUGR). Maternal pre-eclampsia was not associated with risk of any suspected or definite PLIKS in the crude or adjusted analyses (adjusted OR = 1.03, 95% CI 0.50, 2.13; p = 0.929). The estimate of association was slightly stronger where there was additional evidence of IUGR (adjusted OR = 1.30, 95% CI 0.21, 8.00) compared to where there was no evidence of this (adjusted OR = 0.99, 95% CI 0.45, 2.18). However these estimates were based on small numbers of events, and confidence intervals were wide and overlapped substantially.

Independence of effects

We included maternal infection during pregnancy, diabetes during pregnancy, and resuscitation all in the same model to examine whether associations for these exposures were independent of one another. In this full model, the estimates of association between each of these exposures and any suspected or definite PLIKS were virtually unchanged.

Secondary analyses: Frequency of PLIKS & Bizarre PLIKS

There were 165 children (2.6% of those interviewed) who had definite, frequent (occurring ≥monthly) PLIKS, and 233 (3.6% of those interviewed) rated as having any suspected or definite 'bizarre' PILKS. There was no consistent pattern of associations with the exposures being stronger when examining these more stringent outcomes.

Missing data

Compared to subjects completing the PLIKS interview, those with missing data for PLIKS were more likely to have a history of maternal infection during pregnancy (55.4% vs. 48.5%), have been born preterm (6.4% vs. 5.0%), have a low Apgar score (1.3% vs. 0.7%), or have required resuscitation (8.3% vs. 7.4%). Results from the multivariable multiple-imputation models were very similar to those using the main dataset, although more precisely estimated, when we imputed confounders only, and also with additional imputation of the outcome measure too.

DISCUSSION

Prenatal exposures

Maternal infection during pregnancy was associated with increased risk of PLIKS, with no evidence that this association was any stronger for influenza compared to other infections. Although the confidence intervals overlapped substantially, and results from sub-group comparisons should be interpreted cautiously, exposure to infection during early pregnancy appeared to be more strongly associated with risk of PLIKS than exposure during late pregnancy. Adjusting for confounders had only a small effect on explaining this association.

We found no evidence that pre-eclampsia was associated with risk of PLIKS, but maternal diabetes during pregnancy was associated with an increased risk of PLIKS in the offspring. The association between diabetes and PLIKS appeared stronger where there was evidence of poor glucose control. However these findings for diabetes and pre-eclampsia are based on only small numbers of women with these exposures, and the robustness of these findings is therefore uncertain.

Perinatal exposures

There was some evidence that our primary measure of hypoxia, resuscitation, was associated with an increased risk of PLIKS, although evidence for this was not strong. Admission to a neonatal unit following resuscitation is likely to index infants who experienced a greater degree of hypoxia than those not admitted, and indeed estimates of association with PLIKS were larger for such children. While we had limited power to investigate this group of infants separately, infants with encephalopathy did not

seem to have a greater risk of PLIKS than infants admitted without neurological signs. It is plausible that subtle degree of hypoxic damage, insufficient to produce encephalopathy is nevertheless sufficient to impact upon risk of PLIKS. These data are consistent with a continuum of reproductive casualty (Pasamanick *et al.*, 1956), whereby long-term adverse consequences of perinatal hypoxia may occur even in infants without detectable shorter-term neurological sequelae of their hypoxia.

A lower 5-minute Apgar score was also associated with risk of definite, but not suspected, PLIKS. Although low Apgar score is often used as a marker of perinatal hypoxia, low Apgar scores are not specific to hypoxia and may be due to other pathologies (ACOG, 2006). Indeed the correlation between Apgar score and need for resuscitation in our sample was not strong, making it more difficult to postulate possible mechanisms leading to increased risk of PLIKS. We found no evidence of increased risk of PLIKS in pre- or post-term births, even though preterm births in particular have been associated with increased vulnerability to effects of hypoxia and adverse neurological outcomes (Fawke, 2007).

Non-causal explanations

All of the adverse pre- and perinatal exposures we examined were more common in subjects with evidence of maternal depression and other markers of family adversity during pregnancy. The distribution patterns of other confounders were less consistent across exposures. Although residual confounding can never be eliminated from observational studies, adjusting for confounders only explained a small part of the association with maternal infection during pregnancy, and had a minimal effect on results for the other exposures.

Bias due to misclassification of data or attrition could also lead to incorrect estimates of association. Misclassification of data is more likely for self-reported data such as infection during pregnancy. Evidence of association with PLIKS was weaker for maternal self-reports of diabetes than for clinician diagnoses obtained from obstetric records (results available on request), which may be indicative of greater misclassification in the self-reported data. However, misclassification of data, if non-differential, leads to under-estimates of association, and there is no reason to suppose that misclassification of any exposure data examined was differential with respect to PLIKS status in this cohort.

Although this is a large cohort, with a wealth of detailed information, missing data due to attrition and wave non-response in this cohort was not in-substantial, a problem common to other large-scale longitudinal studies (Plewis *et al.*, 2004; Callaway *et al.*, 2007). Estimates for all exposures however were similar in the multiple-imputation analyses, indicating that attrition is unlikely to have substantially biased these results.

Potential biological mechanisms

If the associations we observed for maternal infection, maternal diabetes, and markers of hypoxia are indeed causal in nature, then it is possible to speculate about possible mechanisms that might underlie them. Associations between maternal infections during pregnancy (serological evidence of infection from a variety of pathogens) and schizophrenia (Brown *et al.*, 2004; Byrne *et al.*, 2007) have been attributed to a variety of possible mechanisms (Cannon *et al.*, 2003) that might also increase risk of PLIKS. These include direct toxic effects of infectious agents on foetal brain

development, harmful effects of hyperthermia, or through cytokine production as part of a maternal inflammatory response. Animal studies show that maternal exposure to viral infections during pregnancy can lead to brain gene expression and neuropathology changes in the offspring, and that these changes may vary according to whether exposure occurs early or late during pregnancy (Fatemi *et al.*, 2008). Associations between analgesia use during pregnancy and schizophrenia have also been reported (Sorensen *et al.*, 2004), although adjusting for analgesic use during pregnancy (that was more common in women who reported infections), had no effect on our results.

Hypoxia can lead to cellular damage and death, probably secondary to the development of metabolic acidosis, with vascular watershed areas of the brain within frontal and parietal cortices being particularly susceptible to such damage (Inder *et al.*, 2004). There is an increasing body of evidence that clinically important brain damage can occur even where the hypoxic insult is not significant enough to produce clinical encephalopathy in the early neonatal period. For example, data from the ALSPAC cohort is consistent with hypoxia leading to lower IQ score during childhood even in children without signs of neonatal encephalopathy (Odd *et al* submitted).

Adverse effects of dysfunctional glucose metabolism on cerebral development are also plausible. Poorly controlled maternal diabetes has been associated with increased risk of offspring neurodevelopmental impairment (Ornoy, 2005), although how foetal brain development is effected by maternal glucose levels is far from clear at the present time.

It is perhaps surprising that the associations we observed between PLIKS and maternal infection, resuscitation and depressed Apgar score were not mediated to any degree by childhood IQ score. However, it may be that risk of PLIKS following hypoxic or other cellular injury, is mediated through more subtle effects than those measurable by testing of IQ score, for example through effects on social cognition, sensory gating, or cognitive appraisal.

PLIKS and schizophrenia

At present, the status of PLIKS in relation to rare clinical disorders such as schizophrenia is not clear. However, our results for PLIKS appear reasonably consistent with patterns of associations also reported for schizophrenia in relation to maternal infection during pregnancy (especially early pregnancy), maternal diabetes and markers of perinatal hypoxia (Cannon *et al.*, 2002). All the associations we observed were slightly larger for the narrower outcome of definite PLIKS, but there was no consistent evidence that more frequent symptoms, or specific types of symptoms, indexed stronger associations with the perinatal exposures examined.

Study limitations

The main limitations of this study relate to potential bias from attrition and misclassification, as discussed above. Furthermore, the exposures we examined are all, to varying extents, simply markers of biological exposures that we were attempting to capture. For example, although it is a strength of our study that we required the presence of positive pressure ventilation or cardiac compressions as our primary measure of hypoxia rather than the more commonly used, but less valid,

Apgar score, resuscitation is not a direct measure of whether substantial foetal cellular hypoxia actually occurred. Similarly, maternal diabetes is unlikely to be a strong marker of foetal exposure to adverse glycaemic levels, even where we attempted to incorporate evidence of poor glucose control, whilst maternal self-rated distinction between influenza as opposed to other infections is also unlikely to reflect the true underlying pathology. Despite these limitations, these results nevertheless have the potential to inform the direction of future studies that aim to assist our understanding of the development of psychotic experiences in the population.

Increasing understanding of PLIKS aetiology is likely to be of substantial importance as PLIKS are so common in population-based samples, and as they have been associated with decreased occupational and social functioning over time (Hanssen *et al.*, 2005; Rossler *et al.*, 2007). Such symptoms might therefore have a large impact on population health and quality of life outside the arena of clinical services, in the same way that depression does.

Conclusion

Our results appear consistent with the hypothesis that adverse biological events during early development may lead to an increased risk of developing PLIKS during childhood. Furthermore, the similarity between these results and findings reported for schizophrenia indicate that future studies of PLIKS may help us understand how psychotic experiences and clinical disorders develop throughout the life-course.

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Table 1: Number (%) of children within exposure category with confounder present[a]

	Male	FAI >90th percentile	Mother's age >30	Maternal depression (EPDS≥15)	Medication during pregnancy	Maternal smoking in pregnancy	Rural birth
Infection in pregnancy							
No	2762 (51.2%)	413 (7.7%)	1702 (31.6%)	202 (3.8%)	3102 (57.6%)	1147 (21.3%)	310 (5.8%)
Yes	3061 (51.8%)	731 (12.6%)	1862 (31.5%)	467 (8.1%)	4021 (70.2%)	1774 (30.0%)	326 (5.6%)
Diabetes in pregnancy							
No	1705 (49.9%)	344 (10.6%)	1010 (29.6%)	237 (7.3%)	2094 (65.2%)	934 (27.7%)	164 (4.9%)
Yes	23 (53.5%)	5 (11.6%)	15 (34.9%)	4 (9.3%)	33 (78.6%)	6 (14.0%)	0 (0%)
Pre-eclampsia in pregnancy							
No	1493 (49.8%)	298 (10.4%)	891 (29.7%)	207 (7.3%)	1860 (65.8%)	812 (27.4%)	144 (4.9%)
Yes	51 (60.7%)	8 (10.5%)	32 (38.1%)	13 (17.6%)	45 (63.4%)	19 (23.2%)	2 (2.4%)
Preterm birth							
No	6698 (51.3%)	1265 (10.3%)	3924 (30.1%)	777 (6.4%)	7860 (65.1%)	3555 (27.6%)	709 (5.5%)
Yes	465 (58.1%)	81 (11.0%)	214 (26.8%)	72 (9.8%)	465 (66.4%)	242 (30.7%)	52 (6.5%)
Resuscitated							
No	5853 (51.2%)	1074 (10.0%)	3493 (30.6%)	683 (6.5%)	6865 (65.1%)	3055 (27.1%)	611 (5.4%)
Yes	625 (55.4%)	119 (11.3%)	317 (28.2%)	67 (6.5%)	680 (66.2%)	318 (28.6%)	48 (4.3%)
Apgar score <6							
No	6464 (51.5%)	1189 (10.1%)	3822 (30.5%)	755 (6.5%)	7541 (65.1%)	3374 (27.3%)	672 (5.4%)
Yes	94 (59.9%)	22 (15.3%)	32 (20.5%)	14 (9.6%)	98 (69.5%)	57 (36.8%)	6 (3.9%)

[a] Note that confounding variables dichotomised for the purpose of this table **only** and not for analyses; FAI = Family Adversity Index; EPDS = Edinburgh post-natal depression scale

Table 2: Crude and adjusted odds ratios (95% CI) of PLIKS outcomes for prenatal & perinatal exposures (full sample[a])

			Suspected or definite PLIKS				Definite PLIKS			
	N in sample	Exposure, no PLIKS	Exposure, with PLIKS	*Crude*	*Adjusted*[b]	*p* value	Exposure, with PLIKS	*Crude*	*Adjusted*[b]	*p* value
Infection in pregnancy:										
Influenza		739	124	1.56 (1.24, 1.96)	1.39 (1.10, 1.76)		47	1.45 (1.02, 2.06)	1.22 (0.85, 1.76)	
Non-influenza		1500	219	1.36 (1.12, 1.64)	1.27 (1.05, 1.54)		108	1.68 (1.28, 2.22)	1.55 (1.17, 2.04)	
Any infection	5379	2239	343	1.42 (1.20, 1.68)	1.31 (1.10, 1.56)	0.002	155	1.60 (1.25, 2.07)	1.44 (1.11, 1.86)	0.006
Gestation (per week ↑)	6004	-	-	1.01 (0.97, 1.05)	1.01 (0.96, 1.05)	0.736	-	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)	0.176
Resuscitation status:										
No Resusc		4273	534	1.0	1.0		213	1.0	1.0	
Resusc, not admitted		292	46	1.26 (0.91, 1.74)	1.27 (0.92, 1.76)		21	1.43 (0.90, 2.27)	1.48 (0.93, 2.35)	
Resusc, admitted, no symptoms		25	6	1.92 (0.78, 4.70)	1.84 (0.74, 4.54)		3	2.31 (0.70, 7.66)	2.14 (0.63, 7.28)	
Resusc, admitted, & encephalopathy		17	4	1.88 (0.63, 5.62)	1.82 (0.60, 5.48)		1	1.08 (0.14, 8.07)	0.98 (0.13, 7.35)	
Any resusc vs. none	5197	334	56	1.34 (1.00, 1.81)	1.34 (1.00, 1.81)	0.053	25	1.48 (0.96, 2.27)	1.50 (0.97, 2.31)	0.065
Apgar score (per 1pt ↓)	5262	-	-	1.06 (0.96, 1.21)	1.06 (0.95, 1.19)	0.292	-	1.31 (1.14, 1.51)	1.30 (1.12, 1.50)	<0.001

[a] Analyses restricted to dataset with no missing data for confounding factors; [b] adjusted for Family Adversity Index, sex, urban/rural birth, maternal age, maternal smoking, maternal depression, and medication use during pregnancy

Table 3: Crude and adjusted odds ratios (95% CI) of PLIKS outcomes for prenatal exposures (nested sample[a])

			Suspected or definite PLIKS				Definite PLIKS			
	N in sample	Exposure, no PLIKS	Exposure, with PLIKS	*Crude*	*Adjusted*[b]	*p* value	Exposure, with PLIKS	*Crude*	*Adjusted*[b]	*p* value
Maternal diabetes										
No diabetes		1133	624	1.00	1.00		261	1.00	1.00	
Diabetes (good control)		5	4	1.45 (0.39, 5.43)	1.56 (0.41, 5.92)		3	2.60 (0.62, 10.97)	3.14 (0.71, 13.91)	
Diabetes (poor control)		3	8	4.84 (1.28, 18.32)	4.41 (1.16, 16.81)		3	4.34 (0.87, 21.63)	3.84 (0.74, 19.85)	
Any maternal diabetes	1777	8	12	2.72 (1.11, 6.70)	2.68 (1.08, 6.64)	0.034	6	3.26 (1.12, 9.46)	3.43 (1.14, 10.36)	0.029
Maternal pre-eclampsia	1569	21	12	1.07 (0.52, 2.20)	1.03 (0.50, 2.13)	0.929	4	0.87 (0.30, 2.56)	0.84 (0.28, 2.52)	0.761

[a] Analyses restricted to dataset with no missing data for confounding factors; [b] adjusted for Family Adversity Index, sex, urban/rural birth, maternal age, maternal smoking, maternal depression, and medication use during pregnancy