**Prenatal maternal infections and childhood psychopathology: Findings from the ALSPAC
birth cohort**

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Abstract

Aims: Studies have suggested that exposure to prenatal infections may be a risk factor in the aetiology of neurodevelopmental disorders such as schizophrenia and autism, but that its effects may differ by timing of exposure. Evidence on other psychiatric outcomes, however, is scarce and mixed. The aims of this study were to examine whether exposure to infections, at any point in gestation and during each trimester, is associated with increased odds of psychiatric disorders (pervasive developmental disorders, attention-deficit hyperactivity disorder, behavioural disorders and emotional disorders) at ages 7 and 14.

Methods: Participants were $n = 8859$ mother and child pairs from the UK Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. Exposure to prenatal infections was assessed for each trimester using maternal self-reports. Children's psychiatric status was assessed using the parent-reported Development and Well-being Assessment (DAWBA).

Logistic regressions were used to examine links between prenatal infections and child

outcomes. **Results:** Half of the mothers reported an infection at some point during pregnancy and 7% of children were reported to have a psychiatric condition. Increased odds of children having any psychiatric disorder at age 14 were found in association with infections at any point during pregnancy, $OR = 1.27$ (95% CI 1.04, 1.55) and in the third trimester specifically, $OR = 1.28$ (95% CI 1.02, 1.61), after adjusting for the effects of potential confounds and other covariates. No other links were found in adjusted models.

Conclusions: Findings suggest that associations between prenatal infections and children's psychiatric disorders are weak to non-existent, after adjusting for the effects of other factors.

Keywords: infections; pregnancy; psychopathology; child development; ALSPAC.

Introduction

Mental health difficulties among children are common (Beardsmore, 2015) and are a major contributor to disease burden in young people across the globe (Erskine *et al.*, 2015).

Childhood mental ill-health can have long-term implications, increasing the risk of further mental health problems, difficulties in social functioning, poor academic achievement, substance abuse, criminality, and unemployment (Erskine *et al.*, 2016; Sellers *et al.*, 2019).

Although some mental disorders are not formally diagnosed until adolescence (Dalsgaard *et al.*, 2020), evidence suggests that symptoms may be present from much earlier (Petresco *et al.*, 2014), suggesting delayed detection. This reality works against the evidence on the importance of early intervention in reducing symptom severity and preventing secondary disorders (de Girolamo *et al.*, 2012). In order to facilitate the process of early identification, getting insights into the aetiology of childhood mental illness is vital. A growing body of work has focused on links between maternal immune activation during pregnancy and offspring psychiatric outcomes, with emphasis on infections. In the current study, we examine links between infections during pregnancy and children's psychiatric status at ages 7 and 14 in a large (n=8859) UK birth cohort; the Avon Longitudinal Study of Parents and Children (ALSPAC) (Boyd *et al.*, 2013; Fraser *et al.*, 2013).

Prenatal infections are common, with a prior study showing around 60% of mothers self-reporting an infection during the prenatal period (Collier *et al.*, 2009). Previous work suggests that maternal infections during pregnancy may be linked to increased odds of children developing neurodevelopmental disorders such as schizophrenia and autism spectrum disorders (ASD). A systematic review (Khandaker *et al.*, 2013) found that prenatal infections were associated with increased odds of schizophrenia in offspring, and that the

odds were higher in relation to infections during the early stages of pregnancy compared to later time points. A meta-analysis (Jiang *et al.*, 2016) found an overall association between prenatal infections and increased odds of ASD (OR = 1.13), particularly those which required hospitalisation (OR = 1.30). However, subgroup analyses showed that only infections during the second trimester were associated with increased odds of ASD.

Evidence on outcomes beyond schizophrenia and ASD is scarce and mixed. A few studies have examined the potential association with attention-deficit hyperactivity disorder (ADHD). Though previously conceptualised as a 'disruptive behaviour disorder', ADHD is now recognised to be – like schizophrenia and ASD – a neurodevelopmental disorder (American Psychiatric Association, 2013). Dreier *et al.* (2016) reported increased odds of offspring ADHD in association with maternal fever in gestational weeks 9-12 and genitourinary infections in gestational weeks 33-36, but no associations with infections at other time periods or other types of infections. Mann and McDermott (2011) found significant associations between prenatal exposure to four out of five genitourinary infections, at any point during pregnancy, and ADHD. They did not carry out timing-specific analyses. Ginsberg *et al.* (2019) found an association between any infection at any point during pregnancy and ADHD. However, these links were fully attenuated in sibling comparisons, which are designed to control for within-family confounds.

The impacts of prenatal infection on child development may not be limited to neurodevelopmental disorders. Given the evidence from animal studies that suggest potential widespread effects of maternal immune activation on nervous system development (Knuesel *et al.*, 2014), there is reason to suspect that prenatal infections could

impact neuropsychiatric problems more generally. A systematic review addressing the links between prenatal maternal infections and offspring mood disorders (Simanek and Meier, 2015) found convincing evidence for links between prenatal influenza and bipolar disorder, but findings on associations between other types of infections and other disorders were inconsistent.

A common drawback of studies in this field is that many examine links between prenatal infections and single outcomes in isolation. Given that neuropsychiatric outcomes are strongly related to one another (Rhee, Lahey and Waldman, 2015), this means that most studies are providing only a fragmented picture of the potential impact of prenatal infection. It is also difficult to identify studies that have assessed potential effects of infections at different time points during pregnancy on multiple psychiatric outcomes within the same study. ALSPAC offers a unique opportunity to address these gaps. The study collected data on maternal exposure to prenatal infections for each trimester of pregnancy. In addition, children's psychiatric status was repeatedly assessed throughout their childhood and adolescence.

The ALSPAC data have been used before to address the question of potential links between prenatal infections and children's psychiatric outcomes. Zammit et al. (2009) reported an association between prenatal infections and children's psychotic symptoms at age 12, with larger effect sizes for infections in the first trimester compared to the second and third. The current study builds on the Zammit et al. study, evaluating whether there are associations between prenatal maternal infections and children's psychiatric outcomes more broadly at ages 7 and 14.

The aims of the current study were to: 1) examine whether exposure to infections, at any point during pregnancy, was associated with increased odds of any psychiatric disorder (attention-deficit hyperactivity disorder, behavioural disorders and emotional disorders at the ages of 7 and 14 and pervasive development disorders at age 7; 2) examine whether associations between maternal infections and children's psychiatric outcomes differed depending on the trimester of exposure and outcome examined.

Given the evidence from animal models that maternal immune activation can have pervasive effects on the prenatal development of the nervous system and the preliminary human epidemiological evidence suggesting that maternal immune activation may be associated with a range of psychiatric outcomes, we hypothesise that an infection at any point during pregnancy would be associated with increased odds of children having any psychiatric disorder. As previous studies have shown mixed findings, we explored whether links between prenatal infections and outcomes differed by timing of exposure.

Method

Cohort

Participants included n=8859 child and mother pairs who took part in the Avon Longitudinal Study for Parents and Children (ALSPAC) (Boyd *et al.*, 2013; Fraser *et al.*, 2013), and had available data on both maternal infections during pregnancy and children's psychiatric outcomes at age 7 or 14 (Figure 1). We selected the age 7 time point as it would be expected that early onset child and adolescent psychiatric symptoms would have arisen at this stage (Kessler *et al.*, 2007) and the sample had not yet been affected by substantial

attrition. However, we included the age 14 outcomes as well, in order to also capture children with a later onset in psychiatric symptoms.

ALSPAC is a longitudinal birth cohort study originating in the area of Avon in South-West England. All pregnant women living in the area who were due to give birth between 1 April 1991 and 31 December 1992 were invited to take part in the study. The initial sample consisted of n=14541 pregnancies. These pregnancies resulted in 14062 live births and 13988 children who were alive at 1 year of age. Details on all available data can be found using a fully searchable data dictionary and variable search tool on the ALSPAC website: <http://www.bristol.ac.uk/alspac/researchers/our-data/>.

Exposure

Information on exposure to infections during pregnancy was gathered from interviews with mothers at three time points; during weeks 18 and 32 of gestation and 8 weeks postpartum. At week 18 of gestation, women were asked: "During this pregnancy so far have you had any of the following: urinary infection, influenza, rubella (german measles), thrush (candida), genital herpes, other infection?" Response options were: "Yes, in 1st 3 months"; "Yes, in period 4th month to now"; "No, not at all"; "Don't know." Women were asked about the same infections at week 32 of gestation: "In the last 3 months have you had any of the following [...]" with the response options "Yes, in the last 3 months"; "No, not in the last 3 months"; "Don't know." At week 8 postpartum, women were again asked about the same infections, for the third trimester of pregnancy: "During the last months of pregnancy (from 7 months onwards) did you experience any of the following [...]" with the response options

“Yes, in the last months of pregnancy”; “No, not in the last months of pregnancy”; “Don’t know.”

For the purposes of the current study, if women responded positively to having an infection in the first three months of pregnancy, this was coded as a first trimester infection. If women responded positively to having an infection in the fourth month at the week 18 interview or ‘in the last 3 months’ in the week 32 interview, this was coded as a second trimester infection. If mothers responded positively to having an infection from month 7 onwards in the week 8 postpartum interview, this was coded as a third trimester infection.

Outcomes

Children’s psychiatric outcomes; attention-deficit hyperactivity disorder (ADHD), behavioural disorders (BD; conduct disorder and oppositional defiant disorder) and emotional disorders (ED; anxiety and depressive disorders) were assessed using the parent-reported Development and Well-Being Assessment (DAWBA) at ages 7 and 14. Pervasive development disorders (PDD) was additionally assessed at age 7. The DAWBA combines structured and semi-structured interview questions which map onto diagnostic criteria in line with the 4th edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM) (American Psychiatric Association, 2000) and the International Classification of Diseases (ICD) (Goodman *et al.*, 2000). Response data were compiled into a computer program which generated predictions of likely diagnoses. The computer predictions for age 7 diagnoses were reviewed by psychiatrists trained in clinical assessment who determined whether or not to confirm or reject diagnoses based on parents’ responses to the interview questions. Only the computer predicted scores were available for the age 14 outcomes. The DAWBA

has been shown to have good psychometric properties, as evidenced by studies on large community samples and clinical samples (Goodman *et al.*, 1996, 2000, 2011).

Confounding and covarying factors

Several potential confounders and covariates were selected before conducting analyses, due to their potential relations with prenatal maternal infections and/or children's psychiatric outcomes. These were: maternal age at birth (McGrath *et al.*, 2014; Lean *et al.*, 2017), maternal education, area-based deprivation (Mortensen, Helweg-Larsen and Andersen, 2011; Reiss, 2013), child's sex (Chaplin and Aldao, 2013), maternal prenatal smoking (Wakschlag *et al.*, 2002), maternal prenatal psychological distress (O'Donnell *et al.*, 2014), and maternal history of psychiatric illness (McLaughlin *et al.*, 2012). Birthweight and gestational age at birth were also considered as covariates, but were not included in the models as they can be considered intermediary factors in the relationship between prenatal maternal infections and child outcomes (Slattery and Morrison, 2002; Valero de Bernabé *et al.*, 2004; Hayes and Sharif, 2009).

Data on maternal education were gathered at interviews at 32 weeks gestation and provided as the highest completed UK qualification. For the current study, we collapsed categories to A-level (upper secondary education) or lower. Information on area-based deprivation was gathered using the Index of Multiple Deprivation (Noble *et al.*, 2006) when children were around the age of 8, and the data were provided in quintiles. Data on child sex were collected at birth and provided as male or female. Maternal prenatal smoking was assessed using questionnaires for each trimester of pregnancy, during interviews at 18 and 32 weeks of gestation and 8 weeks postpartum, where mothers reflected on the third

trimester of pregnancy. Smoking data were coded as yes/no for each trimester. Maternal prenatal psychological distress was measured with the Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden and Sagovsky, 1987), a 10-item self-report scale (range: 0-30), with higher scores suggesting more psychological distress. The EPDS was administered at weeks 18 and 32 and expecting mothers were asked to reflect on the past week when answering the questions. Lastly, maternal history of psychiatric illness was assessed at week 12 of pregnancy. Women were asked whether or not they ever had the following psychiatric conditions: bulimia, schizophrenia, anorexia, severe depression, or other psychiatric problem. For the current study, if they responded positively to having ever had any of the conditions, they were coded as having a history of psychiatric illness.

Statistical analysis

Logistic regressions using maximum likelihood estimation were used to examine links between prenatal maternal infections and children's psychiatric conditions at ages 7 and 14. Odds ratios and corresponding 95% confidence intervals are reported. Models on the associations between infections at each trimester and each outcome were fit separately. Unadjusted models and models adjusting for potential covariates were also fit separately. Missing data were dealt with using a full information maximum likelihood (FIML) approach (Enders, 2001), in order to use all available data. Data were cleaned and coded using R version 3.6.2 (R Core Team, 2018) and analyses were carried out using Mplus version 8.4. (Muthén and Muthén, 2015).

Ethics approval

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. For further information see:

<http://www.bristol.ac.uk/alspac/researchers/research-ethics>.

Results

Half (50%) of the mothers in the study reported an infection at any point during pregnancy, 22% in the first trimester, 32% in the second and 20% in the third. The DAWBA assessment resulted in 7% of children having any psychiatric disorder, both at ages 7 and 14 (note that PDD was not assessed at age 14). Full descriptive statistics are shown in Tables 1-3.

Infections at any point during pregnancy

Results from unadjusted logistic regressions showed that infections at any point during pregnancy were associated with increased odds of children having any psychiatric disorder, at age 7, OR 1.33 (95% CI 1.11, 1.59) and age 14, OR = 1.54 (95% CI 1.27, 1.87). When looking at the psychiatric outcomes separately, results showed that infections at any point during pregnancy were associated with increased odds of emotional disorders at age 7, OR = 1.56 (95% CI 1.20, 2.04) and behavioural disorders at age 14, OR = 1.41 (95% CI 1.08, 1.86) but no other outcomes assessed (Table 4). When adjusting for potential confounds and covariates, results showed that infections at any point during pregnancy were associated with increased odds of children having any psychiatric disorders at age 14, OR = 1.27 (95% CI 1.04, 1.55), but no other outcomes examined (Table 4).

First trimester infections

Results from unadjusted logistic regressions showed that first trimester infections were associated with increased odds of children having any psychiatric disorder at age 7, OR = 1.22 (95% CI 1.00, 1.48) and age 14, OR = 1.31 (95% CI 1.06, 1.61). When looking at the psychiatric outcomes separately, results showed that first trimester infections were associated with increased odds of emotional disorders at age 7, OR = 1.33 (95% CI 1.01, 1.76), but no other outcomes assessed (Table 4). When adjusting for potential confounds and covariates, results showed no associations between first trimester infections and any psychiatric disorders (Table 4).

Second trimester infections

Results for second trimester infections revealed essentially the same patterns as infections in the first trimester. Unadjusted models showed that second trimester infections were associated with increased odds of children having any psychiatric disorder at age 7, OR = 1.25 (95% CI 1.04, 1.50) and age 14, OR = 1.48 (95% CI 1.22, 1.79). When looking at the psychiatric outcomes separately, results showed that second trimester infections were associated with increased odds of emotional disorders at age 7, OR = 1.55 (95% CI 1.20, 2.01), but no other outcomes assessed (Table 4). When adjusting for potential confounds and covariates, results showed that second trimester infections were not associated with any psychiatric disorders (Table 4).

Third trimester infections

Results from unadjusted logistic regressions showed that third trimester infections were associated with increased odds of children having any psychiatric disorder at age 7, OR 1.37

(95% CI 1.13, 1.67) and age 14, OR = 1.64 (95% CI 1.33, 2.01). When looking at the psychiatric outcomes separately, results showed that third trimester infections were associated with increased odds of emotional disorders at age 7, OR = 1.63 (95% CI 1.24, 2.16) and age 14, OR = 1.64 (95% CI 1.13, 2.39) as well as behavioural disorders at age 14, OR = 1.45 (95% CI 1.08, 1.95) but no other outcome assessed (Table 4). When adjusting for potential confounds and covariates, results showed that third trimester infections were associated with increased odds of any psychiatric disorder at age 14, OR = 1.28 (95% CI 1.02, 1.61) but no other outcomes examined (Table 4).

Discussion

The aims of this study were to examine links between prenatal maternal infections, self-reported at each trimester, and children's psychiatric disorders, namely attention deficit hyperactivity disorder, emotional disorders, behavioural disorders at ages 7 and 14 and pervasive development disorders at age 7. The results suggest that, overall, these links are weak at best. The only associations observed were between infections at any point during pregnancy, and in the third trimester specifically, and increased odds of any psychiatric disorder at age 14. It will be necessary to assess whether these associations can be replicated in other cohorts because these findings arose in the context of a moderately large number of comparisons.

Firstly, the lack of association observed between prenatal infections and pervasive development disorders, which was replaced by ASD in the DSM-V (American Psychiatric Association, 2013), should be noted, as it contradicts a large body of evidence suggesting the contrary (Jiang *et al.*, 2016). Complementary evidence (Croen *et al.*, 2019) has, however,

suggested that it may not be the infectious agents themselves which are associated with abnormal neurodevelopment, but rather the accompanying immune activation, relating to side attributes such as fever. This aligns with findings from studies reporting links between prenatal levels of biomarkers such as inflammatory cytokines and increased odds of ASD in offspring (Goines *et al.*, 2011; Abdallah *et al.*, 2013; Zerbo *et al.*, 2016).

Secondly, the findings from models on links with ADHD are noteworthy. Even in unadjusted models, no associations were found, neither for ADHD at age 7 nor 14, at any of the prenatal time points examined. These findings suggest that ADHD may not share the same etiological roots the neurodevelopmental disorders schizophrenia (Khandaker *et al.*, 2013) and ASD (Jiang *et al.*, 2016), which have previously been linked to prenatal infections, though not without controversy, as outlined above. Our findings somewhat contradict previous work. Dreier *et al.*, (2016), Mann and McDermott (2011) and Ginsberg *et al.* (2019) all reported associations between prenatal infections and ADHD after adjusting for a range of other factors. However, Dreier *et al.* only found links in a portion of the comparisons carried out. In addition, both Dreier *et al.* and Mann and McDermott reported associations with ADHD specific to genitourinary infections. Unfortunately, we were unable to conduct analyses specific to type of infection on top of timing due to issues concerning statistical power. Ginsberg *et al.* found no associations in sibling comparisons. Both their findings and the ones presented here suggest that there may indeed be other factors than prenatal infections which better explain the variation in children's psychiatric outcomes.

Our findings suggesting no links with emotional disorders contribute to the mixed literature reviewed by Simanek and Meyer (2015) on links between prenatal maternal infections and

offspring mood disorders in offspring. Zammit et al. (2009) reported links between prenatal infections and psychotic symptoms in the ALSPAC cohort. Our findings suggest that these links do not extend to ADHD, emotional disorders, behavioural disorders or pervasive development disorders.

Our findings showed that rates of any psychiatric disorder among children were similar at ages 7 and 14, around 7%. This contradicts existing evidence that rates of psychiatric disorders generally increase as children develop into adolescence, though this varies across disorders (Dalsgaard *et al.*, 2020). The age 14 rates may have been lower than expected because of attrition. Wolke et al. (2009) used simulation techniques to examine loss to follow up in ALSPAC in the context of children's behaviour disorders. They concluded that drop out in the study was systematic and that children who dropped out were more likely to suffer from behaviour disorders. Given high rates of comorbidities of children's psychiatric issues (Rhee, Lahey and Waldman, 2015), this suggests that rates of psychiatric disorders at age 14 in the current study may have been underestimated due to attrition. In addition, the age 14 diagnoses were produced solely from computer predictions, which may have produced more biased estimates compared to age 7, where clinicians confirmed or rejected the computer predicted diagnoses.

Attrition in the space between the prenatal period and the age 7 assessment may also have introduced bias to the overall findings. Evidence suggests that those who drop out from cohort studies, generally tend to be less healthy and more socioeconomically disadvantaged compared to those who continue participation (Goldberg *et al.*, 2001; Knudsen *et al.*, 2010). Post-hoc analyses showed that rates of infections were higher among those who had no

outcome data (over 60%) compared to those who did (50%). Associations between prenatal infections and children's psychiatric status may thus have been attenuated in the current study.

It is worth discussing the role of potential confounders and or covariates in the study. For example, unadjusted models showed links between prenatal infections at all trimesters and emotional disorders at age 7, but none of these remained significant after adjustment. As the links between prenatal infection and psychiatric outcomes remain poorly understood, it can be challenging to be certain which variables represent confounders, as opposed to mediators or variables incidentally related to both predictor and outcome. In the current study we erred on the side of over-adjustment to ensure confounding was addressed; however, statistical models can also be biased as a consequence of too much adjustment (Schisterman, Cole and Platt, 2009). On the other hand, we elected not to adjust for birth weight and gestational age to avoid overadjustment as we judged that these could be mediators in the infection-psychiatric outcome relation. However, it could, for example, be argued that physical illness, such as exposure to infectious diseases, may increase the likelihood of maternal prenatal distress, which in turn can affect children's psychological development, thus making it both a potential mediator and a potential confounder. We aimed to strike a balance with adjusting for important factors within the scope of the ALSPAC data set, while avoiding unnecessary adjustment. However, we cannot be certain that the resulting adjustment strategy introduced no bias to the findings.

Another limitation of the current study is that maternal exposure to prenatal infections relied on maternal self-reports. Although mothers reported on this twice during pregnancy

and once shortly (8 weeks) after giving birth, these measures will have been subject to some degree of self-report and recall bias. Having access to additional data on levels of inflammatory biomarkers would provide a more objective picture of prenatal immune activation. Additionally, such data would allow studies to further tease apart the role of infections themselves and accompanying immune responses in the aetiology of offspring psychiatric outcomes. This is important to examine, as various factors other than infections can contribute to immune activation, one of which being stress (Christian, 2015). Lastly, some previous studies which have found links between prenatal maternal infections and ASD, for example (e.g. Atladottir *et al.*, 2010; Lee *et al.*, 2015), had much larger samples than the current study. It may thus be that the sample size in our study didn't give enough statistical power to detect the small effects previous studies have reported. The studies of Atladottir *et al* and Lee *et al* also differ from the current one in that they used admissions to hospital as indications of infection. This suggests that the infections would have been associated with severe illness, whereas self-reports, as used in this study, also capture milder occurrences of infections.

In conclusion, the current study examined links between self-reported prenatal maternal infections at each trimester and children's psychiatric disorder status at ages 7 and 14. Findings suggest that after adjusting for the effects of other factors, these associations are weak to non-existent.

Acknowledgements

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

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Tables and Figures

Table 1. Descriptive statistics for mothers' infections during pregnancy

Infection at any point	n	%
Yes	4448	50
No	3708	42
<i>Missing</i>	<i>703</i>	<i>8</i>
1 st trimester infection		
Yes	1936	22
No	6287	71
<i>Missing</i>	<i>636</i>	<i>7</i>
2 nd trimester infection		
Yes	2865	32
No	5324	60
<i>Missing</i>	<i>670</i>	<i>8</i>
3 rd trimester infection		
Yes	1777	20
No	6691	76
<i>Missing</i>	<i>391</i>	<i>4</i>

Table 2. Children's psychiatric status by infection status

	Infection (n = 4448)		No infection (n = 3708)	
	n	%	n	%
ADHD age 7				
Yes	91	2.0	60	1.6
No	3946	88.7	3396	91.6
Missing	411	9.2	252	6.8
BD age 7				
Yes	131	2.9	103	2.8
No	3906	87.8	3353	90.4
Missing	411	9.2	252	6.8
ED age 7				
Yes	157	3.5	87	2.3
No	3898	87.6	3378	91.1
Missing	393	8.8	243	6.6
PDD age 7				
Yes	18	0.4	9	0.2
No	4037	90.8	3456	93.2
Missing	393	8.8	243	6.6
Any disorder age 7				
Yes	322	7.2	211	5.7
No	3733	83.9	3254	87.8
Missing	393	8.8	243	6.6
ADHD 14				
Yes	54	1.2	32	0.9
No	3287	73.9	2853	76.9
Missing	1107	24.9	823	22.2
BD age 14				
Yes	141	3.2	87	2.3
No	3189	71.7	2786	75.1
Missing	1118	25.1	835	22.5
ED age 14				
Yes	79	1.8	51	1.4
No	3278	73.7	2850	76.9
Missing	1091	24.5	807	21.8
Any disorder age 14				
Yes	305	6.9	181	4.9
No	2726	61.3	2492	67.2
Missing	1417	31.9	1035	27.9

Table 3. Study confounds and covariates by infection status

	Infection (n = 4448)		No infection (n = 3708)	
	n	%	n	%
Maternal age				
< 25	755	17.0	535	14.4
≥ 25	3693	83.0	3173	85.6
<i>Missing</i>	0	0.0	0	0.0
Maternal education				
Low	2501	56.2	2236	60.3
High	1848	41.5	1459	39.3
<i>Missing</i>	99	2.2	13	0.4
Deprivation				
Lowest quintile	518	11.6	376	10.1
20-39%	556	12.5	443	11.9
40-59%	647	14.5	548	14.8
60-79%	677	15.2	621	16.7
Highest quintile	1069	24.0	1025	27.6
<i>Missing</i>	981	22.1	695	18.7
Maternal smoking (1st trimester)				
Yes	944	21.2	631	17.0
No	3471	78.0	3077	83.0
<i>Missing</i>	33	0.7	0	0.0
Maternal smoking (2nd trimester)				
Yes	712	16.5	468	13.1
No	3355	74.9	2990	80.2
<i>Missing</i>	381	8.6	250	6.7
Maternal smoking in (3rd trimester)				
Yes	723	16.3	498	13.4
No	3546	75.4	3205	86.4
<i>Missing</i>	179	4.0	5	0.1
Maternal prenatal distress (18 weeks)				
High	757	17.0	435	11.7
Low	3431	77.1	3238	87.3
<i>Missing</i>	260	5.8	35	0.9
Maternal prenatal distress (32 weeks)				
High	897	20.2	490	13.2
Low	3382	76.0	3185	85.9
<i>Missing</i>	169	3.8	33	0.9
Maternal history of psychiatric illness				
Yes	636	14.3	310	8.4
No	3470	78.0	3172	85.5
<i>Missing</i>	342	7.7	226	6.1
Child's sex				

Male	2302	51.8	1884	50.8
Female	2146	48.2	1824	49.2
<i>Missing</i>	0	0.0	0	0.0

Note. Infection status was based on whether or not mothers had an infection at any point during pregnancy.

Table 4. Unadjusted odds ratios (OR), adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) for associations between prenatal maternal infections and children's psychiatric disorders at ages 7 and 14.

Infection timing	Age 7		Age 14	
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Any disorder				
Any point	1.33 (1.11–1.59)	1.16 (0.97–1.40)	1.54 (1.27–1.87)	1.27 (1.04–1.55)
1 st trimester	1.22 (1.00–1.48)	1.09 (0.88–1.33)	1.31 (1.06–1.61)	1.13 (0.91–1.41)
2 nd trimester	1.25 (1.04–1.50)	1.04 (0.86–1.27)	1.48 (1.22–1.79)	1.14 (0.92–1.40)
3 rd trimester	1.37 (1.13–1.67)	1.19 (0.96–1.48)	1.64 (1.33–2.01)	1.28 (1.02–1.61)
Attention deficit hyperactivity disorder				
Any point	1.31 (0.94–1.82)	1.15 (0.82–1.62)	1.47 (0.95–2.28)	1.20 (0.76–1.89)
1 st trimester	1.32 (0.92–1.87)	1.26 (0.87–1.81)	1.27 (0.78–2.05)	1.12 (0.68–1.84)
2 nd trimester	1.09 (0.78–1.52)	0.96 (0.67–1.37)	1.53 (0.99–2.36)	1.22 (0.76–1.95)
3 rd trimester	1.12 (0.77–1.63)	0.98 (0.65–1.47)	1.46 (0.91–2.34)	1.11 (0.67–1.85)
Behavioural disorders				
Any point	1.10 (0.84–1.43)	0.94 (0.72–1.23)	1.41 (1.08–1.86)	1.18 (0.89–1.56)
1 st trimester	1.06 (0.78–1.44)	0.94 (0.69–1.29)	1.27 (0.94–1.71)	1.14 (0.83–1.55)
2 nd trimester	1.28 (0.98–1.67)	1.11 (0.83–1.49)	1.30 (0.99–1.70)	1.03 (0.77–1.39)
3 rd trimester	1.28 (0.95–1.72)	1.08 (0.78–1.49)	1.45 (1.08–1.95)	1.19 (0.86–1.63)
Emotional disorders				
Any point	1.56 (1.20–2.04)	1.30 (0.99–1.71)	1.35 (0.94–1.92)	1.04 (0.72–1.51)
1 st trimester	1.33 (1.01–1.76)	1.12 (0.84–1.49)	1.13 (0.76–1.70)	0.96 (0.63–1.45)
2 nd trimester	1.55 (1.20–2.01)	1.20 (0.91–1.59)	1.27 (0.89–1.83)	0.94 (0.63–1.39)
3 rd trimester	1.63 (1.24–2.16)	1.30 (0.96–1.76)	1.64 (1.13–2.39)	1.35 (0.90–2.03)
Pervasive development disorders				
Any point	1.74 (0.78–3.91)	1.69 (0.74–3.83)		
1 st trimester	1.28 (0.57–2.92)	1.18 (0.51–2.75)		
2 nd trimester	1.23 (0.57–2.62)	1.11 (0.48–2.53)		
3 rd trimester	1.35 (0.57–3.17)	1.26 (0.49–3.22)		

Note. Adjusted odds ratios were adjusted for the effects of maternal age at birth, maternal education, and area-based deprivation, child's sex, maternal prenatal smoking, maternal prenatal psychological distress, and maternal history of psychiatric illness. Pervasive development disorders were only assessed at age 7

Figures

Figure 1. Sample exclusions