**Associations between prenatal maternal infections and children's socioemotional
outcomes: Evidence from the ALSPAC cohort**

Hildigunnur Anna Hall MSc,^{1*} Lydia Gabriela Speyer MSc,¹ Michael Vincent Lombardo
PhD,^{2,3} Aja Louise Murray PhD,¹ Bonnie Auyeung PhD^{1, 3}

¹Department of Psychology, University of Edinburgh, Edinburgh, United Kingdom

² Laboratory for Autism and Neurodevelopmental Disorders, Center for Neuroscience and
Cognitive Systems @UniTn, Istituto Italiano di Tecnologia, Rovereto, Italy

³Autism Research Centre, Department of Psychiatry, University of Cambridge, Cambridge,
United Kingdom

*Corresponding author: Hildigunnur Anna Hall, Department of Psychology, University of
Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, United Kingdom; Email:

anna.hall@ed.ac.uk

Abstract

Background: Previous studies have suggested there are links between maternal infections during pregnancy and increased odds of offspring schizophrenia and autism spectrum disorders, particularly for exposure in the first two trimesters. Few studies have examined associations with outcomes beyond these conditions. Evidence is particularly lacking on links with child outcomes measured with instruments which capture the dimensional nature of psychopathology. **Methods:** We used data from the (N = 7484) Avon Longitudinal Study of Parents and Children (ALSPAC) to examine links between prenatal maternal infections, reported by mothers at each trimester, and children's socioemotional outcomes. Child outcomes were measured using the parent-reported Strengths and Difficulties Questionnaire at age 8. Linear regressions were used to assess associations. **Results:** Infections during the first trimester were associated with increased conduct problems ($B = 0.165$, $P = < .001$) and hyperactivity/inattention ($B = 0.185$, $P = .007$). Second trimester infections were associated with increased hyperactivity and/or inattention ($B = 0.163$, $P = .010$). This was found after adjusting for maternal age and education, deprivation, child's sex, maternal prenatal smoking and alcohol use, maternal prenatal distress, history of psychiatric illness and exposure to infections in other trimesters, as well as correcting for multiple comparisons. No associations were found between third trimester infections and child outcomes. **Conclusions:** Findings suggest that the first and second trimester may be a critical period for the effects of prenatal maternal immune activation on childhood conduct problems and hyperactivity/inattention. Potential implications include increased emphasis on preventing common infections in the prenatal period.

Keywords: pregnancy; infections; child development; socioemotional difficulties; ALSPAC.

Background

Previous studies have suggested that prenatal maternal infections may be associated with increased odds of offspring psychosocial outcomes, with the most well-studied links being those with schizophrenia spectrum disorders (SSD) and autism spectrum disorders (ASD) (1,2). Evidence from these studies shows that there may be critical periods during pregnancy, where stronger associations between prenatal infections and child disorders are observed, compared to other time points. However, it remains somewhat unclear which periods are most consequential for specific outcomes. A review by Khandaker et al. (2) for example, presented evidence for higher odds of SSD in association with infections in the early stages of pregnancy. The review by Jiang et al. (1) however, showed that only infections in the second trimester were associated with increased odds of ASD.

The links between prenatal infections and key developmental outcomes beyond SSD and ASD also remains unclear. Despite animal models suggesting that prenatal infections may be linked to a range of developmental abnormalities (3), investigations of the links between prenatal maternal infections and children's broader psychosocial development in humans have been limited. A few studies have examined links with attention deficit hyperactivity disorder (ADHD). Mann and McDermott (4) reported links between prenatal maternal genitourinary infections and offspring ADHD, though they did not examine timing of exposure. Dreier et al. (5) examined timing-specific associations and found increased odds of ADHD to be associated with maternal fever in weeks 9-12 of pregnancy and genitourinary infections in weeks 33-36. Simanek and Meier (6) reviewed studies on links between prenatal infections and offspring mood disorders. They concluded that findings were conflicting; the most convincing evidence concerned associations between prenatal exposure to influenza and offspring bipolar disorder. Green et al. (7) reported associations between prenatal

maternal infections, at any point during pregnancy, and childhood developmental vulnerabilities, using a measure of children's physical, social, emotional, cognitive and communicative development. However, they did not examine the timing of exposure.

The aims of the current study were to examine links between prenatal maternal infections, at each trimester, and children's socioemotional outcomes at age 8, as measured with the Strengths and Difficulties Questionnaire (SDQ), in the (N = 7484) Avon Longitudinal Study of Parents and Children (ALSPAC). We hypothesised that infections at any point during pregnancy would be associated with increased overall difficulties. Due to the lack of clarity in the literature, we explored whether associations would differ depending on the timing of exposure, as well as domain of socioemotional development by examining links with scores on the different subscales of the SDQ. We expected associations to be attenuated after adjusting for the effects of potential confounds and covariates.

Methods

Population

Participants were the N = 7484 child and mother pairs who took part in the Avon Longitudinal Study for Parents and Children (ALSPAC) (8,9) who had information on both maternal prenatal infections and children's socioemotional development at age 8. We chose this time point as we expected early symptoms of childhood and adolescent mental health issues to be captured by that time (10,11). It was also a time point when the sample had not been subject to substantial attrition. ALSPAC is a longitudinal birth cohort study, which has followed children born in the South-West England area of Avon between 1991 and 1992, and their families, since pregnancy.

During the initial recruitment phase, ALSPAC enrolled 14541 pregnancies, comprising 14676 foetuses. These pregnancies resulted in 14062 live births and 13988 children who were alive at 1 year of age. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool: <http://www.bristol.ac.uk/alspac/researchers/our-data/>.

Measures

Data on mothers' exposure to prenatal infections were collected from interviews at three time points; during weeks 18 and 32 of gestation and 8 weeks postpartum. At the week 18 interview, 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?' with the response options: 'Yes, in 1st 3 months'; 'Yes, in period 4th month to now'; 'No, not at all'; 'Don't know'. Mothers were queried about these same infections around 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'. Eight weeks after birth, mothers were again asked about the same infections, and were asked to reflect on the last 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'. 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 with 'Yes, in period 4th month to now' at the week 18 interview or 'Yes, in the last 3 months' in the week 32 interview, this was coded as a second trimester infection. If mothers responded positively to having had an infection from month 7 onwards in the interview in week 8 postpartum, this was coded as a third trimester infection (Figure 1).

[FIGURE 1]

Children's socioemotional outcomes were assessed at age 8 using the parent-reported Strengths and Difficulties Questionnaire (12). The SDQ is a 25-item scale comprising five subscales of five items each; 1) emotional symptoms, 2) conduct problems, 3) hyperactivity/inattention, 4) peer relationship problems, and 5) prosocial behaviour. Parents were asked to reflect on their child's behaviour in the past six months and respond to each item, which was a statement about their child (e.g., 'is constantly fidgeting or squirming'), using the following response options: 0 = 'doesn't apply'; 1 = 'applies somewhat'; 2 = 'certainly applies'. Total scores were computed for each subscale (range 0–10) as well as a total difficulties score (range 0–40), which is the sum of scores on all the subscales except prosocial behaviour. While the SDQ has been critiqued for limited data on cultural validity, criterion validity and test-retest reliability, it is considered to have good structural, discriminative and convergent validity (13). The scale has further shown good predictive validity for a range of mental disorders (14–16), good sensitivity and specificity for detecting conditions such as ADHD (17,18), as well as good developmental invariance (19) and cross-informant invariance (20).

Potential confounders and covariates were selected before analyses were conducted. Potential confounders, selected on the basis of their possible association with maternal infections during pregnancy and child outcomes, were: *maternal age at birth* and *maternal education*. Potential covariates, selected on the basis of their possible association with children's socioemotional outcomes, were: *area-based deprivation*, *child's sex*, *maternal prenatal smoking*, *maternal prenatal alcohol consumption*, *maternal prenatal psychological distress* and *maternal history of psychiatric illness*. In models examining trimester-specific associations, we also adjusted for infections in the other two trimesters. *Birth weight* and

gestational age were considered as potential confounders, but were not included in the analyses as they can be argued to mediate the association between prenatal infections and child development (21–23).

Information on *maternal age* was gathered at birth. Information on *maternal education* was gathered at week 32 of pregnancy, with the highest completed UK qualification provided (CSE, Vocational, O-level, A-level, Degree). For the purposes of the current study, we recoded this variable to A-level (high) or lower (low). A-levels equate to the International Standard Classification of Education (ISCED) level 3 (upper secondary education). *Area based deprivation* was assessed using the postcode-based Index of Multiple Deprivation 2000 (24), at the same time as children's socioemotional outcomes were measured (age 8). The IMD 2000 is a composite measure comprising six domains: 1) income deprivation; 2) employment deprivation; 3) health deprivation and disability, 4) education, skills, and training deprivation; 5) geographical access to services; 6) housing stress. This was the earliest time point the IMD was available, and thus this is only considered a potential covariate and not a confounder. Information on *child's sex* was gathered at birth and registered as male or female. Information on *maternal prenatal smoking* was gathered from questionnaires at weeks 18 and 32 of pregnancy and 8 weeks postpartum (where mothers were asked about the final trimester of pregnancy). From the week 18 interview, data on smoking were provided as yes/no answers to whether mothers had smoked in the first trimester. In the week 32 questionnaire, data were provided on the number of cigarettes smoked daily during the second trimester. In week 8 postpartum, data on smoking were provided with an ordinal variable representing the number of cigarettes smoked daily. For the current study, we decided to keep the coding as provided, in order to retain as much information as possible. Data on *prenatal maternal alcohol consumption* were also gathered at weeks 18 and 32 of gestation and 8 weeks postpartum. In the week 18 interview, data on

prenatal alcohol consumption were provided as an ordinal variable measuring the number of
 glasses of alcohol mothers drank in the first trimester. The same type of variable was
 provided from the week 8 postpartum interview, where mothers reported on their alcohol
 consumption in the last trimester. From the week 32 interview, data on alcohol consumption
 were provided as a continuous variable on the number of alcoholic units women drank per
 week during the second trimester. Again, for the purposes of the current study, we retained
 the data in the original format in order to retain as much information as possible. *Maternal*
prenatal psychological distress was assessed using the Edinburgh Postnatal Depression Scale
 (EPDS) (25) at weeks 18 and 32 of pregnancy. The EPDS is a 10-item self-report
 questionnaire with scores ranging from 0 to 30. Higher scores represent more psychological
 distress. Information on *maternal history of psychiatric illness* was gathered from
 questionnaires at week 12 gestation. Mothers were asked if they had a range of psychiatric
 problems (bulimia, schizophrenia, anorexia, severe depression, or other psychiatric problem).
 For the purposes of the current study, if they responded having had any of the above, this was
 coded as ‘yes’.

Statistical analysis

Linear regressions using a robust maximum likelihood estimation (MLR) were used to assess
 associations between prenatal maternal infections and children’s socioemotional outcomes.
 Missing data were dealt with using a full information maximum likelihood (FIML) approach
 (26) in order to use all available data. We corrected for multiple comparisons using a false
 discovery rate (FDR) estimation (27), separately for unadjusted and adjusted models. Data
 were analysed using *R* version 3.6.2 (28) and *Mplus* version 8.4 (29).

Results

Around half (49.9%, $n = 3738$) of the participating mothers reported a prenatal infection at some point during pregnancy, 21.7% ($n = 1627$) reported an infection during the first trimester, 32.3% ($n = 2417$) during the second and 19.9% ($n = 1487$) during the third. Descriptive statistics for all study variables by infection status are shown in Tables 1 and 2.

[TABLE 1]

[TABLE 2]

Infections at any point during pregnancy

Results from unadjusted linear regressions showed that infections at any point during pregnancy were associated with higher scores on the total difficulties scale ($B = 0.742$, $P < .001$), the conduct problems ($B = 0.174$, $P < .001$), emotional symptoms ($B = 0.159$, $P < .001$), hyperactivity/inattention ($B = 0.323$, $P < .001$), and peer relationship problems ($B = 0.082$, $P = .026$) subscales, but not the prosocial behaviour scale ($B = -0.047$, $P = .306$) (Table 3).

After adjusting for potential confounds and covariates, results showed that infections at any point during pregnancy were associated with higher scores on the total difficulties scale ($B = 0.396$, $P = .001$), representing a 0.4 point increase on a scale ranging from 0 to 40, the conduct problems subscale ($B = 0.105$, $P = .002$), representing a 0.1 score point increase on a scale ranging from 0 to 10, and the hyperactivity/inattention subscale ($B = 0.225$, $P < .001$), representing a 0.23 score point increase on a scale ranging from 0 to 10. No associations were found between infections at any point and scores on the emotional symptoms subscale ($B = 0.052$, $P = .226$), the peer relationship problems subscale ($B = 0.007$, $P = .838$), or the prosocial behaviour subscale ($B = -0.002$, $P = .973$) (Table 3).

First trimester infections

Unadjusted models showed associations between first trimester infections and higher scores on the total difficulties scale ($B = 0.639, P < .001$), the conduct problems ($B = 0.210, P < .001$), emotional symptoms ($B = 0.148, P = .004$) and hyperactivity/inattention ($B = 0.248, P < .001$) subscales, but not the peer relationship problems ($B = 0.037, P = .400$) or prosocial behaviour ($B = -0.049, P = .365$) subscales (Table 3).

After adjusting for potential confounds and covariates, results showed that first trimester infections were associated with higher scores on the total difficulties scale ($B = 0.405, P = .004$), representing a 0.4 score point increase on a scale ranging from 0 to 40, the conduct problems subscale ($B = 0.165, P < .001$), representing a 0.17 score point increase on a scale ranging from 0 to 10 and the hyperactivity/inattention subscale ($B = 0.185, P = .007$), representing a 0.19 score point increase on a scale ranging from 0 to 10. No associations were found between first trimester infections and scores on the emotional symptoms subscale ($B = 0.075, P = .145$), the peer relationship problems subscale ($B = -0.017, P = .692$), or the prosocial behaviour subscale ($B = -0.018, P = .742$) (Table 3).

Second trimester infections

Unadjusted models showed associations between second trimester infections and higher scores on the total difficulties scale ($B = 0.533, P < .001$), and the conduct problems ($B = 0.113, P = .002$), hyperactivity/inattention ($B = 0.253, P < .001$) and peer relationship problems ($B = 0.087, P = .024$) subscales, but not the emotional symptoms ($B = 0.083, P = .072$) or prosocial behaviour subscales ($B = -0.062, P = .196$) (Table 3).

Only links between second trimester infections and hyperactivity/inattention ($B = 0.163$, $P = .010$) remained significant after adjusting for potential covariates and confounders, representing a 0.16 score point increase on a scale ranging from 0 to 10. No associations were found between second trimester infections and scores on the total difficulties scale ($B = 0.204$, $P = .123$), or the conduct problems ($B = 0.029$, $P = .452$), emotional symptoms ($B = -0.015$, $P = .748$), peer relationship problems ($B = 0.025$, $P = .534$) or prosocial behaviour ($B = -0.031$, $P = .530$) subscales (Table 3)

Third trimester infections

Unadjusted models showed associations between third trimester infections and higher scores on the total difficulties scale ($B = 0.515$, $P = .001$), the conduct problems ($B = 0.133$, $P = .002$), emotional symptoms ($B = 0.128$, $P = .016$), hyperactivity/inattention ($B = 0.153$, $P = .033$) and peer relationship problems ($B = 0.103$, $P = .021$) subscales, but not prosocial behaviour ($B = -0.026$, $P = .634$). None of these links remained significant after adjusting for potential confounders (Table 3).

[TABLE 3]

Discussion

This study examined links between prenatal infections during any point in pregnancy, and during specific trimesters, and children's socioemotional outcomes at the age of 8. We found that around half of women experienced any infection at any point during pregnancy, which is in line with previous research where women have been asked about specific infections in pregnancy (30). Infections at any point during pregnancy were associated with increased overall difficulties, based on the total difficulties score, increased conduct problems and

hyperactivity/inattention, after adjusting for several potential confounds and covariates. No link was found with children's emotional symptoms, peer problems or prosocial behaviour in adjusted models. When examining trimester-specific associations, results from adjusted models showed that infections during the first trimester of pregnancy were associated with greater overall difficulties as well as increased conduct problems and hyperactivity/inattention. Second trimester infections were also associated with increased symptoms of hyperactivity/inattention. No associations were observed between third trimester infections and any of the socioemotional outcomes studied, after adjusting for potential covariates and confounds. The associations observed between infections at any point during pregnancy and increased conduct problems and hyperactivity/inattention can, therefore, likely be explained by exposure to infections in the first and second trimesters. These findings suggest that the first two trimesters may be a sensitive period for potential adverse effects of prenatal immune activation on children's development, in particular hyperactivity and/or inattention and conduct problems.

These results are somewhat consistent with studies on SSD (2) and ASD (1), which have shown stronger links between infections during the first two trimesters of pregnancy and offspring neurodevelopmental issues. However, we found no associations between prenatal infections and peer problems or prosocial behaviour. Although the SDQ does not contain items which map directly onto clinical criteria for ASD, these two subscales can be argued to be indirectly related to symptoms of ASD (31). Our findings support those of Dreier et al. (5) who reported increased odds of ADHD in association with fever in the first trimester of pregnancy. In contrast to our findings they also reported links between genitourinary infections in late pregnancy and ADHD. Dreier et al. did not, however, adjust for infections at other time points during gestation in their study.

These findings also contradict our previous work (32) on another UK cohort, where the SDQ was also used to assess children's socioemotional outcomes, although at age 3. There, we found an association between maternal-reported prenatal infections and increased emotional symptoms and no association with hyperactivity/inattention or conduct problems in fully adjusted models. In addition, the rates of self-reported infections were much lower in that study compared to the current one (7.6%). These discrepancies in findings may be explained by key differences in the methodology of the two cohort studies. In our previous study, women were not asked about particular infections specifically, but about illness in pregnancy in general, responses to which were later coded into illness categories. Further, this information was collected at 9 months postpartum, where women reflected on the entire period of pregnancy, introducing more risk of recall bias. Both our previous study and the current one are limited by the fact that they rely on mothers' memory of past events and assessment of whether a particular episode of illness was an infection or not. Future studies could combine maternal self-reports of infections with biological markers of prenatal maternal immune activation, such as C-reactive protein and inflammatory cytokines, to get a more detailed picture of these associations and reduce the potential impact of recall bias.

The observed increases in conduct problems and hyperactivity/inattention associated with first and second trimester were under 0.20 score points, where the highest possible score on each subscale was 10 points (standardised effect sizes also shown in Table 3). These are small effects from a clinical perspective, but may nonetheless be important at the population level, given the considerable economic costs of conduct problems and ADHD (33,34).

Findings from this study could have implications for health care policy, highlighting potential risks associated with infections in the first and second trimesters of pregnancy. Centres for

Disease Control and Prevention provide recommendations to pregnant women on how to prevent infections during pregnancy (35) which include personal hygiene measures, avoiding certain foods and practicing safe sex. However, the focus of this guidance is on a limited selection of infections, namely cytomegalovirus, group B strep, listeriosis and Zika virus. Given the observed associations in the current study and others, it may be of benefit to emphasise measures to prevent more common infections as well.

The findings from this study should be considered in the context of several limitations. Severity of infections was not considered, so we are not able to compare our results to findings in the literature which show that associations between prenatal maternal infections requiring admission to hospital may be stronger than links with infections considered less severe (1). Further, the assessment of prenatal exposure to infections was limited to maternal self-reports, where women reflected on the preceding three months of pregnancy, there is a risk of recall bias. In addition, although ALSPAC has a wealth of biological samples, no biomarkers for infection or inflammation were examined in the period of pregnancy, making it impossible to determine whether our findings support the hypothesis that it is the body's immune response which is associated with abnormalities in child development rather than the infective agents.

Over 2000 children of the initial ALSPAC sample did not have any information on exposure to prenatal infections and were thus excluded from our study sample. Of those, around 300 had available data on socioemotional outcomes at age 8. The mean total difficulties score was slightly higher in this group ($\bar{x} = 9.44$) compared to what we found in our study sample ($\bar{x} = 7.76$). Over 6000 children of those in the initial ALSPAC sample who had data on prenatal exposure did not have any data on socioemotional development available. We found that the

rate of prenatal infection in this group was higher (60% had some infection at any point during pregnancy) than what we found in our study sample (50%). This suggests that our findings may be biased, potentially towards an attenuated association between prenatal infections on children's socioemotional development, though no firm conclusions can be drawn. The strengths of this study lie in its longitudinal design and the use of a continuous outcome measure. It is generally recognised that most psychopathologies are dimensional in nature, yet most studies on links between prenatal infections and child outcomes rely on dichotomous outcomes, most frequently psychiatric diagnoses.

Conclusions

The current study presents evidence for increased symptoms of conduct problems and hyperactivity/inattention in association with infections in the first two trimesters of pregnancy. These findings contribute to the growing literature on trimester-specific effects of prenatal infections on child outcomes and suggest that the first and second trimesters may be critical periods for potential adverse effects of prenatal maternal immune activation on child development. The study further introduces novel evidence on associations between prenatal infections and broad psychosocial phenotypes assessed on a continuum. Findings suggest public health advice should emphasise preventing common infections in the period of pregnancy.

375 **Abbreviations**

376 SSD – schizophrenia spectrum disorders

377 ASD – autism spectrum disorders

378 ADHD – attention deficit hyperactivity disorder

379 SDQ – Strengths and Difficulties Questionnaire

380 ALSPAC – Avon Longitudinal Study of Parents and Children

381

382 **Acknowledgements**

383 We are extremely grateful to all the families who took part in this study, the midwives for
384 their help in recruiting them, and the whole ALSPAC team, which includes interviewers,
385 computer and laboratory technicians, clerical workers, research scientists, volunteers,
386 managers, receptionists and nurses. We further thank the UK Economic and Social Research
387 Council and the Scottish Graduate School of Social Sciences for their generous support.

References

1. Jiang HY, Xu LL, Shao L, Xia RM, Yu ZH, Ling ZX, et al. Maternal infection during pregnancy and risk of autism spectrum disorders: A systematic review and meta-analysis. *Brain Behav Immun*. 2016;58:165–72.
2. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. *Psychol Med*. 2013;43(2):239–57.
3. Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, et al. Maternal immune activation and abnormal brain development across CNS disorders. *Nat Rev Neurol*. 2014;10(11):643–60.
4. Mann JR, McDermott S. Are maternal genitourinary infection and pre-eclampsia associated with ADHD in school-aged children? *J Atten Disord*. 2011;15(8):667–73.
5. Dreier JW, Nybo Andersen AM, Hvolby A, Garne E, Andersen PK, Berg-Beckhoff G. Fever and infections in pregnancy and risk of attention deficit/hyperactivity disorder in the offspring. *J Child Psychol Psychiatry*. 2016;57(4):540–8.
6. Simanek AM, Meier HCS. Association Between Prenatal Exposure to Maternal Infection and Offspring Mood Disorders: A Review of the Literature. *Curr Probl Pediatr Adolesc Health Care*. 2015;45(11):325–64.
7. Green MJ, Kariuki M, Dean K, Laurens KR, Tzoumakis S, Harris F, et al. Childhood developmental vulnerabilities associated with early life exposure to infectious and noninfectious diseases and maternal mental illness. *J Child Psychol Psychiatry*. 2017;59(7):801–10.

8. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort Profile: The 'Children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol*. 2013;42(1):111–27.
9. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, et al. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol*. 2013;42(1):97–110.
10. Dalsgaard S, Thorsteinsson E, Trabjerg BB, Schullehner J, Plana-Ripoll O, Brikell I, et al. Incidence Rates and Cumulative Incidences of the Full Spectrum of Diagnosed Mental Disorders in Childhood and Adolescence. *JAMA Psychiatry*. 2020;77(2):155–64.
11. Goodman R, Ford T, Simmons H, Gatward R, Meltzer H. Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. *Br J Psychiatry*. 2000;177(6):534–9.
12. Goodman R. The Strengths and Difficulties Questionnaire: A Research Note. *J Child Psychol Psychiatry*. 1997;38(5):581–6.
13. Kersten P, Czuba K, McPherson K, Dudley M, Elder H, Tauroa R, et al. A systematic review of evidence for the psychometric properties of the Strengths and Difficulties Questionnaire. *Int J Behav Dev*. 2015;40(1):64–75.
14. Nielsen LG, Rinvall MK, Clemmensen L, Munkholm A, Elberling H, Olsen EM, et al. The predictive validity of the Strengths and Difficulties Questionnaire in preschool age to identify mental disorders in preadolescence. *PLoS ONE*. 2019;14(6):e0217707.

15. Overgaard KR, Madsen KB, Oerbeck B, Friis S, Obel C. The predictive validity of the Strengths and Difficulties Questionnaire for child attention-deficit/hyperactivity disorder. *Eur Child Adolesc Psychiatry*. 2019;28(5):625–33.
16. Rimvall MK, Elberling H, Rask CU, Helenius D, Skovgaard AM, Jeppesen P. Predicting ADHD in school age when using the Strengths and Difficulties Questionnaire in preschool age: a longitudinal general population study, CCC2000. *Eur Child Adolesc Psychiatry*. 2014;23(11):1051–60.
17. Caye A, Agnew-Blais J, Arseneault L, Gonçalves H, Kieling C, Langley K, et al. A risk calculator to predict adult attention-deficit/hyperactivity disorder: generation and external validation in three birth cohorts and one clinical sample. *Epidemiol Psychiatr*. 2020;29:e37.
18. Riglin L, Collishaw S, Thapar AK, Dalsgaard S, Langley K, Smith GD, et al. Association of Genetic Risk Variants With Attention-Deficit/Hyperactivity Disorder Trajectories in the General Population. *JAMA Psychiatry*. 2016;73(12):1285–92.
19. Murray AL, Speyer LG, Hall HA, Valdebenito S, Hughes C. A longitudinal invariance analysis of the Strengths and Difficulties Questionnaire across ages 3,5,7,11 and 14 in a large UK-representative sample [Preprint]. *PsyArXiv*. 2020.
<https://doi.org/10.31234/osf.io/zs6q5>
20. Murray AL, Speyer LG, Hall HA, Valdebenito S, Hughes C. Teacher versus parent informant invariance of the Strengths and Difficulties Questionnaire [Preprint]. *PsyArXiv*. 2020. <https://doi.org/10.31234/osf.io/u89rb>
21. Hayes B, Sharif F. Behavioural and emotional outcome of very low birth weight infants – literature review. *J Matern Fetal Neonatal Med*. 2009;22(10):849–56.

22. Slattery MM, Morrison JJ. Preterm delivery. *The Lancet*. 2002;360(9344):1489–97.
23. Valero de Bernabé J, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martínez D, et al. Risk factors for low birth weight: a review. *Eur J Obstet Gynecol Reprod Biol*. 2004;116(1):3–15.
24. Noble M, Wright G, Smith G, Dibben C. Measuring Multiple Deprivation at the Small-Area Level. *Environ Plan Econ Space*. 2006;38(1):169–85.
25. Cox JL, Holden JM, Sagovsky R. Detection of Postnatal Depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry*. 1987;150(6):782–6.
26. Enders CK. The Performance of the Full Information Maximum Likelihood Estimator in Multiple Regression Models with Missing Data. *Educ Psychol Meas*. 2001;61(5):713–40.
27. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc Ser B Methodol*. 1995;57(1):289–300.
28. R Core Team. A language and environment for statistical computing [Internet]. Vienna, Austria: A Foundation for Statistical Computing; 2018. <https://www.R-project.org/>
29. Muthén LK, Muthén BO. Mplus. *Compr Model Programme Appl Res Users Guide*. 2015;5.
30. Collier SA, Rasmussen SA, Feldkamp ML, Honein MA, National Birth Defects Prevention S. Prevalence of self-reported infection during pregnancy among control mothers in the National Birth Defects Prevention Study. *Birth Defects Res Clin Mol Teratol*. 2009;85(3):193–201.

31. Salayev, KA, Sanne, B. The strengths and difficulties questionnaire (SDQ) in autism spectrum disorders. *Int J Disabil Hum Dev*. 2017;16(3):275–80.
32. Hall HA, Speyer LG, Murray AL, Auyeung B. Prenatal maternal infections and children's socioemotional development: findings from the UK Millennium Cohort Study. *Eur Child Adolesc Psychiatry* [Advanced online publication]. 2020.
<https://doi.org/10.1007/s00787-020-01644-y>
33. Foster EM, Jones DE. The High Costs of Aggression: Public Expenditures Resulting From Conduct Disorder. *Am J Public Health*. 2005 Oct 1;95(10):1767–72.
34. Le HH, Hodgkins P, Postma MJ, Kahle J, Sikirica V, Setyawan J, et al. Economic impact of childhood/adolescent ADHD in a European setting: the Netherlands as a reference case. *Eur Child Adolesc Psychiatry*. 2014;23(7):587–98.
35. Centres for Disease Control and Prevention. Prevent Infections During Pregnancy. 2019. <https://www.cdc.gov/features/prenatalinfections/index.html>

Tables

Table 1. Descriptive statistics for study outcomes and continuous confounds/covariates by infection status

	Prenatal infection (N = 3738)					No prenatal infection (N = 3228)				
	N	M	SD	Min	Max	N	M	SD	Min	Max
Outcome variables										
Conduct problems	3732	1.57	1.48	0	9	3225	1.39	1.43	0	10
Emotional symptoms	3732	1.73	1.87	0	10	3225	1.57	1.76	0	10
Hyperactivity/inattention	3732	3.46	2.49	0	10	3223	3.14	2.39	0	10
Peer problems	3731	1.33	1.58	0	10	3223	1.25	1.5	0	9
Prosocial behaviour	3736	7.99	1.88	1	10	3226	8.04	1.92	0	10
Total difficulties	3728	8.08	5.23	0	33	3220	7.34	5.04	0	36
Continuous confounds/covariates										
Maternal age	3738	29.14	4.61	15	44	3228	29.13	4.37	15	42
Prenatal distress (first trimester)	3520	6.96	4.74	0	28	3201	5.98	4.40	0	26
Prenatal distress (second trimester)	3620	7.15	5.00	0	29	3206	6.04	4.67	0	27
Cigarettes smoked p/day in (second trimester)	3451	1.76	4.77	0	40	3014	1.39	4.19	0	35
Alcoholic units consumed p/week (second trimester)	2174	1.83	3.81	0	54	2017	1.71	3.61	0	46

Note. Infection status refers to infection at any point during pregnancy.

Table 2. Descriptive statistics for categorical confounds/covariates by infection status

	Prenatal infection (N = 3738)		No prenatal infection (N = 3228)	
	N	%	N	%
Maternal education				
Low	2051	56	1897	59
High	1621	44	1325	41
Index of Multiple Deprivation (quintiles)				
Lowest quintile	540	15	381	12
20–40%	573	16	452	15
40–60%	649	19	556	18
60–80%	690	19	640	21
Highest quintile	1091	31	1033	34
Child's sex				
Male	1890	51	1631	51
Female	1848	49	1597	49
Smoking (first trimester)				
Yes	762	21	529	16
No	2951	79	2699	84
Cigarettes smoked p/day (third trimester)				
5 or more	448	12	313	10
1–4	126	3	113	4
None	3047	84	2798	87
Alcohol consumption (first trimester)				
1+ glasses p/day	82	2	44	1
1+ glasses p/week	507	14	437	14
< 1 glass p/week	1535	41	1303	41
None	1576	43	1431	45
Alcohol consumption (third trimester)				
1+ glasses p/day	72	2	49	1
1+ glasses p/week	607	17	502	16
< 1 glass p/week	1314	36	1158	36
None	1616	45	1507	47
Maternal psychiatric history				
Yes	519	15	266	9
No	2953	85	2774	91
Birthweight				
< 2500g	166	5	111	3
≥ 2500g	3518	95	3085	97
Gestational age				
< 37 weeks	204	5	135	4
≥ 37 weeks	3534	95	3093	96

Note. Infection status refers to infection at any point during pregnancy.

Table 3. Regression parameters for models on associations between prenatal infections and children's scores on the SDQ.

	Unadjusted				Adjusted			
	<i>B</i>	<i>SE</i>	<i>P</i>	β	<i>B</i>	<i>SE</i>	<i>P</i>	β
Total difficulties					Total difficulties			
Any point	0.742	0.124	< .001*	0.072	0.396	0.120	.001*	0.039
1st trimester	0.639	0.146	< .001*	0.052	0.405	0.142	.004*	0.034
2nd trimester	0.533	0.130	< .001*	0.049	0.204	0.132	.123	0.019
3rd trimester	0.515	0.151	.001*	0.040	0.028	0.154	.853	0.002
Conduct problems					Conduct problems			
Any point	0.174	0.035	< .001*	0.059	0.105	0.034	.002*	0.036
1st trimester	0.210	0.041	< .001*	0.061	0.165	0.041	< .001*	0.048
2nd trimester	0.113	0.037	.002*	0.037	0.029	0.038	.452	0.009
3rd trimester	0.133	0.042	.002*	0.037	0.027	0.044	.536	0.008
Emotional symptoms					Emotional symptoms			
Any point	0.159	0.044	< .001*	0.044	0.052	0.043	.226	0.014
1st trimester	0.148	0.052	.004*	0.034	0.075	0.051	.145	0.018
2nd trimester	0.083	0.046	.072	0.022	-0.015	0.048	.748	-0.004
3rd trimester	0.128	0.053	.016*	0.028	0.012	0.055	.826	0.003
Hyperactivity/inattention					Hyperactivity/inattention			
Any point	0.323	0.059	< .001*	0.066	0.225	0.057	< .001*	0.046
1st trimester	0.248	0.070	< .001*	0.043	0.185	0.068	.007*	0.032
2nd trimester	0.253	0.062	< .001*	0.049	0.163	0.063	.010*	0.032
3rd trimester	0.153	0.072	.033*	0.025	-0.036	0.073	.626	-0.006

Table 3 (continued).

	Unadjusted				Adjusted			
	<i>B</i>	<i>SE</i>	<i>P</i>	β	<i>B</i>	<i>SE</i>	<i>P</i>	β
Peer relationship problems					Peer relationship problems			
Any point	0.082	0.037	.026*	0.027	0.007	0.037	.838	0.002
1st trimester	0.037	0.044	.400	0.010	-0.017	0.044	.692	-0.005
2nd trimester	0.087	0.039	.024*	0.027	0.025	0.040	.534	0.008
3rd trimester	0.103	0.045	.021*	0.027	0.023	0.047	.617	0.006
Prosocial behaviour					Prosocial behaviour			
Any point	-0.047	0.046	.306	-0.012	-0.002	0.045	.973	< 0.001
1st trimester	-0.049	0.054	.365	-0.011	-0.018	0.054	.742	-0.004
2nd trimester	-0.062	0.048	.196	-0.015	-0.031	0.050	.530	-0.008
3rd trimester	-0.026	0.055	.634	-0.006	0.022	0.058	.697	0.005

Note. Regression parameters are betas (*B*), standard errors (*SE*), probability values (*P*) and standardised betas (β) *Significant at $p > .05$ after FDR correction. All adjusted models controlled for the effects of maternal age at birth, maternal education, area-based deprivation, child's sex, maternal prenatal smoking and alcohol use, maternal prenatal psychological distress, maternal history of psychiatric illness. Trimester-specific models were additionally adjusted for infections in other trimesters. Note that the Total difficulties scale ranges from 0–40 and all other scales range from 0–10, and thus *B* coefficients should be interpreted accordingly. Standardised betas (β) are additionally provided to allow direct comparisons of effect sizes.

Figures

Figure 1. Coding of prenatal infection data.