

*Sex differences in foetal origins of child emotional symptoms: a test of evolutionary hypotheses in a large, general population cohort*

Article

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**Sex-differences in foetal origins of child emotional symptoms: a test of evolutionary hypotheses in a large, general population cohort**

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3 **Sex-differences in foetal origins of child emotional symptoms: a test of evolutionary**  
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5 **hypotheses in a large, general population cohort**  
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8 Sex-dependent foetal origins of child emotional symptoms  
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## Abstract

### Background

Based on previous findings from the Wirral Child Health and Development Study (WCHADS), and on evolutionary hypotheses, we pre-registered analyses of data from a large epidemiological sample (<https://osf.io/fn5g9/register/564d31db8c5e4a7c9694b2be>), to test for sex-dependent moderation by prenatal maternal depressive symptoms of the association between postnatal maternal depressive symptoms and child emotional problems.

### Methods

8,354 mothers and children were followed from pregnancy to 3.5 years in the Avon Longitudinal Study of Parents and Children (ALSPAC). Self-report measures of prenatal and postnatal maternal depressive symptoms, and maternal report of child emotional symptoms were administered.

### Results

There was a three-way interaction between maternal prenatal and postnatal depression, and child sex (Coeff .042 95% CI .015 to .068,  $p=.002$ ). This arose from moderation by prenatal depression, in opposite directions in boys and in girls. In boys the association between postnatal depression and child emotional symptoms was weaker following lower prenatal depressive symptoms (interaction term coeff = .030,  $p=.001$ ) and in girls, to a lesser extent, the association was stronger following lower prenatal depressive symptoms (interaction term coeff = -.012,  $p=.221$ ).

### Conclusions

We replicated the finding from the WCHADS that prenatal depression modifies the association between postnatal depression and children's emotional problems in a sex-dependent fashion. In ALSPAC, the sex difference was explained mainly by a protective effect of low prenatal depression in boys, while in WCHADS it arose from greater

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3 vulnerability of girls to postnatal depression following low prenatal depression. In the light of  
4 these findings, in evaluating and implementing early interventions, there is need to consider  
5 that risks associated with postnatal depression may vary depending on maternal mood  
6 during pregnancy, and may differ between boys and girls.  
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12 **Abbreviations**  
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15 WCHADS, Wirral Child Health and Development Study  
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18 ALSPAC, Avon Longitudinal Study of Parents and Children  
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For Peer Review

## Introduction

According to the 'foetal origins' hypothesis, fetal adaptations occur *in utero* in anticipation of later environmental exposures (Barker, 2007). This theory was first proposed to account for associations between low birth weight and later obesity, cardiovascular disease and type II diabetes, whereby low birthweight reflects an evolved adaptive mechanism that confers advantages in later environments of food scarcity, but simultaneously creates risk in the presence of a high calorie diet. It is evident, however, that adaptations prior to birth that anticipate later environments are found across species, reflecting a conserved 'Predictive Adaptive Response' (PAR) mechanism (Bateson, Gluckman & Hanson, 2014; Wells, 2017). More generally, it is hypothesised that matched prenatal and postnatal environments will be associated with positive offspring outcomes, whereas a mis-match between the pre and postnatal environment confers risk for poor outcomes.

There is also evidence that foetal adaptations to *in utero* environmental conditions vary by sex. The Trivers-Willard (T-W) hypothesis frames this difference within an evolutionary context based on reproductive fitness (Trivers & Willard, 1973). According to the T-W hypothesis, if maternal health during pregnancy predicts later offspring reproductive fitness, then mothers in good health will 'invest' in males leading to more male than female births, because healthy males compete more successfully for females. Alternatively, when maternal conditions are poor, investment in females is favoured and the sex ratio is reversed, to avoid bearing unsuccessful males. This hypothesis is consistent with well documented observations that male foetuses are more vulnerable than females to threats such as preterm birth and maternal asthma, and are also more likely to suffer neurodevelopmental consequences of foetal insults (Aiken & Ozanne, 2013).

The prediction from the two hypotheses jointly is that if foetal adaptations anticipate later environments, and the female foetus is more able than the male to adapt to poor maternal conditions, then we expect female offspring of mothers with poor conditions during pregnancy later exposed to adverse environments to have better outcomes than males who have been

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3 similarly exposed. Conversely, female offspring who are not exposed to poor maternal  
4 conditions during pregnancy are less well prepared, and hence have poorer outcomes  
5 compared to males, when exposed to a negative environment.  
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10 If these mechanisms apply to prenatal and postnatal exposures to maternal mood, and  
11 to behavioural outcomes, the implication is that, in addition to independent contributions of  
12 prenatal and postnatal depression or anxiety, their interaction may also influence children's  
13 outcomes. This has not been tested formally using moderation models, prior to publications  
14 from WCHADS. However the predictions based on the T-W and PAR hypotheses have been  
15 examined comparing matched prenatal and postnatal depression groups (low-low, high-high)  
16 with mismatched groups (low-high, high- low) (Sandman, Glynn & Davis, 2013). Prenatal-  
17 postnatal matching was associated with better cognitive and motor outcomes over the first  
18 year of life than mis-matching, and at 6 months this effect was only evident in females  
19 (Sandman, Glynn & Davis, 2013). In analyses of data from the WCAHDS, prenatal maternal  
20 depressive symptoms modified the association between postnatal depression and child  
21 anxious depressed symptoms as predicted by the PAR hypothesis, and in a sex-dependent  
22 manner as predicted by the T-W hypothesis. In girls, the association between postnatal  
23 depressive symptoms and child anxious depressed symptoms was stronger among those  
24 exposed to lower prenatal maternal depression, in contrast to those exposed to higher levels  
25 (Hill et al., 2017). Furthermore this effect was mediated via *NR3C1* methylation levels at 14  
26 months (Hill et al. 2019a). This mis-match effect was not seen in males, and the sex difference  
27 was supported by a three-way interaction between prenatal and postnatal depression and  
28 child sex. We have also shown moderation by prenatal anxiety of the association between  
29 postnatal maternal anxiety and child irritability at age 7 years, further moderated by levels of  
30 maternal stroking during infancy (Hill, Pickles, Wright, Braithwaite & Sharp, 2019b). This effect  
31 also was seen only in girls.  
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57 The aim of the current study was to replicate the sex-dependent moderator effect of  
58 prenatal depression on the association between postnatal depression and child emotional  
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3 symptoms found in the WCHADS study, using data from a larger birth cohort: the Avon  
4 Longitudinal Study of Parents and Children (ALSPAC). We pre-registered the hypothesis that  
5 there will be a three-way interaction between prenatal and postnatal maternal depressive  
6 symptoms and child sex in the prediction of children's emotional symptoms at age 3.5 years  
7 (Braithwaite, 2018). We also predicted that this would arise from a stronger association  
8 between postnatal depression and child symptoms following low, contrasted with high, levels  
9 of prenatal depression, and seen only in girls. We further planned and pre-registered  
10 exploratory analyses to examine timing effects of prenatal depression (second vs third  
11 trimester), and to test whether similar effects were evident for maternal anxiety.  
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## 23 **Methods**

### 24 *Participants and Procedure*

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28 The present study is an analysis of data collected as part of the Avon Longitudinal  
29 Study of Parents and Children (ALSPAC). ALSPAC is a large, population based longitudinal  
30 study in which pregnant women resident in Avon, UK with expected dates of delivery 1st April  
31 1991 to 31st December 1992 (Boyd et al., 2013; Fraser et al., 2013) were invited to take part  
32 in the study. The initial number of pregnancies enrolled was 14,541. Of these initial  
33 pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988  
34 children who were alive at 1 year of age. Questionnaires were sent to parents at regular  
35 intervals during pregnancy and after childbirth.  
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46 The WCHADS report, on which the pre-registration was based, made use of maternal  
47 reports of depressive symptoms at 20 weeks gestation, and 9 weeks, 7 months and 14 months  
48 after birth. In ALSPAC, maternal depressive symptoms were available at 18 weeks gestation,  
49 and at 8 weeks, 8 months and 21 months after birth. In WCHADS maternal reports of child  
50 emotional difficulties at ages 2.5, 3.5 and 5 years were available and in ALSPAC at age 3.5  
51 years. Variables included as confounders were reported by mothers during pregnancy, as they  
52 were for the WCHADS sample. For the planned and pre-registered exploratory analyses  
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3 respectively, we used maternal reports of prenatal depression at 32 weeks gestation (to test  
4 for prenatal timing effects) and maternal reports of prenatal anxiety at 18 and 32 weeks  
5 gestation, and at 8 weeks, 8 months and 21 months after birth (to examine specificity to  
6 depression).  
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12 *Ethical considerations.* Ethical approval was obtained from the ALSPAC law and ethics  
13 committee, and from local research and ethics committees. Informed consent for the use of  
14 data collected via questionnaires and clinics was obtained from participants following the  
15 recommendations of the ALSPAC Ethics and Law Committee at the time.  
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## 20 21 *Measures*

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24 *Maternal depression.* Mothers self-reported symptoms of depression during pregnancy (18  
25 and 32 weeks gestation) and during the postnatal period (8 weeks, 8 months and 21 months  
26 after birth) using the Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden &  
27 Sagovsky, 1987). The EPDS is the most widely used self-report questionnaire to identify  
28 symptoms of depression during the perinatal period. The scale consists of 10 items that  
29 describe common symptoms of depression; however, the scale does not include somatic  
30 symptoms of depression, such as a change in appetite or fatigue, which are commonly  
31 experienced in pregnancy. Each item is scored from 0 to 3, and there is a maximum score of  
32 30. For the measure of maternal postnatal depression, an average of the scores reported at 8  
33 weeks, 8 months and 21 months after birth (all correlated ~ .5) was used. The maternal  
34 prenatal and postnatal depression measures were square-root transformed to normalise the  
35 distribution. The EPDS was also used to measure prenatal and postnatal depression in the  
36 WCHADS cohort.  
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52 *Maternal anxiety.* At 18 and 32 weeks of pregnancy, and at 8 weeks, 8 months and 21 months  
53 after birth, maternal anxiety was assessed using the anxiety subscale from the Crown Crisp  
54 Index, a validated self-rating inventory (Birtchnell, Evans & Kennard, 1988). The Crown Crisp  
55 Index is a 24-item questionnaire with four subscales, each composed of eight items.  
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3 Participants were asked to rate their responses to questions relating to feelings and  
4 behaviours on a 4-point scale from “very often” to “never”. For the measure of maternal  
5 postnatal anxiety, an average of the scores reported at 8 weeks, 8 months and 21 months  
6 after birth was used. The maternal prenatal and postnatal anxiety measures were square-root  
7 transformed to normalise the distribution.  
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14 *Child emotional symptoms.* Mothers rated child emotional symptoms when the child was aged  
15 3.5 years using the emotional difficulties subscale of the Revised Rutter Scale for Preschool  
16 Children (Elander & Rutter, 1996). The scale comprises 43 statements describing child  
17 behaviours, and mothers were required to rate the extent to which each item described their  
18 child using a 3-point Likert scale of: certainly true, sometimes true and never true. Responses  
19 are aggregated to create scores on four domains: emotional difficulties, conduct difficulties,  
20 hyperactivity and prosocial behaviour. A square-root transformation was applied to reduce  
21 the skew in the distribution of the emotional difficulties variable. In the WCHADS cohort, child  
22 symptoms were assessed by maternal report using the preschool Child Behaviour Checklist  
23 (CBCL), which includes an anxious-depressed subscale (Rescorla et al., 2011).  
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36 *Confounding variables.* Mothers reported on the following variables during pregnancy that  
37 were included in analyses as confounders: highest educational qualification (binary: degree  
38 and above), smoking status at 32 weeks of pregnancy (grouped number of cigarettes per day,  
39 in the following categories: none, 1-9, 10-19, >20), household crowding at 8 weeks of  
40 pregnancy (binary: top quintile of crowding index (the number of residents living in a dwelling  
41 divided by the number of rooms in a dwelling) and other), maternal age at birth (categorical:  
42 <21, 21-30, >30) and relationship status (binary: living with partner and other).  
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### 51 *Statistical Analyses*

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54 Analyses for the main hypothesis were conducted in accordance with the pre-registered  
55 analysis plan, (Braithwaite, 2018), “Ordinary regression will be used to estimate the emotional  
56 difficulties outcome at 3.5 years predicted by the square-root and standardized transformed  
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3 pre- and post-natal depression scores, and child sex, their product (the three-way interaction  
4 effect) and the main effects of the confounders listed above. Coefficients, 95% confidence  
5 intervals and p-values will be reported for the main effects and the interaction effect.”  
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10 To account for non-random attrition we used the pre-registered method, “The  
11 association of available prenatal variables for the probability of inclusion by way of complete  
12 data, will be examined. Those variables that, in the presence of the confounders, show a  
13 significant association with inclusion will be factored into quintiles and included in a logistic  
14 model to estimate attrition weights, calculated as the inverse of the predicted probability of  
15 inclusion. These weights will be used as probability weights in the analyses.”  
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23 The two-way interactions in girls and boys were displayed according to the preregistered  
24 plan, “Plots of the simple regression line (with 95% confidence interval) of post-natal  
25 depression score (X) for emotional problems (Y) will be displayed for participants with high  
26 and low prenatal depression (median split), for boys and girls.” In addition, and in order to  
27 display the sex differences at different levels of prenatal depression, plots of simple regression  
28 lines of postnatal depression score for emotional problems contrasting boys and girls at low,  
29 medium and high (terciles) levels of prenatal depression were prepared. We also generated  
30 post-estimation heat (contour) maps from the model fitted in the pre-registered analysis to  
31 show, marginal to the other variables, the joint contributions of prenatal and postnatal maternal  
32 depressive symptoms to emotional symptoms in boys and girls, and to the difference between  
33 them. These allow us to show the effects directly from the preregistered analysis, rather than  
34 from follow up analyses of the two-way interactions, and to see how risks for child symptoms  
35 arise as prenatal and postnatal depression scores change. The different coloured regions  
36 demarcate contour lines representing equal steps across the distribution of child emotional  
37 problems scores generated from the model.  
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55 We conducted planned exploratory analyses with maternal depressive symptoms at  
56 32 weeks gestation instead of 18 weeks, and to examine the three-way interaction of prenatal  
57 by postnatal maternal anxiety by child sex.  
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3 The study website <http://www.bristol.ac.uk/alspac/researchers/our-data/> contains  
4 details of all the data that are available, through a fully searchable data dictionary and variable  
5 search tool.  
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## 10 **Results**

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13 Summary statistics for the measures included in the models are displayed in Table 1,  
14 split by child sex. Of the 14,853 cases in the ALSPAC cohort, multivariate logistic regression  
15 indicated that sample attrition was associated with maternal depression (EPDS) score at 18  
16 weeks gestation, and with maternal depression (EPDS) and anxiety (CCEI) scores at 32  
17 weeks gestation, and with maternal depression (EPDS) and anxiety (CCEI) scores at 32  
18 weeks gestation.  
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### 23 *Examination of the main hypothesis*

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27 A regression was fitted to the 8354 complete data cases, weighted for attrition, with the  
28 square-root emotional difficulties subscale of the Rutter Revised Scale at 3.5 years as the  
29 outcome variable. The predictors were the main effects, and two-way and three-way  
30 interactions of the square-root transformed maternal depression scores at 18 weeks of  
31 pregnancy, the average of the three postnatal scores (at 8 weeks, 8 months and 21 months),  
32 and a dummy variable for female child. The depression variables were standardized to a mean  
33 of zero and variance of one to aid in their interpretation. **There was a positive three-way**  
34 **interaction (.034, 95%CI = .009 to .060, p=0.008) which arose from the two-way interactions**  
35 **shown below, and the arbitrary coding of female = 1 and male = 2. The addition of the possible**  
36 **confounding effects of maternal age, education, crowding, partner and smoking status**  
37 **somewhat increased the strength of the three-way interaction (.042, 95%CI = .015 to .068,**  
38 **p=.002). Figure 1 illustrates the pattern of association represented by the interaction in**  
39 **accordance with the pre-registered method. In boys, the slope of the regression line of those**  
40 **exposed to higher prenatal depression was greater than that in the low prenatal depression**  
41 **group and this difference was reflected in a positive two-way interaction that was statistically**  
42 **significant (coeff = .030, 95% CI = .012 to .048, p=.001). In girls, by contrast, the slope of**  
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3 those exposed to higher prenatal depression was lower, reflected in a negative coefficient,  
4 although the test of the two-way interaction was non-significant (coeff = -.012, 95% CI -.031  
5 to .007,  $p=.221$ ). The sex difference is further illustrated in Figure 2, which shows contrasting  
6 regression lines for males and females in low, mid and high prenatal depression terciles. It  
7 can be seen that in the presence of low prenatal depression the rate of increase in child  
8 emotional symptoms with increasing postnatal depressive symptoms was higher in girls than  
9 in boys, consistent with the hypothesis that mis-match between prenatal and postnatal  
10 conditions (low prenatal – high postnatal depression) leads to poorer outcomes in females  
11 than in males. By contrast, in the panel showing the sex difference following high prenatal  
12 depression, it is the boys exposed to matched (high prenatal – high postnatal) conditions who  
13 have the higher emotional symptoms than the girls.  
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27 Figures 3 and 4 show, from the model fitted to the whole sample, how levels of child  
28 emotional symptoms varied with changes in prenatal and postnatal maternal depression  
29 scores. Figure 3 shows that risk of elevated child emotional symptoms associated with  
30 maternal postnatal depressive symptoms arose only among those exposed to prenatal  
31 depression – the top right of the map for boys. In girls, by contrast high levels of emotional  
32 symptoms associated with maternal postnatal depressive symptoms arose more commonly  
33 among those not exposed to prenatal depression – the lower right of the map for girls. Figure  
34 4 maps the sex difference in child symptoms, and brings out how the mis-matched low  
35 prenatal-high postnatal maternal depression, and to a lesser degree the mis-matched high  
36 prenatal low postnatal depression, seen in opposite corners of the map, were associated with  
37 higher symptoms in girls compared to boys. By contrast, it is the matched high prenatal-high  
38 postnatal depression that was associated with greater emotional symptoms in boys than in  
39 girls.  
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#### 55 *Exploratory analyses*

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58 We did not pre-register an examination of whether the predicted sex-dependent effects  
59 would differ according to the timing of postnatal maternal depression. However we conducted  
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3 exploratory analyses as a possible basis for future research, which revealed three-way  
4 interactions with maternal depression at each time point: 8 weeks  $p < .001$ , 8 months  $p = .045$ ,  
5 21 months  $p = .021$ . Pre-registered exploratory analyses of moderation by maternal  
6 depressive symptoms at 32 weeks made use of data from the 7769 cases for which 32 weeks  
7 EPDS scores were available, and were weighted in the same way for attrition. These gave  
8 very similar results with a 3-way prenatal by postnatal by sex of child interaction ( $.030$  95% CI  
9 =  $.004$  to  $.057$ ,  $p = .026$ ) and a significant two-way interaction for boys ( $p = .035$ ) and non-  
10 significant for girls ( $p = .285$ ) with differences in slopes as illustrated in Figure 1. By contrast,  
11 equivalent models for anxiety symptoms at 20 and 32 weeks gestation were entirely non-  
12 significant.  
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## 25 Discussion

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27 We followed up on previous findings from the Wirral Child Health and Development  
28 Study by pre-registering replication analyses to be employed with data from ALSPAC, a larger  
29 general population longitudinal cohort. We replicated the previous finding that the association  
30 between postnatal maternal depressive symptoms and child emotional symptoms is  
31 moderated by the level of prenatal depressive symptoms in a sex-dependent manner.  
32 However, in ALSPAC the sex difference was explained mainly by a protective effect of low  
33 prenatal depression in boys, while in WCHADS it arose from greater vulnerability of girls to  
34 postnatal depression following low prenatal depression.  
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45 The findings add further support for a phenomenon that we have reported in three  
46 previous publications from WCHADS, that prenatal affective symptoms moderate associations  
47 between postnatal exposures and child outcomes, assessed as *NR3C1* methylation at age 14  
48 months (Murgatroyd, Quinn, Sharp, Pickles & Hill, 2015), child emotional symptoms up to age  
49 5 years (Hill et al., 2017, 2019a) and irritability at age 7 years (Hill et al., 2019b). In each case,  
50 these effects were modified by sex of child. Taken together the WCHADS and the ALSPAC  
51 findings suggest that the combined effects of the PAR and T-W mechanisms can give rise to  
52 outcomes in at least two different ways. In WCHADS, the sex difference was accounted for  
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3 largely by the vulnerability of girls exposed to the sequence of low prenatal anxiety or  
4 depression, followed by high postnatal exposure, which we interpreted as reflecting a lack of  
5 the anticipatory effect of high prenatal maternal symptoms. In ALSPAC, as can be seen in the  
6 left hand panel of Figure 1, the larger contribution to the sex difference arose from a protective  
7 effect of exposure to low maternal depressive symptoms *in utero* prior to high postnatal  
8 symptoms, which we interpret as reflecting the advantages for the male foetus of good  
9 maternal conditions during pregnancy in line with T-W theory. Equally, as shown in the right  
10 hand panel of Figure 1, in girls, low prenatal depressive symptoms followed by high postnatal  
11 depression were associated with higher child emotional symptoms, as in WCHADS, although  
12 this interaction was non-significant.  
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25 A key strength of the current study is the use of a large, general population cohort, which  
26 accounted for a number of plausible confounds and factors associated with attrition.  
27 Additionally, we planned, pre-registered and tested distinct hypotheses based on our previous  
28 research, and we have ensured transparency by also pre-registering additional, exploratory  
29 analyses. Limitations include that maternal perinatal depression, child emotional symptoms  
30 and confounders were all measured by maternal report, therefore it is possible that common  
31 method variance across predictor and outcome variables and biasing effects of maternal mood  
32 may have inflated main effects. Maternal mood was not assessed in the ALSPAC study at 3.5  
33 years so we were not able to include it as a covariate in the analyses.  
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45 As we described earlier, the hypotheses for this study were derived by considering the  
46 joint implications of the Predictive Adaptive Response (PAR) theory and the Trivers-Willard  
47 sex biased reproductive investment theories. While these have received relatively little  
48 attention in research into human development, they have been extensively investigated in  
49 animal studies, where the problems of reporter bias do not arise. Effects consistent with these  
50 hypotheses have been shown across many species and environmental conditions, for  
51 example in the relationship between sea ice conditions and reproduction in Arctic migratory  
52 birds (Jean-Gagnon et al, 2018), and links between exposure of Salamander eggs to the  
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3 chemical cues of a predator's presence and subsequent shelter-seeking behaviour (Mathis,  
4 Ferrari, Windel, Messie & Chivers, 2008). A series of elegant experiments in starlings  
5 examined predictions based on the PAR and T-R hypotheses (Love & Williams, 2008a,  
6 2008b). Prenatal stress was mimicked by injection of corticosterone into starling eggs, and  
7 stressful postnatal conditions for chicks were created by wing clipping of mothers after  
8 hatching. Corticosterone levels in chicks following a standard stressor were greatest in those  
9 who had been exposed to the mismatch condition of no corticosterone injection followed by  
10 rearing by wing clipped mothers, and this effect was greater in females than males, as  
11 evidenced in a significant sex by matching condition interaction. Furthermore, there was a  
12 higher mortality among male chicks from the matched conditions of corticosterone injected  
13 eggs reared by wing clipped mothers, significantly shifting the sex ratio in favour of females.  
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27 In a test of the implications of the T-W hypothesis for nutritional variations in humans,  
28 Mathews, Johnson & Neil (2008) showed that more males than females were born to mothers  
29 with high energy intake during pregnancy, while the sex ratio was reversed in the children of  
30 mothers with low energy diets. Support for the predictions of the PAR hypotheses in humans  
31 without the limitations of reporting biases is provided by the studies of Sandman and  
32 colleagues based on assessments of motor and mental development over the first year of life  
33 in infants assessed using the Bayley Scales. The performance of infants exposed to congruent  
34 levels of maternal depression, either high prenatal and high postnatal, or low prenatal and low  
35 postnatal, was higher than those whose mothers had incongruent prenatal and postnatal  
36 levels of depression. At 6 months, this PAR effect was confined to female infants, consistent  
37 with the T-W hypothesis, although the sex difference was no longer evident by 12 months  
38 (Sandman et al 2013). As outlined earlier, we have previously shown higher *NR3C1*  
39 methylation levels in the children of mothers with the incongruent low prenatal and high  
40 postnatal depression than congruent high prenatal-high postnatal levels, and mediation by  
41 *NR3C1* methylation of the association with later anxious depressed symptoms, in girls only  
42 (Murgatroyd et al 2015, Hill et al 2019). Further studies with outcomes that are not confounded  
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3 by reporter effects for example of observed behaviour or biological measures are needed.  
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5 While we have interpreted the findings within a foetal origins framework which assumes  
6 environmental mediation of prenatal and postnatal effects, the design of the study does not  
7 allow us to test for competing genetic explanations.  
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## 10 11 12 **Conclusion** 13

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15 Apart from the work of Sandman and colleagues, the possibility of sex-dependent foetal  
16 origins effects of maternal mental health in humans has not previously been investigated.  
17 However, evidence for sex-dependent foetal vulnerability to maternal conditions (Aiken &  
18 Ozanne, 2013; Meakin, Saif, Jones, Aviles & Clifton, 2017) and for sex-dependent  
19 associations between prenatal anxiety and depression and child outcomes is now substantial  
20 (Sutherland & Brunwasser, 2018; McEwen, 2019). Many of these findings have implicated  
21 glucocorticoid mechanisms (Hill et al., 2017; Graham et al., 2019; Enlow et al., 2018;  
22 Braithwaite, Murphy, Ramchandani & Hill, 2017; Buss et al., 2012). The implications for the  
23 investigation of prenatal and postnatal contributions of maternal depression and anxiety are  
24 that they need to take account of interdependent as well as independent contributions to risk,  
25 and of the likelihood that the processes differ between males and females. Although our  
26 predictions drew on the PAR and T-W hypotheses, it cannot be assumed that the proposed  
27 mechanisms account for our findings. However, they do suggest further hypotheses for  
28 testing. For example, if the postnatal association is environmentally mediated, we predict sons  
29 of mothers with low prenatal anxiety or depression will be protected from effects of postnatal  
30 adversities, while daughters will be more vulnerable. There are implications also for  
31 stratification of analyses of cohort studies and trials. As a result of moderation by prenatal  
32 maternal mental health and by child sex, main effects of risks or treatments that are small or  
33 absent may conceal larger, important effects in subgroups.  
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- Sex-dependent moderation of postnatal effects by prenatal maternal mood, is predicted by evolutionary hypotheses, but their relevance to human development is yet to be established
- Statistically this predicts a three-way interaction, which may be vulnerable to chance findings, making replication crucial.
- Using pre-registered analyses based on our previous findings we provided for the first time robust support for sex-dependent moderation by prenatal depression of the association between postnatal depression and child emotional problems.
- The implication of the findings is that planning for evaluation and implementation of early interventions needs to consider that risks associated with postnatal depression may vary depending on maternal mood during pregnancy, and may differ between boys and girls.

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13 study and take responsibility for the integrity of the data and the accuracy of the data analysis.  
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21 London. The views expressed are those of the author(s) and not necessarily those of the NHS,  
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23 the NIHR or the Department of Health and Social Care.  
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**Table 1** Descriptive statistics for maternal and child variables by child sex.

	Male				Female			
	N	mean	SD	%	N	mean	SD	%
Prenatal depression - 2nd trimester	4004	6.50	4.58	-	3773	6.44	4.57	-
Prenatal depression - 3rd trimester	4001	6.66	4.95	-	3768	6.56	4.82	-
Postnatal depression - 8 weeks	3905	5.87	4.60	-	3690	5.65	4.53	-
Postnatal depression - 8 months	3865	5.22	4.60	-	3643	5.10	4.52	-
Postnatal depression - 21 months	4004	5.53	4.70	-	3773	5.48	4.71	-
Prenatal anxiety - 2nd trimester	3997	4.63	3.38	-	3753	4.65	3.40	-
Prenatal anxiety - 3rd trimester	3990	4.87	3.50	-	3748	4.87	3.46	-
Postnatal anxiety - 8 weeks	3903	3.27	3.19	-	3688	3.27	3.16	-
Postnatal anxiety - 8 months	3899	3.53	3.25	-	3690	3.47	3.23	-
Postnatal anxiety - 21 months	4004	3.70	3.28	-	3773	3.70	3.30	-
Maternal age at birth	4004				3773			
20 years and younger				2.8				3.1
Between 20 and 30 years				60.8				62.9
Maternal relationship status: living with partner	4004			95.7	3773			95.8
Maternal crowding index: top quintile	4004			4.3	3773			3.6
Maternal highest educational qualification: degree or above	4004			14.6	3773			15.6
Maternal 3rd trimester smoking (any)	4004			15.6	3773			15.2
Child emotional symptoms age 3.5 years	4004	2.47	1.74		3773	2.55	1.69	

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3 **Figure 1 Title:** Graphs showing how levels of prenatal depression moderate the association  
4 between postnatal maternal depression and child emotional symptoms differently in boys and  
5 girls.  
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12 **Figure 1 Legend:** Plots are shown of the simple regression lines (with 95% confidence  
13 interval) of post-natal depression scores for emotional symptoms at age 3.5 years in high and  
14 low prenatal depression groups (median split), for boys and girls. In the left hand panel it can  
15 be seen that, in boys, following low levels of maternal depression during pregnancy, postnatal  
16 depression is more weakly associated with child symptoms than after elevated prenatal  
17 depression. In girls the pattern is reversed with the stronger association between postnatal  
18 maternal depression and child emotional symptoms seen after low prenatal depression (NB  
19 in girls the interaction is non-significant).  
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33 **Figure 2 Title:** Associations between maternal postnatal depression and child emotional  
34 symptoms, showing sex differences at three levels of prenatal depression  
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41 **Figure 2 Legend:** Plots are shown of the simple regression lines contrasting boys and girls  
42 at low, mid and high prenatal depression terciles of prenatal depression scores. In the  
43 presence of low prenatal depression the rate of increase in child emotional symptoms with  
44 increasing postnatal depressive symptoms is higher in girls than in boys. It can be seen that  
45 girls exposed to the mis-match between prenatal and postnatal conditions (low prenatal – high  
46 postnatal depression) have higher emotional symptoms than the boys. In the panel showing  
47 the sex difference following high prenatal depression the boys exposed to matched (high  
48 prenatal – high postnatal) conditions have higher emotional symptoms than the girls.  
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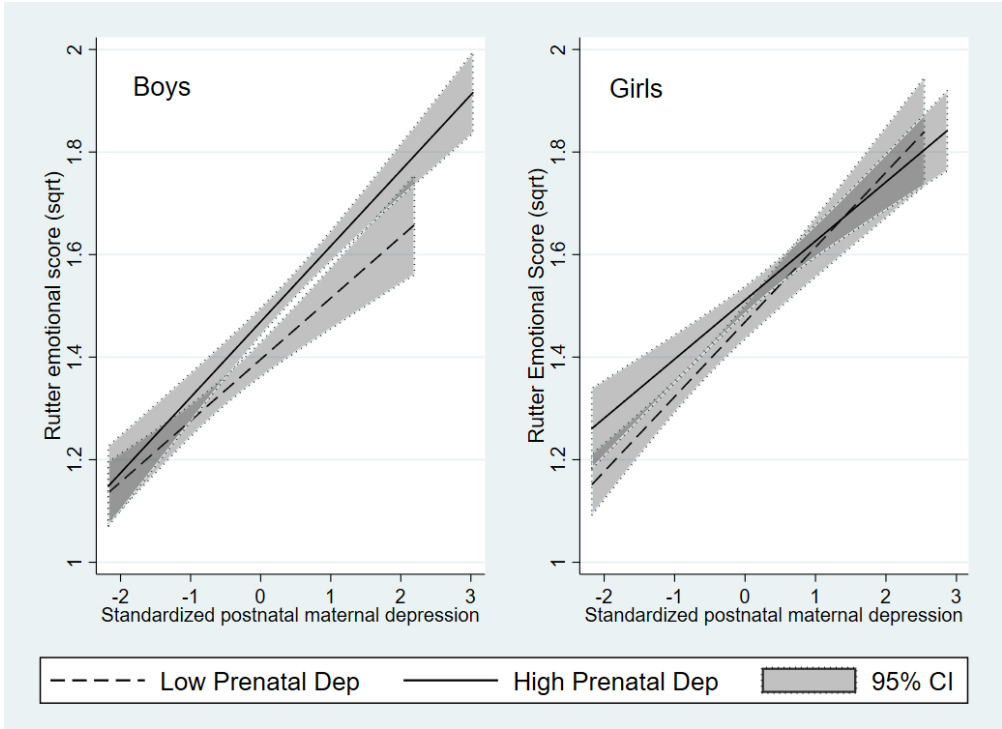
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3 **Figure 3 Title:** Contour map showing variation in colour intervals of equal sized steps in the  
4 level of child emotional problems from high (red) to low (blue) by prenatal and postnatal  
5 maternal depressive symptoms for boys and girls.  
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12 **Figure 4 Title:** Contour map showing the higher (red) to lower (blue) predicted emotional  
13 problem score of girls compared to boys as this difference varies with prenatal and postnatal  
14 maternal depressive symptoms.  
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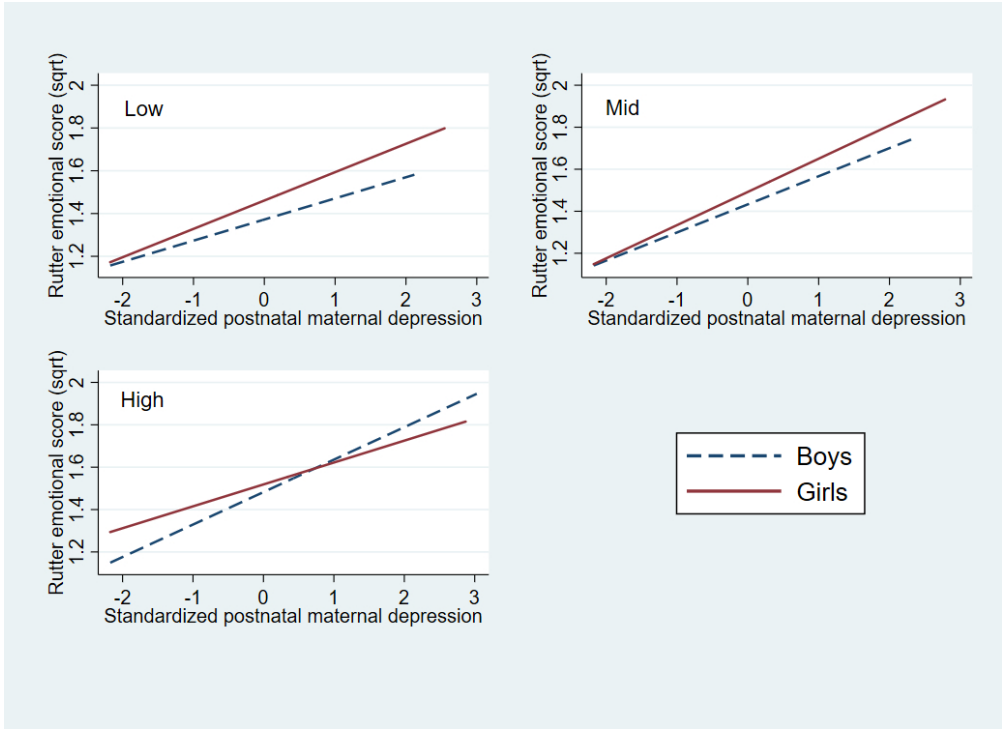
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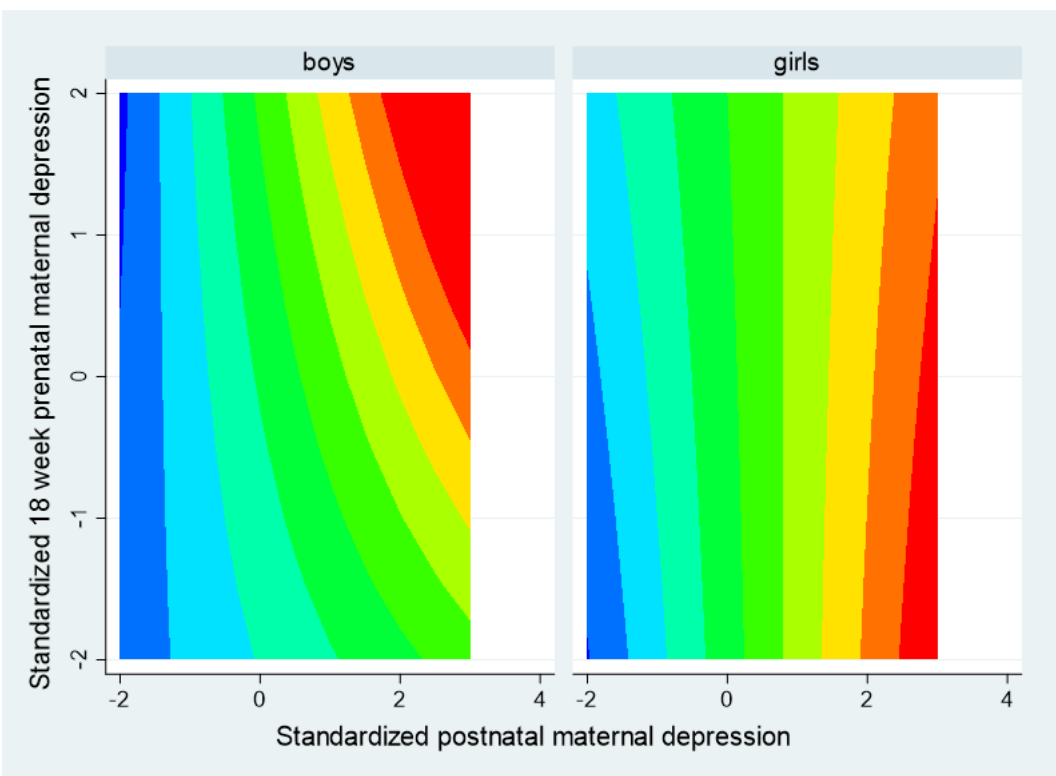
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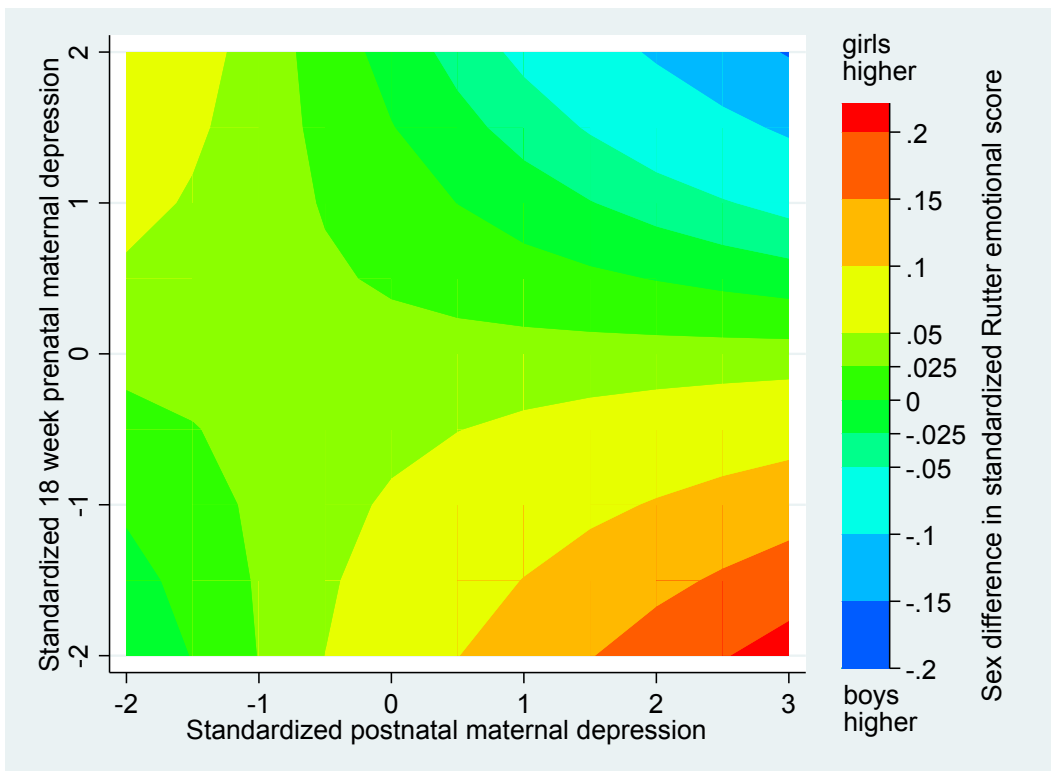
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