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Exploring sex differences in fetal programming for childhood emotional disorders

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ABSTRACT

In examining maternal depression, placental *11β-HSD2* mRNA expression and offspring cortisol regulation as a potential fetal programming pathway in relation to later child emotional disorders, it has become clear that sex differences may be important to consider. This study reports on data obtained from 209 participants in the Mercy Pregnancy and Emotional Wellbeing Study (MPEWS) recruited before 20 weeks of pregnancy. Maternal depressive disorders were diagnosed using the SCID-IV and maternal childhood trauma using the Childhood Trauma Questionnaire. Placental *11β-HSD2* mRNA was measured using qRT-PCR. For assessment of stress-induced cortisol reactivity, salivary cortisol samples were taken at 12 months of age. At 4 years of age, measurement of Childhood Emotional Disorders (depression and anxiety) was based on maternal report using the Preschool Age Psychiatric Assessment (PAPA) and internalizing symptoms using the Child Behavior Checklist (CBCL). Maternal depression in pregnancy and postpartum, and infant cortisol reactivity, was associated with internalizing symptoms for females only. For female offspring only, increased 12-month cortisol reactivity was also associated with increased emotional disorders at 4 years of age; however, there was no association with placental *11β-HSD2* mRNA expression. In females only, the combination of lower placental *11β-HSD2* mRNA expression and higher cortisol reactivity at 12 months of age predicted increased internalising problems. These findings suggest there may be sex differences in prenatal predictors and pathways for early childhood depression and anxiety symptoms and disorder.

1. Introduction

Over the past decade there has been substantial increase in our understanding of the importance of prenatal programming through stress pathways, as a predictor of later child psychopathology (Chen et al., 2021; Cottrell and Seckl, 2009; Glover, 2011; Glover et al., 2010; Kim et al., 2015). In understanding the significance of this potential programming pathway for later psychopathology, the type of stress, timing of stress and sex difference in offspring are all important. Recent findings indeed support the importance of programming effects and also of genetic risk for child mental health outcomes in the context of maternal antenatal depression (Chen et al., 2021; Kim et al., 2015).

In previous studies with the Mercy Pregnancy and Emotional Wellbeing Study (MPEWS). maternal depression and history of childhood trauma experiences have both been identified as important potential stressors in pregnancy that may influence offspring psychopathology (Galbally et al., 2020a, 2020b). Furthermore, both depression and trauma experiences are also associated with an increased likelihood of additional exposures in pregnancy, such as smoking and alcohol use, which, in turn, also influence fetal development and subsequent child outcomes (Blalock et al., 2005; Kim et al., 2015; O'Donnell et al., 2011; Seth et al., 2015). These factors affecting fetal development are linked to

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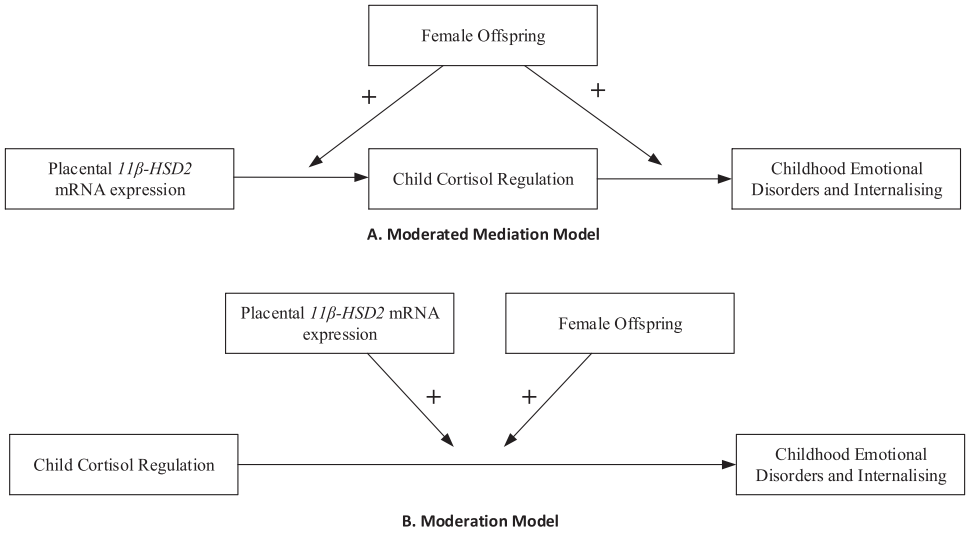

Fig. 1.. Alternative conceptual models being tested. + denotes a positive path.

dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis of the offspring, which can predispose to later life disease. Timing of depression in pregnancy may also be important, with earlier exposure to current maternal depression more likely to influence early HPA axis development in offspring (Goodman and Gotlib, 1999; Lewis et al., 2014). Maternal childhood trauma has also been associated with altered epigenetic DNA methylation pathways in mother and infant. This finding supports the intriguing concept that maternal childhood trauma is an important consideration in the programming pathway to the offspring (Scorza et al., 2020).

The impact of early prenatal stress on HPA axis development is potentially dependent on the sex of the fetus. Prenatal stress may produce sex-dependent signals via the placenta to the developing brain, underpinning sex differences in child mental health outcomes (Bale, 2016; Clifton, 2010; Mueller and Bale, 2007, 2008). These sex differences include the fetal response to glucocorticoids and inflammatory influences, such as maternal asthma (O'Callaghan et al., 2020). This is very relevant, since recent evidence based on transcriptomics of the sex chromosome complement pointed to neuro-immune and inflammatory mediators as primary mediators of sex differences in brain and behavior, which are then enabled by organisational sex hormone action (McCarthy, 2020; McCarthy et al., 2012). Moreover, the glucocorticoid-responsive transcription patterns of inflammatory and immune genes are sexually dimorphic: only females are resistant to the anti-inflammatory action of glucocorticoids, and the sexes show different and sometimes opposite responses to glucocorticoid treatment that can be explained by sex differences in whole genome expression patterns. Sexual dimorphism in glucocorticoid action was also noted in metabolism and brain function (Bale, 2016; Duma et al., 2010; Kroon et al., 2020; Mahfouz et al., 2016; Quinn and Cidlowski, 2016). The glucocorticoid stress response in healthy individuals and in patients suffering from affective disorders also displays a sex bias (Moisan, 2021).

Glover and Hill first postulated an evolutionary perspective that prenatal stress is likely to activate stress and anxiety responses specifically in female offspring, predisposing them to be more vigilant, and thus better equipped to cope in a predicted hostile environment (Glover and Hill, 2012). Sandman and colleagues went on to suggest there may be a "viability-vulnerability" difference between female and male offspring, with females adjusting better to adversity *in utero*, albeit with increased vulnerability to later psychopathology. In contrast, males do not adjust their development but, rather, preference *in utero* growth, rather than conserving growth as females do, and, thus, their early life viability is more vulnerable to the impact of adverse influences *in utero* (Sandman et al., 2013).

More recently, there have been a number of publications concluding that sex differences are important in understanding the prenatal programming pathway, see for review (Sutherland and Brunwasser, 2018). Three series of studies identified specific aspects of the programming pathway in female offspring. Firstly, an elevated basal cortisol level in pregnancy was associated with an increased right amygdala volume and connectivity to areas involved in sensory processing, and subsequent vulnerability to internalizing symptoms specifically in girls (Buss et al., 2012; Graham et al., 2019; Kim et al., 2017) The second series of studies demonstrated prenatal depression was associated specifically with increased right amygdala connectivity to a cortico-striatal-limbic network in female offspring (Qiu et al., 2015; Rifkin-Graboi et al., 2013, 2015; Soe et al., 2018). The third series of studies identified a role for placental CRH in cortical thinning and mental health outcome of girls (Sandman et al., 2018), that was previously found to be associated with depression (Sandman et al., 2015). Interestingly, CRH synthesis in placenta and neonatal amygdala is enhanced by cortisol, which would explain why genetic variation in FKBP5 -a modulator of the glucocorticoid receptor (GR) activation - may moderate the association between antenatal depressive signals and limbic brain connectivity(Wang et al., 2018).

It should be noted that 11beta-hydroxysteroid dehydrogenase type 2 enzyme (11β-HSD2) is an important regulator of fetal exposure to maternal cortisol and previous studies have examined both epigenetic regulation as well as mRNA expression in relation to maternal depression (O'Donnell et al., 2011; Stroud et al., 2016). For instance, a study examining the impact of maternal major depression in pregnancy found increased infant cortisol reactivity in female offspring only, and this was moderated by placental *11β-HSD2* methylation (Stroud et al., 2016). A recent commentary highlighted important caveats to progressing research on sex differences, including the importance of careful design and statistical approach, and documenting the hormonal influences such as menstruation, menopause, oral contraceptive use, and in pregnancy (Galea et al., 2020).

There have also been a number of studies that have highlighted sex differences in placental functioning, including regulation of fetal cortisol exposure via *11β-HSD2*; a key mechanism in fetal HPA axis development and potentially influenced by maternal mental health and stress (Bale, 2016; Clifton, 2010; Cottrell et al., 2014; O'Donnell et al., 2011; Seth et al., 2015). Overall, in the recent review of sex differences and prenatal stress programming, five studies were identified that examined depression and anxiety outcomes in offspring, and five that examined cortisol responses in offspring, but none included both these parameters with

placental *11β-HSD2* (Sutherland and Brunwasser, 2018). However, a recent explorative study found indications for an association between maternal distress, as deducted from elevated basal saliva cortisol levels, with a decreased placenta *11-HSD2* mRNA expression (and increased *11-HSD2* DNA methylation) with enhanced stress-induced saliva cortisol reactivity, particularly in two-months old girls rather than boys (Jahnke et al., 2021).

Previously we found in a pilot study that maternal depression was associated with lower placental *11β-HSD2* mRNA expression suggesting an increased cortisol exposure (Seth et al., 2015). In a larger sample, we found maternal depression in pregnancy was associated with cortisol response in offspring at 12 months of age, mediated by placental *11β-HSD2* mRNA expression (Galbally et al., 2021). However, we did not examine sex differences or their implications for later child mental health outcomes. We have also separately shown that maternal depression and a maternal history of childhood trauma predicted childhood anxiety and emotional disorders but again, sex differences were not specifically examined (Galbally et al., 2020a, 2020b).

In this study, we examined sex differences in the associations between placental *11β-HSD2* mRNA expression and infant stress-induced cortisol reactivity at 12 months of age with childhood emotional disorder (depression and anxiety) and internalizing symptoms at 4 years of age. Unlike many previous studies we utilise diagnostic measures for maternal and child mental disorders in addition to dimensional symptom measures. Specifically, we tested two alternative models: the first is a moderated mediation model whereby *11β-HSD2* mRNA expression is positively associated with childhood emotional disorders and internalising indirectly via higher cortisol reactivity for female offspring only (Fig. 1A); the second is an interaction model whereby a combination of higher cortisol reactivity and higher *11β-HSD2* mRNA expression is positively associated with childhood emotional disorders and internalising for female offspring only (Fig. 1B).

2. Materials and methods

2.1. Participants

This study draws on data from the Mercy Pregnancy and Emotional Wellbeing Study (MPEWS) (Galbally et al., 2017b). MPEWS uses a selected cohort design with targeted recruitment of women into three groups: women with a depressive disorder (past and present), women taking antidepressants during pregnancy and a control group. This study uses 209 participants where placental tissue was collected and child mental outcomes followed until 4 years of age within the cohort. The Mercy Health Human Research Ethics Committee approved this study, and a written informed consent statement was obtained from each woman. Inclusion and exclusion criteria have been previously reported (Galbally et al., 2017b).

3. Measures

3.1. Maternal Mental Health

At recruitment, the Structured Clinical Interview for DSM-IV (SCID-IV) Mood disorders schedule was administered to assess lifetime depression (First et al., 1997). In this paper, depression is coded as a current depressive disorder or a past episode within two years of conception. In addition, the repeat Edinburgh Postnatal Depression Scale (EPDS) was used to assess depressive symptoms twice in pregnancy and at each postpartum timepoint including when children were 4 years of age (Cox et al., 1987). The scale has been validated for use with Australian women during the perinatal period (Boyce et al., 1993).

3.2. Maternal Childhood Trauma

As previously reported, maternal childhood trauma history was measured using the brief screen version of the Childhood Trauma Questionnaire, which is a 28-item self-report measure (Bernstein and Fink, 1998; Bernstein et al., 2003; Galbally et al., 2019b). In this study, we used a dichotomised total CTQ score because of the positively skewed reports of CTQ, with many women reporting no history. Responses were dichotomised using severity cut-off scores, provided by the CTQ manual to create binary groups (*None-to-Minimal* versus *Moderate-to-Severe*).

3.3. Antidepressant Use

Antidepressant type, usage, dosage, and timing were assessed by a self–report questionnaire at recruitment and in the third trimester; and confirmed in hospital records at delivery. As previously described, the antidepressant medications included Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Noradrenaline Reuptake Inhibitors (SNRIs) (Galbally et al., 2017a, 2017b).

3.4. 11β-HSD2 mRNA expression in placental tissue

As previously described placentas were collected and processed within 30 min of delivery and the time of delivery was recorded and consistent sites where samples were collected from the placentas and stored at − 80 °C (Galbally et al., 2021). As previously described in detail *11β-HSD2* mRNA expression was determined by quantitative RT-PCR (Galbally et al., 2021; Seth et al., 2015). In this study, *11β-HSD2* represents the relative expression of the *11β-HSD2* mRNA compared to internal control ribosomal protein L19, computed using the 2^(-Delta-DeltaCT) method.

3.5. Infant Cortisol Regulation at 12 Months Postpartum

As previously reported at 12 months of age, infant salivary samples were collected at three times during a maternal-infant separation and reunion task: baseline (prior to mother and child beginning the task, after a rest period), 20 min from baseline (beginning of task period), and 40 min from baseline and following task completion (Galbally et al., 2019a). In summary, salivary samples were stored at − 80 °C within an hour of the procedure and subsequently measured using a commercially available ELISA assay (Salimetrics, USA), in duplicate, according to the manufacturer's instructions. Infant corticosteroid use was measured (oral and topical). There were no infants on oral corticosteroids and 16 infants with intermittent topical use. As previously reported, there were no significant differences for child cortisol (either AUCg or AUCi) between those that had used intermittent topical corticosteroid cream and those who did not (Galbally et al., 2019a).

Infant stress-induced cortisol reactivity was expressed using two cortisol response indices, Area Under the Curve relative to ground, or zero (AUCg), and AUC relative to increase (AUCi), using equations outlined in Pruessner et al. (Pruessner et al., 2003). In this current study, AUCg measures infant cortisol response, that is an infants' total cortisol levels during the period prior to commencing and at 30 min after completing the task, whereas AUCi measures cortisol reactivity, that is infants' change in cortisol relative to their baseline cortisol level.

3.6. Childhood mental health

Childhood Emotional Disorders (depression and anxiety disorders) were assessed at 4 years of age using the Preschool Age Psychiatric Assessment (PAPA). This is a structured diagnostic interview for 3–8 years of age children was administered to the mothers of the children. It takes approximately 1 h to administer and draws on DSM-V based symptoms to use computer algorithms to generate DSM-V diagnoses. Our research team has undertaken training with Duke University, Developmental Epidemiology (Egger et al., 2006). Both the test-retest reliability and the inter-rater reliability have been established (Egger

Table 1
Sample Sociodemographic and Other Key Characteristics ($N = 209$).

	n	%
Ethnicity (missing = 1)		
Oceania/European	187	89.9
Aboriginal and Torres strait islander Australians	2	1.0
Asian	16	7.7
Middle eastern	3	1.4
University education (missing = 1)	140	67.0
Fulltime, part-time, or casual employment status at recruitment (missing = 1)	194	93.3
Married, de facto, or otherwise stable relationship (missing = 1)	196	94.2
Nulliparous	190	90.9
Major depression (SCID-IV)	42	20.1
Antidepressant use during pregnancy	36	17.2
History of moderate-to-severe childhood trauma (missing = 5)	64	31.4

et al., 2006; Luby et al., 2014). To assess maternally reported Internalizing symptoms, the Child Behavior Checklist (CBCL) was also administered at 4 years of age. The CBCL 1.5–5 consists of 99 items related to problem behaviours including an anxiety problem scale. Psychometrics of the instrument have been well demonstrated including in an Australian sample (Achenbach and Rescorla, 2001; Hensley, 1988).

4. Statistical analyses

Data were managed and descriptive analyses conducted using SPSS version 24. We begin by presenting sociodemographic characteristics of the mothers in this sample who were recruited into the Cohort during early pregnancy (less than 20 weeks gestation). Then, using $\chi 2$ tests for categorical variables and F-tests for continuous variables, we present and identify differences between male and female offspring across key maternal and child study variables. For categorical association tests with expected cell counts below 5, a Fisher's exact $\chi 2$ test is reported. For ANOVA tests comparing offspring sex across heterogenous group variances, a Welsch's robust test of means is presented.

To address the main aim of examining sex differences in associations between prenatal predictors with offspring emotional disorders and internalising symptoms at 4 years of age, we conducted regression pathway modelling to predict any childhood emotional disorder diagnosed using the PAPA at 4 years of age (logistic regression) and CBCL Internalizing Problems (raw score) at 4 years of age (linear regression). To test the hypothesised indirect effect from *11β-HSD2* mRNA expression to childhood mental health through infant AUCi (i.e., mediated pathway shown in Fig. 1A), the product of the two individual pathway coefficients was estimated using 10,000 bootstrapped samples. To test the hypothesised interaction effect between infant AUCi and *11β-HSD2* mRNA expression on child mental health (i.e., moderation shown in Fig. 1B), an interaction term was computed by multiplying the *11β-HSD2* mRNA expression and AUCi variables and was included in the models. Significant interaction terms were plotted and probed using simple slopes analysis. To examine the overarching moderating effect of offspring sex in these models, we utilised the multiple group framework to fit a model for the whole sample and then allowing the regression coefficient of one predictor at a time to estimate freely for each sex group. All parameter estimates that differed significantly between male and female groups using a Wald test were freed to be estimated between the groups in the final models.

In addition to the focal predictors, placental *11β-HSD2* mRNA expression and infant cortisol AUCi, the following set of covariates were included in all models: maternal moderate-to-severe childhood trauma, maternal major depression during early pregnancy, maternal antidepressant use during pregnancy, gestational age at birth, maternal depressive symptoms at 4 years postpartum. Prior to entry into regression models, *11β-HSD2* mRNA expression was transformed using a natural logarithm, which improved normality in the distribution. All continuous variables used in the regression models were centred prior to entry to allow meaningful interpretation of the model intercept. All modelling was conduct using Mplus version 8.

Table 2
Sex differences across key variables ($N = 209$).

	Male offspring ($n = 119$)	Female offspring ($n = 90$)	
	n (%)	*n* (%)	$\chi 2$ *p*-value
Maternal moderate-to-severe childhood trauma *(missing = 5)*	37 (31.4%)	27 (31.4)	.995
Maternal major depression in early pregnancy	23 (19.3)	19 (21.1)	.750
Maternal antidepressant use during pregnancy	18 (20.5)	18 (20)	.355
Maternal smoking during pregnancy	13 (11.0)	9 (10.1)	.834
Maternal alcohol consumption during pregnancy	40 (33.9)	30 (33.7)	.977
Maternal obesity at early pregnancy ($kg/m^2 \geq 30$)	24 (20.3)	14 (15.6)	.376
Caesarean section	43 (36.1)	29 (32.2)	.556
Small for gestational age	8 (6.7)	8 (8.9)	.560
Large for gestational age	9 (7.6)	9 (10.0)	.534
Any emotional disorder at 4 years of age (missing = 7)	47 (41.2)	35 (39.8)	.835
Separation anxiety	14 (12.3)	16 (18.2)	.242
Generalized anxiety disorder	11 (9.6)	10 (11.4)	.692
Specific phobia	33 (32.7)	25 (28.4)	.933
Social phobia	17 (15.0)	14 (15.9)	.866
Panic attacks	0 (0.0)	1 (1.1)	.436^
Agorophobia without panic attacks	3 (2.6)	5 (5.7)	.229^
Major depression	1 (0.9)	3 (3.4)	.320^
Dysthymia	2 (1.8)	2 (2.3)	1.000^
Depression, not otherwise specified	2 (1.8)	3 (3.4)	.355^
	M (*SD*)	*M* (*SD*)	F-test p-value^
Maternal depressive symptoms during early pregnancy *(missing = 2)*	6.01 (4.55)	6.68 (4.76)	0.303
Maternal depressive symptoms at 4 years postpartum *(missing = 17)*	5.83 (4.80)	6.39 (4.22)	0.401
Relative *L19/11B-HSD2* expression[a] *(missing = 22)*	.95 (0.73)	1.01 (0.64)	.585
Gestation at birth	39.30 (1.71)	39.40 (1.68)	.680
APGAR at 1 min *(missing = 1)*	7.88 (1.92)	8.14 (1.48)	.266^
APGAR at 5 min *(missing = 1)*	8.92 (1.01)	8.99 (0.71)	.538^
Infant salivary cortisol at 12 months postpartum (missing = 39)			
Baseline	4.66 (10.71)	3.12 (3.79)	.266
+ 20 min	4.26 (3.58)	6.00 (9.14)	.104^
+ 40 min	4.47 (2.91)	5.21 (4.39)	.191^
Infant AUCg during SSP at 12 months postpartum *(missing = 39)*	173.79 (156.51)	202.11 (248.99)	.364
Infant AUCi during SSP at 12 months postpartum *(missing = 39)*	21.07 (104.17)	77.81 (129.96)	.002
Internalising problems at 4 years of age *(missing = 9)*	7.13 (5.41)	8.61 (8.29)	.152^

^Fisher's exact test when expected cell counts were less than 5, and Welch's F test when groups variances are heterogenous.
[a] log-transformed descriptives: male (M = −0.35, SD =0.85), female (M =0.22, SD =0.75)

5. Results

5.1. Sample Characteristics

The average age of women from this sample of the MPEWS cohort was 31.74 y (SD = 4.63 y), ranging between 19 and 48 years of age. Table 1 presents the sociodemographic and other key characteristics of the women within this study. The prevalence of major depression in the sample was 20.1% and 31.4% of women reported a moderate-to-severe history of childhood trauma.

Table 3
Zero-order Bivariate Correlations for Variables Considered for the Multiple Group Regressions by Female ($n = 90$) and Male ($n = 119$) offspring.

Female Offspring Correlations	1	2	3	4	5	6	7	8	9	10
1. Internalising problems at 4 years of age	–									
2. Any emotional disorder at 4 years of age[a]	.50 * **	–								
3. Maternal moderate-to-severe childhood trauma[a]	.22 *	.20	–							
4. Maternal major depression in early pregnancy[a]	.22 *	.19	.21	–						
5. Maternal antidepressant use during pregnancy[a]	.20	.16	.11	.56 * *	–					
6. Gestational age at birth	-0.25 *	-0.23 *	.07	.04	-0.19	–				
7. Maternal anxious symptoms during early pregnancy	.33 * *	.26 *	.42 * **	.42 * **	.31 * *	-0.06	–			
8. Maternal depressive symptoms during early pregnancy	.35 * *	.34 * *	.42 * **	.35 * *	.19	-0.07	.81 * **	–		
9. Maternal depressive symptoms at 4 years postpartum	.41 * **	.28 *	.18	.35 * *	.26 *	-0.09	.46 * **	.58 * **	–	
10. Placental Relative 11β-HSD2 Expression	.10	.22	-0.12	-0.09	.05	-0.19	-0.03	.04	.09	–
11. Infant AUCi at 12 Months Postpartum	.26 *	.20	-0.05	.05	.11	-0.07	-0.06	-0.04	.08	.14
Male Offspring Correlations	1	2	3	4	5	6	7	8	9	10
1. Internalising problems at 4 years of age	–									
2. Any emotional disorder at 4 years of age[a]	.15	–								
3. Maternal moderate-to-severe childhood trauma[a]	.12	.19 *	–							
4. Maternal major depression in early pregnancy[a]	.07	.13	.18	–						
5. Maternal antidepressant use during pregnancy[a]	-.03	.03	-0.03	.27 * *	–					
6. Gestational age at birth	.03	-0.09	.07	-0.06	-0.23 *	–				
7. Maternal anxious symptoms during early pregnancy	.18	.06	.33 * **	.37 * **	.12 *	-0.09	–			
8. Maternal depressive symptoms during early pregnancy	.18	.05	.43 * **	.33 * **	.18	-0.04	.72 * **	–		
9. Maternal depressive symptoms at 4 years postpartum	.34 * **	.03	.24 *	.08	.12	-0.03	.38 * **	.38 * **	–	
10. Placental Relative 11β-HSD2 Expression	.12	.03	-0.01	-0.06	-0.04	-0.14	-0.19	-0.16	.03	–
11. Infant AUCi at 12 Months Postpartum	.12	.06	-0.10	-0.10	-0.10	-0.18	-0.02	.01	.15	.25 *

Notes. [a]Correlations with a binary variable represent point-biserial association, and between two binary variables represent *phi* coefficients. * $p < .05$ * * $p < .01$ * ** $p < .001$

5.1.1. Offspring sex differences

Table 2 presents key variables by offspring sex. Interestingly, male and female offspring were comparable across almost every study variable. The prevalence of childhood emotional disorders at 4 years of age in the sample was comparable between offspring sex, at approximately 40%. Within emotional disorders, the prevalence of specific childhood anxiety and depressive disorders did not differ by offspring sex, with anxiety disorders more prevalent than depressive disorders.

5.2. Placental 11β-HSD2 mRNA expression, Infant Cortisol Reactivity, and Offspring Mental Health at 4 Years of Age by Sex

Table 3 displays zero-order bivariate correlations between study variables by offspring sex; correlations for females are above the diagonal and below the diagonal for males. Meeting diagnostic criteria for any childhood emotional disorder at 4 years of age was significantly positively associated with internalizing problems at 4 years of age for female offspring, but not for male offspring. Maternal depression diagnosis and symptoms in early pregnancy and depressive symptoms at 4 years postpartum were all significantly positively associated with emotional disorders and internalizing symptoms in female offspring at 4 years of age. In contrast, only maternal depressive symptoms at 4 years postpartum were significantly positively associated with internalising problems, but not an emotional disorder, in male offspring at 4 years of age. For both male and female offspring, placental relative *11β-HSD2* mRNA expression was not associated with emotional wellbeing (disorder or symptoms) at 4 years of age; however, early cortisol reactivity at 12 months of age positively associated with internalizing problems at 4 years of age in female offspring only.

5.3. Placental 11β-HSD2 mRNA expression mediation model

For the moderated mediational model (Fig. 1A), there was no significant association between *11β-HSD2* mRNA expression and infant AUCi, and this association did not vary significantly by offspring sex. Further, for female offspring only, higher AUCi was significantly associated with higher odds of an emotional disorder at 4 years of age, whereas AUCi was not significantly associated with internalising problems for either sex. Given the lack of significant individual pathways in this model, bootstrapped indirect effects analyses was not undertaken. These results suggest that placental *11β-HSD2* mRNA expression does not predict childhood mental health through infant AUCi for either female or male offspring. The focal results for these models are presented in Supplementary Figure 1.

5.4. Infant AUCi and placental 11β-HSD2 mRNA expression interaction model

Emotional disorders at 4 years of age. In the multiple-group regression model predicting any emotional disorder at 4 years of age, the interaction between *11β-HSD2* mRNA expression and AUCi was not significant, and the magnitude of the interaction was not significantly different between the male and female offspring models. As such, this interaction term was removed from the final model predicting any emotional disorder at 4 years of age, which is presented in Table 4. In the final model, only the regression coefficient from AUCi to emotional disorder differed significantly in magnitude between male and female offspring (Wald $\chi 2$ [$df = 1$] = 3.86, $p = .049$). For female offspring only, higher cortisol reactivity during the separation and reunion task at 12 months of age was associated with increased odds of meeting diagnostic criteria for an emotional disorder at 4 years of age. Specifically, female offspring with a one standard deviation higher AUCi than the mean ($M = 77.81$, $SD = 129.96$) demonstrated 1.78-fold increase in the odds of having an emotional disorder. Maternal major depression was associated with a 4.24-fold increase in the odds of an emotional disorder at 4 years of age, irrespective of sex.

Internalising problems at 4 years of age. Table 4 also presents the estimates for the multiple-group regression model predicting internalising problems at 4 years of age. Four parameters were free to estimate for each group: maternal antidepressant use during pregnancy, placental relative *11β-HSD2* mRNA expression, infant AUCi at 12 months postpartum, and the interaction between *11β-HSD2* expression and AUCi. Collectively, the magnitude of the differences in the estimates between male and female offspring groups was significant (Wald $\chi 2$[$df = 4$] = 12.06, $p = .017$). Although the magnitude of the difference was significant between the male and female groups for maternal antidepressant use during pregnancy as a predictor of internalising problems at 4 years of age, neither of the estimates reached significance. The interaction between *11β-HSD2* mRNA expression and AUCi was a significant predictor of internalising problems in female offspring at 4 years of age, but

Table 4
Results of the multiple group regression models predicting child internalising symptoms at 12 months and 4 years of age, and the any childhood emotional disorder at 4 years of age.

	Any Emotional Disorder at 4 Years of Age ($n = 147$)		
	B (95% CI's)[a]	*SE*	*OR*
Intercept	1.08 [.51, 1.66]	.29	
Moderate-to-severe childhood trauma	0.74 [− 0.05, 1.52]	⊡40	2.09
Maternal major depression in pregnancy	**1.45 * * [.43, 2.46]**	⊡52	**4.24**
Maternal antidepressant use during pregnancy	-0.17 [− 1.28,.94]	.57	0.84
Gestational age at birth	-0.21 [− 0.46,.05]	.13	0.82
Maternal depressive symptoms at 4 years postpartum	0.07 [− 0.01,.16]	.04	1.08
Placental relative *11β-HSD2* expression	0.39 [− 0.09,.87]	.25	1.48
Infant AUCi at 12 months postpartum	**.006 * * [.002,.01]** (.00 [−0.004,.004])	.002 (.002)	**1.006** (1.00)
R^2	.27 * * (.21 **)		
	Internalising Problems at 4 Years of Age ($n = 144$)		
	B (95% CI's)[a]	*SE*	*B*
Intercept	7.53 [6.35, 8.71]	.60	
Maternal moderate-to-severe childhood trauma	-0.20 [− 2.00, 1.60]	⊡92	-0.01
Maternal major depression in pregnancy	.95 [− 2.27, 4.16]	1⊡64	.04
Maternal antidepressant use during pregnancy	4.61 [− 1.31, 10.53] (−.72 [−3.99, 2.56])	3.02 (1.67)	.20 (−.05)
Gestational age at birth	-0.21 [− 0.81,.39]	.31	.05
Maternal depressive symptoms at 4 years postpartum	**.53 * ** [.33,.74]**	.10	.35
Placental relative *11β-HSD2* expression	-1.00 [− 3.66, 1.67] (1.07 [−0.04, 2.18])	1.40 (.57)	-0.09 (.16)
Infant AUCi at 12 months postpartum	.01 [− 0.001,.03] (−.001 [−0.02, −0.01])	.01 (.01)	.19 (−.01)
AUCi 11β-HSD2*	**-0.02 * * [− 0.04, − 0.01]** (−.004 [−0.02,.01])	.01 (.01)	**-0.28** (−.05)
R^2	.30 * * (.24 **)		

[a] Where unique parameters were estimated for male and female models, estimates for females appear first and estimates for males appear second in parenthesis. Cases missing data were handled using case-wise omission. * * p < .01 * ** p < .001

not for male offspring. Fig. 2 illustrates the pattern of the interaction between *11β-HSD2* mRNA expression and AUCi on internalising problems at 4 years of age for female (Fig. 1a) and for male (Fig. 1b) offspring. The simple slopes demonstrate that for females with cortisol reactivity scores one standard deviation above the sample mean, low *11β-HSD2* mRNA expression was associated with highest internalising problems at 4 years of age. However, increases in *11β-HSD2* mRNA expression were associated with lower internalising scores at 4 years of age ($b = -3.98$, p = .019). For female offspring with cortisol reactivity scores one standard deviation below the sample mean, *11β-HSD2* mRNA expression was not associated with internalising problems at 4 years of age ($b = 1.99$, $p = .290$). Taken together, this interaction suggests that for female offspring, but not male offspring, lower placental *11β-HSD2* mRNA expression combined with an increased cortisol response to stress in early life are associated with increased internalising problems at preschool age. For male and female offspring equally, maternal depressive symptoms at 4 years postpartum was also a significant positive predictor of internalising problems at 4 years of age. However, antidepressant treatment in pregnancy was not a predictor.

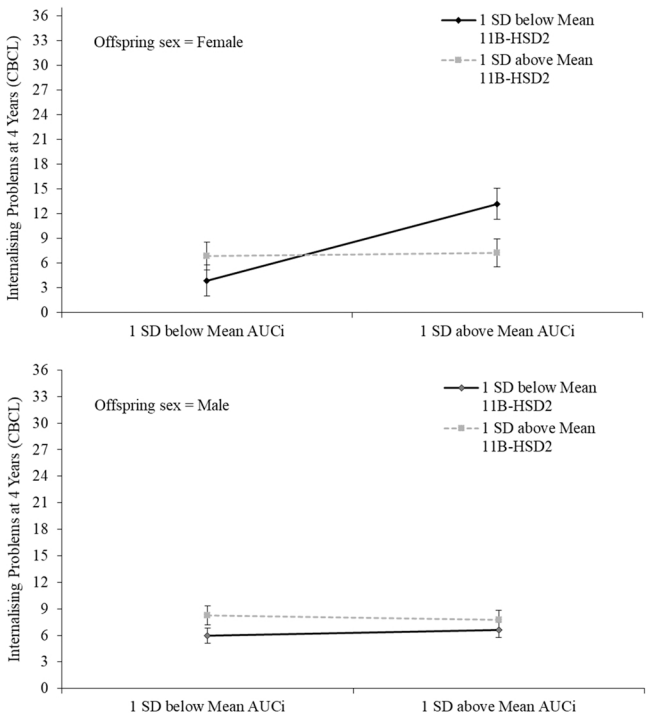

Fig. 2.. Model-estimated means depicting the pattern of the interaction between placental *HSD11B2*mRNA expression and infant stress reactivity during the separation reunion task at 12 months of age (AUCi) on (a) internalising scores of female offspring at 4 years of age, and (b) internalising scores of male offspring at 4 years of age. Error bars represent standard error. CBCL, Child Behavior Checklist 1–5 years, SD, standard deviation.

6. Discussion

Firstly, we found no differences within our cohort between male and female offspring for placental *11β-HSD2* mRNA expression, infant salivary cortisol levels or cortisol response (AUCg). However, female offspring did have higher stress-induced cortisol reactivity (AUCi) within this cohort. Secondly, maternal depressive disorder in pregnancy was a significant predictor for emotional disorders at 4 years of age in all offspring. Similarly, a one standard deviation higher infant cortisol reactivity at 12 months of age was associated with an 78% increase in the odds of females developing an emotional disorder at 4 years of age, as measured on the PAPA. For internalizing symptoms, the interaction between *11β-HSD2* mRNA expression and increased cortisol reactivity in females significantly predicted internalizing symptoms, an effect not seen in males. Finally, although we found differences for antidepressant exposure in an earlier study examining *11β-HSD2* mRNA expression, we did not find antidepressant exposure was a significant predictor when examining later child outcomes (Galbally et al., 2021).

Overall, our study suggests there are different predictors and pathways for preschool emotional health (disorder and symptoms) in female and male offspring. For female offspring, there is vulnerability from maternal depression, gestational age at delivery, placental function and subsequent cortisol reactivity and this was not the same for males. For males while maternal depression was associated with emotional disorders, infant cortisol reactivity did not predict emotional disorders at 4 years of age. While these findings only provide part of the puzzle towards understanding the earliest predictors of intergenerational transmission of vulnerability to emotional disorders it provides evidence for some of the important variables for future focus. There was also some variation in findings depending on whether mental health was measured using a diagnostic measure or dimensional symptom measures were examined, and although emotional disorders and internalizing symptoms were highly correlated for girls, the sex differences in pathways

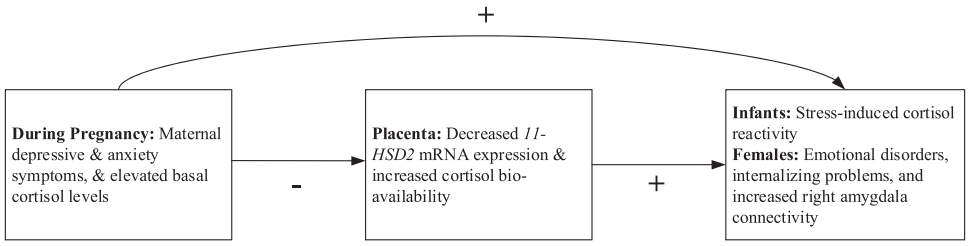

Fig. 3.. Conceptual model of a potential programming pathway from maternal depression to emotional vulnerability of females only.

remained. This suggests potential important differences when examining preschool mental health, in understanding increased symptoms, which may suggest vulnerability compared to those who have reached diagnostic threshold for a mental disorder. Findings for symptoms but not for disorder or vice versa is not surprising given the much higher threshold of psychopathology symptoms that must be reached to meet diagnostic criteria. Following up children to older ages and repeating these measures may shed further light on this finding.

Understanding any sex differences in the earliest pathways towards mental disorders is important in shedding light on the sexually dimorphic responses in mental health across the lifespan. For emotional disorders such as depression and anxiety in early childhood, there is usually parity found in rates of illness between sexes, however from adolescence onwards there is an increase in female prevalence only (Cyranowski et al., 2000). Furthermore, across reproductive changes such as in pregnancy and menopause, there is evidence of a further increased vulnerability to emotional disorders in females (Deecher et al., 2008; Gavin et al., 2005; Vivian-Taylor and Hickey, 2014). Despite this sexual dimorphism after adolescence, there has been increasing focus on understanding mental disorders in preschool age children, in light of evidence that these disorders predict ongoing vulnerability to poorer mental health (Luby et al., 2014). One of the most examined risk factors in early life for later emotional disorders is maternal distress, which is operationalised variably as depression, anxiety and/or trauma.

Previously it had been considered that the mechanism by which maternal distress, including depression, anxiety and stress, may impact on children was through changes in maternal behaviours and the child rearing environment within the postnatal period, however increasing evidence suggests that maternal distress in pregnancy has an independent impact on child emotional outcomes (Capron et al., 2015). For the latter outcome to be possible, there must be a mechanistic pathway by which maternal distress impacts fetal programming of later emotional disorders. A potential pathway is suggested by difference researchers as possibly through maternal factors and placental function, and the subsequent infant HPA axis regulation and programming (Cottrell and Seckl, 2009; de Kloet et al., 2005; Glover, 2011). Furthermore, there are likely distinct differences for female offspring in maternal antenatal cortisol and HPA axis functioning in pregnancy, placental function and in the infant's HPA axis regulation (Hicks et al., 2019).

Our findings of sex differences in the interaction between *11β-HSD2* mRNA expression and infant cortisol reactivity in predicting in girls 1) internalizing symptoms at 4 years of age, 2) higher cortisol reactivity and 3) as a predictor of emotional disorders, are supported by previous findings. These include lower *11β-HSD2* mRNA expression in placentas of female fetuses, and higher cortisol reactivity in girls following exposure to maternal depressive symptoms (de Bruijn et al., 2009; Jahnke et al., 2021; Mina et al., 2015). This is suggestive that in comparison to males, female placentas have an increased permeability to glucocorticoids (Clifton, 2010). While our study was unable to either confirm this potential explanation or explain why this might be the case, there may be a number of plausible reasons including key differences in sex hormones when women carry female compared to male fetuses and also differences in sex dimorphic fetal and newborn stress responses (Sandman et al., 2013). Further research with a different design would be required to elucidate this, and to what extent a sexual dimorphic cortisol action explains the association between increased volume and connectivity of the right amygdala with internalizing symptoms in young girls. While we did not find lower *11β-HSD2* mRNA expression in placentas of female offspring, we did find sex differences when we examined the interaction with cortisol reactivity as a predictor of later internalizing symptoms.

To address the question "why are boys and girls responding to early adversity with different emotional developmental outcomes?", we have incorporated the results of the current study in a model (Fig. 3) of a potential programming pathway from maternal depression to emotional vulnerability of girls only. Briefly, increased fetal/neonatal cortisol exposure in females is thought to exert a sexual dimorphic action on the emotional brain; this increased fetal/neonatal cortisol exposure would be due to downregulated placental *11-HSD2*, possibly in coordination with increased placental and fetal CRH exposure (Buss et al., 2012; Graham et al., 2019; Sandman et al., 2018; Soe et al., 2018).

While this study has a number of strengths, including prospective design and the quality and depth of measurement of mental health, including the use of diagnostic measures for maternal and child mental health as well as dimensional symptom scales, there are limitations. These limitations include the age at assessment for child mental health, where an older age may be associated with greater numbers of children who meet diagnostic criteria for depression, because this sample was heavily weighted towards anxiety disorders. Furthermore, examination of a broader range of mental disorders in older children, such as externalizing symptoms and attention deficit hyperactivity disorder, would be beneficial. The diagnostic measures available for children of this age group require maternal rather than direct child interview, unlike diagnostic interviews with older children and adults which are undertaken directly with the individual. While we included antidepressant treatment, the addition of information on other treatments may be of benefit. This study also does not preclude a possible role of genetic variation. Finally, maternal cortisol and specific epigenetic changes in the placenta may also be important but to include in a model would require a larger sample size. It should also be noted that not all studies examining the early developmental origins of sex differences have findings in a similar direction to this study and as such findings require replication in future studies.

The importance of understanding the earliest trajectories towards mental disorders is in allowing the development of novel effective prevention and early interventions that may reduce ongoing vulnerability to poorer mental health across an individual's lifespan. This early trajectory includes the identification of targets for treatment in pregnancy that may optimise placental functioning. Early and middle childhood is an opportune time for studying vulnerability for emotional disorders and as such understanding the earliest predictors is crucial. This study brings together a number of important aspects previously individually examined including prenatal maternal mental health, placental function, infant cortisol as well as sex differences to build a further understanding of this puzzle.

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CRediT authorship contribution statement

Megan Galbally: Conceptualization, Resources, Supervision, Project administration, Methodology, Funding acquisition, Writing – original draft. **Stuart Watson:** Formal analysis, Project administration, Writing – original draft **Martha Lappas:** Methodology, Writing – review & editing. **E.Ron de Kloet:** Funding Acquistion, Writing – orignal draft, Writing – review & editing. **Peter Mark:** Writing – review & editing. **Caitlin Wywroll:** Writing – review & editing, **Andrew Lewis:** Resources, Funding acquistion, Supervision, Writing – review & editing.

Conflict of Interest

The authors have no disclosures or financial interests or potential conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105764.

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