



Trans-generational stress regulation: Mother-infant cortisol and maternal mental health across the perinatal period

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ABSTRACT

Understanding maternal mental health and cortisol regulation across pregnancy and the relationship to the development of the offspring's stress regulation is critical to a range of health outcomes. The aim of this study was to investigate infant and maternal cortisol in women with depression. Data were obtained from 241 pregnant women within the Mercy Pregnancy and Emotional Wellbeing Study (MPEWS), a selected pregnancy cohort study. Depression was measured using the Structured Clinical Interview for DSM-IV (SCID-IV) and repeat Edinburgh Postnatal Depression Scale (EPDS). Repeated measures of antidepressant use, stressful events, anxiety symptoms and maternal hair cortisol concentrations (HCC) and infant cortisol at 12 months postpartum in saliva and hair. Socio-emotional outcomes were measured at 12 months by maternal report on the Brief Infant and Toddler Socio-emotional Assessment (BITSEA). This study found that maternal depression was not associated with maternal HCC. Anxiety, stress and antidepressant use were not associated with maternal HCC. Independently, higher maternal 3rd trimester maternal depressive and anxiety symptoms were associated with lower infant cortisol response at 12 months of age. A higher number of postpartum stressful events was associated with lower infant cortisol response. Lower infant stress reactivity was associated with higher externalizing symptoms at 12 months of age. Future studies are required to understand implications for later mental health.

1. Introduction

Research continues to show that maternal perinatal depression predicts less than optimal child outcomes, including a range of child mental health problems (Gentile, 2017; Lewis et al., 2014). However, there is less certainty as to the potential mechanism for this transmission (Lewis et al., 2014). The relationship between the experience of stress and the vulnerability to depression is well established and theoretically, it is suggested that the earlier the exposure to stress the stronger the relationship (De Kloet et al., 2005; Lupien et al., 2009). Clearly, such findings point to a possible role of the hypothalamic-pituitary-adrenal (HPA) axis where maternal mental health and cortisol regulation may play an early role in fetal neurodevelopment and subsequent vulnerability for child socio-emotional and developmental outcomes (Gunnar and Quevedo, 2007). Understanding the interaction between maternal depression and cortisol in pregnancy and how this

might influence the development of infant stress regulation is the first step in then understanding a potential fetal programming pathway across early life that may influence vulnerability to later psychopathology (Glover, 2015; Glover et al., 2010).

A recent review of cortisol and perinatal depression identified 47 relevant studies but one of the key findings was the considerable variation in measurement of cortisol and the frequent reliance on screening self-report measures for depressive symptoms (Seth et al., 2016). Only four studies identified in this review were rated as high quality through meeting minimum criteria for measurement of cortisol. This review found that *hypercortisolemia* was associated with an increase in short-term depressive symptoms in the early postpartum and *hypocortisolemia* was associated with chronic depressive symptoms. A major limitation identified within this review was a paucity of studies that utilized diagnostic measures for mental health and use of community samples with low rates of clinically significant symptoms.

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Notably, none of the studies identified in the Seth et al review utilized hair cortisol measurement. There are a number of significant advantages of hair for examination of cortisol. Hair can be more consistently collected than saliva or urine, since it will not be as affected by short-term environmental influences and provides average cortisol levels across time (Short et al., 2016). A systematic review has examined the emerging research examining hair cortisol and prenatal distress (Mustonen et al., 2018). This included perceived stress, symptoms of anxiety or depression or pregnancy related stress. Of the six studies identified in the review, none used diagnostic measures of mental disorders, all drew samples from a community with low levels of symptoms of mental illness and only one study used an additional measure of cortisol in conjunction with hair cortisol (Kramer et al., 2009; Mustonen et al., 2018). Of note, the two studies that found an association between hair cortisol and distress utilized hair samples collected in pregnancy. Furthermore, separately, both maternal emotional health in pregnancy and pregnancy cortisol have been associated with later child cortisol functioning (O'Connor et al., 2013; Pearson et al., 2015).

A review of research that has examined the link between adverse early experiences and child psychopathology has highlighted the importance of understanding cortisol regulation in infants as a potential pathway from early exposures to later vulnerability to psychopathology (Koss and Gunnar, 2018). While findings have been mixed, there have across several studies been trends to suggest increased levels may be associated with vulnerability to internalizing disorders and a clearer association with reduced cortisol associated with externalizing disorders (Kao et al., 2018; Koss and Gunnar, 2018; Ruttle et al., 2011). The HPA system and cortisol response change substantially over the first year of life with some stability and lower responsiveness to everyday stressors only being achieved around 12 months of age, supporting measurement of infant cortisol at 12 months or older (Gunnar and Quevedo, 2007; Lupien et al., 2009).

While it is important to understand the potential influence of maternal psychopathology on maternal and infant cortisol over the perinatal period, it is equally important to understand the impact of treatments. Yet none of these recent reviews of perinatal distress and depression and cortisol have reported on perinatal antidepressant use and cortisol despite the widespread use of antidepressants to treat depression and anxiety in pregnancy (Jimenez-Solem et al., 2013). Antidepressant treatment has been found to alter HPA functioning and impact cortisol levels (Kieviet et al., 2016; Manthey et al., 2011).

In our study, we firstly aim to examine the relationship between maternal hair cortisol concentrations (HCC) and depression across pregnancy and 12 months postpartum. In addition, we will examine if antenatal HCC is associated with antidepressant use in pregnancy. Secondly, we aim to test our hypothesis that maternal HCC across the perinatal period will predict infant HCC and salivary cortisol response and reactivity. Thirdly, we test the hypothesis that maternal mental health in pregnancy will be indirectly associated with infant cortisol (both HCC and cortisol reactivity at 12 months postpartum) through maternal cortisol. Finally, we examine if infant cortisol measures are associated with externalizing or internalizing symptoms at 12 months of age.

2. Materials and methods

This is a prospective cohort study of 241 pregnant women recruited before 20 weeks of pregnancy (Wave 1), and followed up during third trimester (Wave 2), at delivery (Wave 3), six months (Wave 4) and 12 months (Wave 5). Data was excluded from the study if participants had withdrawn prior to or after Wave 3, if they were missing both postpartum waves, or if they had no hair cortisol concentration data. Women who reported taking oral steroid medication were excluded ($n = 3$). Study participants comprised two groups: those with depression at recruitment (Depressed; $n = 51$), and control women ($n = 190$). Further details of the study are described in the published study

protocol (Galbally et al., 2017b). Demographic data and information on physical health, pregnancy complications and outcomes, body mass index, smoking, alcohol and illicit drug use were collected. In addition, infant sex is reported for this paper. The demographic characteristics of the sample analyzed here do not differ significantly to the full baseline MPEWS cohort ($n = 282$) demographic characteristics reported in the published study protocol. Mercy Health Human Research Ethics Committee approved this study and all participants provided informed, written consent.

2.1. Measures

2.1.1. Mental health

At recruitment the Structured Clinical Interview for DSM-IV (SCID-IV) Mood disorders schedule was undertaken (First et al., 1997). In addition, the Edinburgh Postnatal Depression Scale (EPDS) was administered at Waves 1, 2, 4 and 5 (Cox et al., 1987). The scale is validated for use with Australian women during the perinatal period (Boyce et al., 1993). The state anxiety subscale of the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) was also administered at Waves 1, 2, 4 and 5. The STAI is validated for use in Australian women in pregnancy (Grant et al., 2008).

2.1.2. Stressful life events

At Waves 1, 2, 4 and 5, women completed a 23-item stressful life events and social health questionnaire (Brown et al., 2011) to determine incidence of both common and pregnancy-specific life stressors. This scale has been adapted from Pregnancy Risk Assessment Monitoring System (PRAMS) for the Australian context (Whitehead et al., 2003). We grouped women into those who reported fewer than 3 stressful life events at each Wave ($< 3 SLE = 0$), and those who reported 3 or more at each wave up ($\geq 3 SLE = 1$). A systematic review suggested cortisol was more likely to be associated with high levels of stress (Mustonen et al., 2018).

2.1.3. Antidepressant use

Antidepressant type, usage, dosage and timing during pregnancy was self-reported by women and obtained from hospital records at delivery. Maternal blood was collected and analyzed for antidepressant drug levels and has previously been reported to confirm exposure (Galbally et al., 2017a,b). There were 43 women taking antidepressant medication across a range of antidepressants, further details are published (Galbally et al., 2017a,b).

2.1.4. Hair cortisol

Maternal hair was collected post-delivery and maternal and infant hair at 12 months postpartum. Maternal HCC from hair collected post-delivery is able to retrospectively provide an average cortisol level for each trimester of pregnancy (Manenschijn et al., 2011; Smy et al., 2016). HCC providing a measure of chronic rather than short-term transient maternal physiological stress and is a reliable and valid biomarker of mean cortisol concentrations (Manenschijn et al., 2011). A hair questionnaire was administered at each collection to assess the recent use of bleaching, hair treatments including products, dyes and hair washing, and corticosteroid use. Approximately 20 g (150 strands) of hair was collected from the posterior vertex of the scalp cut close to the scalp. At least 5 mg of the most proximal 3 cm of hair was weighed for each hair sample. Samples were processed and analyzed as described previously (Noppe et al., 2015). In short, in order to extract cortisol from hair, all 3 cm-hair samples were cut into one-centimetre pieces and washed in LC-MS grade isopropanol for 2 min. After solid phase extraction, hair cortisol was quantified by liquid chromatography - tandem mass spectrometry using a Xevo TQ-S system (Waters, Milford MA).

2.1.5. Salivary cortisol levels: response and reactivity

At 12 months of age, salivary samples in the infant 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), 10 min after completing the task (+20 min from baseline), and 30 min after completing the task (+40 min from baseline). At the commencement of the task, the mother and child were left alone for three minutes to settle themselves in the room, after which time the stranger entered, sitting silently for one minute, then talking for one minute and then playing for one minute. The task then comprised of two separations and two reunions each at three-minute intervals. The stranger remained in the room for the duration of the first separation, leaving at the first reunion. After a further three minutes, the mother left the child alone in the room for three minutes until the second reunion. After completing the separation and reunion task, parents were asked to free-play with their infant. Salivary samples were collected using a salivette, centrifuged and stored at -80°C .

Salivary cortisol was measured using a commercially available ELISA assay (Salimetrics, USA), in duplicate according to the manufacturer's instructions. Salivary cortisol using these assays has been correlated well with matched serum cortisol concentrations ($r = .91$). Assay sensitivity was $0.003\ \mu\text{g/dL}$, and intraassay variability was 4.4% and interassay variability was 4.9%. All salivary cortisol levels are expressed in SI units, nmol/L.

Infant 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. (2003). AUCg and AUCi were introduced to capture a single cortisol response measurement using repeated measurement data, and to attempt to standardise the method for reporting change in cortisol so that findings could be easily understood and compared across research (Khouri et al., 2015; Pruessner et al., 2003). In this 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.

2.1.6. Social-emotional development

The Brief Infant Toddler Social Emotional Assessment (BITSEA) is a parent-report questionnaire used to screen for social-emotional problems in young children aged 12–36 months and was collected at 12 months for this study (Briggs-Gowan et al., 2013). The BITSEA can be scored for Internalizing and Externalizing Scales validated against the Preschool Age Psychiatric Assessment, a diagnostic measure for mental health disorders in young children (Briggs-Gowan et al., 2013; Egger et al., 2006).

2.2. Data preparation and statistical analysis

During collection of the hair samples at birth and at 12 months postpartum, women reported whether they had bleached their hair and whether they had taken any oral steroid medication. At birth, 13 women reported having bleached their hair during pregnancy, and at 12 months postpartum, 25 women reported bleaching their hair. In addition, 90 women reported treating their hair during pregnancy, and at 12 months postpartum, 96 women reported treating their hair. Both bleaching and treating hair during pregnancy and at 12 months postpartum was not associated with differences in HCC.

Prior to running inferential analyses using HCC, we log-transformed raw HCC due to strong, negative skew of the distributions. Although these transformations improved negative skew, there were between 3 and 4 women with univariate outliers ($z \geq |3|$) in maternal HCC at each wave during pregnancy. We recoded these outlying concentrations to missing to be handled using Full-Information Maximum Likelihood estimation during modelling.

The four repeated HCC measures were fitted to a univariate latent-

growth curve model, adding depression diagnosis as a covariate of the growth factors. Next, we conducted multivariate growth models to test for associations between changes in depressive and anxious symptoms, and changes in maternal HCC during the perinatal period. Prior to conducting this multivariate model, we fit the repeated measurements of depressive symptoms and state anxiety to individual univariate latent growth curve models, and individually added these univariate growth models to the HCC growth model to fit a parallel process model.

We next conducted a series of cross-lagged panel models to examine the lagged and cross-sectional associations between repeated measurements of depressive symptoms and maternal HCC, state anxiety and maternal HCC, and stressful life events and maternal HCC during the perinatal period. These models also facilitate testing of indirect effects from maternal mental health and stress to infant cortisol, through maternal HCC. Due to the large number of hypotheses tests conducted for the estimated parameters across these three models, we corrected for the False Discovery Rate (FDR) using the Benjamini-Hochberg procedure. FDR-correct significance ($q\text{-value} < 0.10$) was set at 10%.

Due to non-normal distributions, maximum-likelihood with robust standard errors (MLR) was used to estimate models. Descriptive analyses were conducted using SPSS Version 24 (IBM Corp., 2016) and all modelling was conducted using Mplus version 8. Tests were considered significant when $p < .05$.

3. Results

3.1. Sociodemographic data

Table 1 presents sociodemographic statistics for the total sample, and by group. Women were all above 18 years old ($M_{\text{age}} = 31.38$, $SD_{\text{age}} = 4.66$, ranging 19–48 years old).

3.2. Maternal hair cortisol concentration (HCC) during pregnancy and 12 months postpartum

Inspection of observed log-transformed maternal HCC means suggested a non-linear model would accurately describe the data. After fitting an intercept-only ($\chi^2[d.f. = 8] = 325.52$, $p < .001$, $CFI = .36$, $RMSEA = 0.41$, $SRMR = 1.21$) and linear slope model ($\chi^2[d.f. = 6] = 224.91$, $p < .001$, $CFI = .57$, $RMSEA = 0.39$, $SRMR = .15$), adding a quadratic growth factor resulted in the best-fitting model for the HCC data ($\chi^2[d.f. = 2] = 17.58$, $p = .002$, $CFI = 0.97$, $RMSEA = 0.18$, $SRMR = 0.04$). In this unconditional non-linear model, the average of the intercept ($M = 1.07$, $p < .001$), slope ($M = 0.25$, $p < .001$) and quadratic factors ($M = 0.05$, $p < .001$) were significant. These average change factors indicate starting maternal HCC was significantly different from zero and increased significantly during pregnancy; however, this initial rate of increase slowed significantly during pregnancy, and HCC levels decreased between third trimester and 12 months postpartum. In addition, the variance estimates for each of these growth factors were also significant, suggesting that women's individual HCC trajectories varied significantly (Intercept = 1.33 , $p < .001$; Slope = $.20$, $p < .001$; Quadratic = $.005$, $p < .001$). When added as a time-invariant covariate, a depression diagnosis was not a significant predictor of starting ($\beta = 0.04$, $p = .529$), slope ($\beta = -.13$, $p = .106$) or quadratic ($\beta = .12$, $p = .119$) maternal HCC growth factors.

Table 2 reports correlations between self-report antidepressant use in pregnancy at recruitment and maternal and infant cortisol with no significant associations. Using only women taking antidepressants during pregnancy, antidepressant concentration in their venous plasma taken directly after childbirth was not associated with their third trimester maternal HCC, $r(n = 39) = 0.08$, $p = .601$. Table 2 also reports all bivariate zero-order Pearson correlations between maternal and infant hair cortisol, maternal mental health and infant stress reactivity at 12 months. Regarding infant salivary cortisol measurements during

Table 1
Demographic and Other Characteristics by Group (N = 241).

	Not Depressed (n = 190)	Depressed (n = 51)	Total Sample (N = 241)
	n (% ^a)	n (% ^a)	n (% ^a)
<i>Ethnicity</i>			
Oceania/European	167 (88.4%)	45 (88.2%)	212 (88.3%)
ATSI	1 (0.5%)	1 (2.0%)	2 (0.8%)
Asian	18 (9.5%)	3 (5.9%)	21 (8.8%)
Middle-eastern	3 (1.6%)	2 (3.9%)	5 (2.1%)
<i>Educational attainment</i>			
Did not complete high school	15 (8.0%)	5 (10.0%)	20 (8.5%)
Completed tertiary certificate or apprenticeship	44 (23.5%)	17 (34.0%)	61 (25.8%)
Completed tertiary university degree	133 (65.8%)	28 (56.0%)	161 (67.7%)
<i>Relationship status</i>			
Not currently in a relationship	5 (2.7%)	4 (8.0%)	9 (3.8%)
Married (first)	122 (65.2%)	29 (58%)	151 (63.7%)
Married (second or later)	5 (2.7%)	1 (2.0%)	6 (2.5%)
De facto	46 (24.6%)	13 (26.0%)	59 (24.9%)
Stable relationship but not living together	6 (3.2%)	1 (2.0%)	7 (3.0%)
Same-sex relationship	1 (0.5%)	1 (2.0%)	2 (0.8%)
Separated	2 (1.1%)	1 (2.0%)	3 (1.3%)
<i>Employment status at recruitment</i>			
Full-time	135 (72.2%)	25 (50.0%)	160 (67.5%)
Part-time	25 (13.4%)	8 (16.0%)	33 (13.9%)
Casual	13 (7.0%)	9 (18.0%)	22 (9.3%)
Unemployed	4 (2.1%)	3 (6.0%)	7 (3.0%)
Studying	3 (1.6%)	1 (2.0%)	4 (1.7%)
Full-time home duties	3 (1.6%)	1 (2.0%)	4 (1.7%)
Smoking during pregnancy	19 (10.2%)	5 (10.0%)	24 (9.9%)
BMI > 24 (overweight and obese) at recruitment	90 (48.1%)	32 (64.0%)	122 (51.1%)
<i>Parity</i>			
Nulliparous	172 (91.0%)	46 (92.0%)	218 (91.2%)
Primiparous	10 (5.3%)	3 (6.0%)	13 (5.4%)
Multigravida	7 (3.7%)	1 (2.0%)	8 (3.3%)
Pregnancy-induced hypertension	5 (2.6%)	9 (17.6%)	14 (5.8%)
Infant sex (male)	105 (55.3%)	28 (54.9%)	133 (55.2%)
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
<i>EPDS</i>			
Early pregnancy	5.57 (3.94)	10.00 (5.79)	6.48 (4.72)
Third trimester	5.48 (3.91)	9.14 (5.19)	6.24 (4.46)
Six months postpartum	5.30 (3.84)	8.25 (5.84)	5.93 (4.49)
12 months postpartum	5.76 (4.53)	9.34 (5.07)	6.42 (4.83)

Note. ATSI, Aboriginal and Torres Strait Islander; BMI, Body Mass Index, EPDS, Edinburgh Postnatal Depression Scale. ^a Percent indicates percentage of full sample, including univariate missing.

the maternal-infant separation and reunion task, 67.1% of infants experienced an increase in cortisol levels 10 min after completing the separation task (baseline: M = 3.32 nmol/L, SD = 3.67 nmol/L; plus 20 min: M = 5.02 nmol/L, SD = 6.60 nmol/L; plus 40 min: M = 4.92 nmol/L, SD = 4.26 nmol/L).

3.3. Maternal mental health and (HCC) during pregnancy and to 12 months postpartum

Fig. 1 presents the correlations between growth factors in the multivariate parallel process models for (a) maternal depressive symptoms and HCC, and (b) maternal state anxiety and HCC. Both the starting and the slope factors for maternal depressive symptoms and state anxiety were uncorrelated with maternal HCC starting and slope change factors. This suggests within a parallel process model that average changes in maternal HCC across pregnancy were independent

of average changes in maternal mental health symptoms during the same period.

3.3.1. Perinatal maternal depressive symptoms and HCC, and infant cortisol at 12 months

Fig. 2 displays the results of a model testing autoregressive, cross-sectional, and cross-lagged associations between maternal depressive symptoms and HCC during the first trimester and third trimester, and at 12 months postpartum. Infant cortisol measurements at 12 months postpartum were also included in the model as outcomes of maternal mental health and HCC. Although not shown in the figure, we controlled for the effect of infant sex in each of the three infant cortisol outcomes at 12 months postpartum. Infant sex was only significantly associated with AUCi, such that male infants had lower AUCi. The autoregressive association between first trimester and 12 month HCC suggests low stability (i.e., considerable individual variability) in maternal HCC during the perinatal period. In contrast, depressive symptoms across the same period were more stable, suggesting less variance over time. At each time point, there were no cross-sectional associations between depressive symptoms and maternal HCC. Higher maternal depressive symptoms during the third trimester were associated with significantly lower overall cortisol response (AUCg) in the infant during the observational separation reunion task at 12 months. At 12 months, there were also significant cross-sectional correlations, such that higher maternal HCC and depressive symptoms were associated with higher infant HCC.

3.3.2. Perinatal state anxiety symptoms and HCC, and infant cortisol at 12 months

Fig. 3 displays the results of a model testing autoregressive, cross-sectional, and cross-lagged associations between maternal state anxiety and HCC during the first trimester and third trimester, and at 12 months postpartum. Again, infant cortisol measurements at 12 months postpartum were also included in the model as outcomes of maternal constructs, with significantly lower AUCi observed for male infants. Maternal state anxiety across the perinatal period was less stable when compared to depressive symptoms in the previous model; however, the autoregressive coefficient was significant, suggesting a degree of stability over time. None of the cross-sectional or cross-lagged associations between state anxiety and maternal HCC were significant, suggesting that maternal state anxiety and HCC were relatively independent of each other during the perinatal period. Similar again to the depressive symptoms model, higher maternal state anxiety during the third trimester was associated with significantly lower overall cortisol response (AUCg) in the infant during the task at 12 months.

3.3.3. Perinatal stressful life events and HCC, and infant cortisol at 12 months

Fig. 4 displays the results of a model testing the autoregressive, cross-sectional and lagged associations between maternal stressful life events and HCC during the first trimester and third trimester, and at 12 months postpartum, and including infant 12 months cortisol outcomes. This model differs to the depressive symptoms and state anxiety models above because there is no basis to hypothesize that earlier HCC is predictive of later stressful life events. As in the previous two models, infant sex was a significant predictor of AUCi. The non-significant autoregressive coefficient for stressful life events suggests instability in the construct during the perinatal period, such that reporting 3 or more stressful life events in early pregnancy was not associated with reduced or increased odds of reporting 3 or more stressful events at each subsequent time point. None of the cross-lagged or cross-sectional paths from maternal stressful life events to HCC were significant, suggesting that maternal HCC was unrelated to reporting 3 or more stressful life events during the perinatal period. Inconsistent with the pattern of associations in the depressive and anxiety symptoms models, reporting 3 or more stressful life events during the third trimester was not

Table 2
Bivariate Zero-order Pearson Correlation Coefficients between Maternal Hair Cortisol, Mental Health Symptoms during the Perinatal Period, and Infant Cortisol Measures at 12 months Postpartum.

Variable	Timepoint	1	2	3	4	5	6	7	8	9	10
1. Maternal Hair Cortisol ^a	T1	–									
2. Maternal Hair Cortisol ^a	T2	.92**	–								
3. Maternal Hair Cortisol ^a	T3	.77**	.89**	–							
4. Maternal Hair Cortisol ^a	W5	.22**	.28**	.28**	–						
5. Depression Diagnosis (SCID-IV) ^b	W1	.02	.01	–.04	.02	–					
6. Antidepressant Treatment ^b	W1	–.02	.00	–.02	.04	.47**	–				
7. EPDS	W1	.02	.01	.09	.10	.38**	.27**	–			
8. STAI (State)	W1	.01	–.01	.03	.04	.37**	.24**	.78**	–		
9. ≥ 3 SLES ^b	W1	.05	.06	.05	.02	.07	.05	.35**	.34**	–	
10. EPDS	W2	.01	–.02	.04	.03	.33**	.20**	.66**	.59**	.24**	–
11. STAI (State)	W2	–.01	–.07	.00	–.02	.27**	.16*	.60**	.64**	.27**	.78**
12. ≥ 3 SLES ^b	W2	.09	.07	.08	.00	.17**	.06	.38**	.32**	.56**	.31**
13. EPDS	W4	–.06	–.06	–.04	–.01	.27**	.22**	.49**	.42**	.23**	.55**
14. STAI (State)	W4	–.02	–.02	–.01	.00	.25**	.13	.42**	.49**	.26**	.54**
15. ≥ 3 SLES ^b	W4	–.01	–.02	.03	.01	.05	.04	.41**	.41**	.24**	.30**
16. EPDS	W5	–.03	–.06	–.04	.06	.29**	.15*	.53**	.44**	.20**	.60**
17. STAI (State)	W5	–.08	–.09	–.06	.08	.37**	.20**	.57**	.50**	.27**	.63**
18. ≥ 3 SLES ^b	W5	.03	–.02	–.07	.11	.14*	–.01	.29**	.28**	.20**	.26**
19. Infant Sex (Male) ^b	Birth	.06	.07	.05	.11	.00	–.04	–.03	–.09	–.12	–.07
20. Infant Hair Cortisol ^a	W5	.09	.13	.01	.29**	.02	–.06	–.06	–.03	.08	–.09
21. AUC ^a	W5	–.07	–.08	–.14	–.03	–.06	–.01	–.17*	–.14	–.07	–.17*
22. AUCI	W5	–.22**	–.16*	–.13	–.12	–.08	.01	–.11	–.08	.04	–.02
Mean		1.04	1.22	1.41	.90	.21	.18	6.48	34.81	.25	6.24
Standard Deviation		1.12	1.10	.97	.62	.41	.38	4.72	11.19	.44	4.46
Range		0.26-4.63	0.26-4.33	0.26-4.30	0.26-2.90	0-1	0-1	0-27	20-75	0-1	0-25

Variable	11	12	13	14	15	16	17	18	19	20	21	22
1. Maternal Hair Cortisol ^a												
2. Maternal Hair Cortisol ^a												
3. Maternal Hair Cortisol ^a												
4. Maternal Hair Cortisol ^a												
5. Depression Diagnosis (SCID-IV) ^b												
6. Antidepressant Treatment ^b												
7. EPDS												
8. STAI (State)												
9. ≥ 3 SLES ^b												
10. EPDS												
11. STAI (State)												
12. ≥ 3 SLES ^b	.28**	–										
13. EPDS	.42**	.27**	–									
14. STAI (State)	.56**	.31**	.72**	–								
15. ≥ 3 SLES ^b	.28**	.35**	.24**	.31**	–							
16. EPDS	.54**	.14*	.64**	.54**	.22**	–						
17. STAI (State)	.62**	.25**	.55**	.61**	.29**	.77**	–					
18. ≥ 3 SLES ^b	.24**	.24**	.21**	.28**	.36**	.26**	.23**	–				
19. Infant Sex (Male) ^b	–.13*	–.12	–.05	–.07	–.09	.03	.03	.03	–			
20. Infant Hair Cortisol ^a	–.06	–.01	–.03	–.13	–.14	.07	–.16*	–.05	.10	–		
21. AUC ^a	–.19*	–.17*	–.08	–.18*	.00	–.05	–.10	–.10	–.02	.14	–	

(continued on next page)

Table 2 (continued)

Variable	11	12	13	14	15	16	17	18	19	20	21	22
22. AUCi	-.02	.04	.02	-.01	-.05	-.06	-.05	-.03	-.19*	-.03	.53**	-
Mean	34.30	.21	5.93	31.75	.19	6.42	33.87	.19	.55	2.19	4.95	41.69
Standard Deviation	10.52	.41	4.50	9.15	.39	4.83	10.27	.39	.50	1.50	.61	90.36
Range	20-73	0-1	0-24	20-58	0-1	0-25	20-60	0-1	0-1	0.26-5.35	3.83-7.62	-195.-19, 347.12

SCID-IV, Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; EPDS, Edinburgh Postnatal Depression Scale; STAI, State-Trait Anxiety Scale - State Scale; SLES, Stressful Life Events; AUCg, Area Under the Curve relative to Ground; AUCi, Area Under the Curve relative to Increase; T1, Trimester 1; T2, Trimester 2; T3, Trimester 3; W1, Wave 1 Early Pregnancy; W2, Wave 2 Trimester 3; W4, Wave 4 6 Month Postpartum; W5, Wave 5 12 Months Postpartum. Missing data handled using case-wise deletion.

^a log-transformed, ^b correlations with these variables are point-biserial.

** p < 0.01 * p < 0.05.

associated with significantly lower total cortisol response by the infant during the task at 12 months. However, reporting 3 or more stressful life events at 12 months postpartum was cross-sectionally associated with significantly lower infant HCC.

3.4. Infant cortisol and socio-emotional problems

Supplementary Table 1 reports bivariate correlations between infant cortisol measures, infant HCC, infant saliva cortisol response and cortisol reactivity with BITSEA internalizing and externalizing scales. Increased externalizing symptoms were found to be significantly associated with lower infant cortisol reactivity. No other significant associations were identified.

4. Discussion

This study presents unique data, including repeat maternal HCC in pregnancy and postpartum, infant HCC, infant salivary cortisol, and utilized diagnostic and self-report measures of depression as well as anxiety, stress and antidepressant use for women, and then a maternal report of socio-emotional symptoms at 12 months for infants. Against prediction we found no significant differences in maternal HCC across pregnancy and at 12 months postpartum between women with a diagnosis of depression and control women. Likewise we found no difference if women were taking antidepressant medication or not. However, early pregnancy depressive symptoms, measured on the EPDS, predicted higher maternal HCC in 3rd trimester, while stress and anxiety symptoms had no impact on maternal HCC. Overall, maternal HCC showed a small increase across pregnancy for all women with a subsequent decline across the postpartum.

In examining whether maternal perinatal mental health and cortisol predicted infant cortisol outcomes, we found higher maternal late pregnancy HCC was associated with lower cortisol reactivity in the infant at 12 months. Postpartum maternal HCC was also associated with infant hair cortisol at 12 months. Furthermore, higher late pregnancy depressive and anxiety symptoms were both associated with lower salivary cortisol response (AUCg) at 12 months of age in response to a separation-reunion task. While a recent systematic review did not show a clear relationship between maternal perinatal depression and maternal cortisol, what our data suggests is that maternal mental health symptoms are potentially important mechanisms in pregnancy that influence HPA axis development and regulation in offspring (Seth et al., 2016).

Our study also found infant salivary cortisol response at 12 months were lower where there were an increased number of stressful life events in the postpartum but not in pregnancy. A recent meta-analysis that examined all hair cortisol studies and a range of mental health outcomes identified an increase in hair cortisol during chronic stress, while a significant decrease in HCC was commonly observed with anxiety disorders and notably PTSD (Stalder et al., 2017). They found less evidence for an effect on hair cortisol reported in studies examining depression. Our findings show specifically that lower infant HCC and cortisol response were both associated with late pregnancy maternal stress. Lower cortisol in children has been associated with increased vulnerability to externalizing disorders and less consistently with internalizing disorders (Koss and Gunnar, 2018). In examining infant cortisol and symptoms of externalizing or internalizing symptoms we found lower infant cortisol reactivity was cross-sectionally associated with higher externalizing symptoms. This is an important finding, but requires replication in older children, to ascertain any functional significance with regards to vulnerability to diagnostic mental disorders.

Our measure of infant stress response and reactivity, measured through repeat salivary cortisol, was collected specifically in the context of a separation and reunion task with the infant's mother at 12 months of age. The importance of this early primary caregiver relationship between mother and infant in the development of early stress

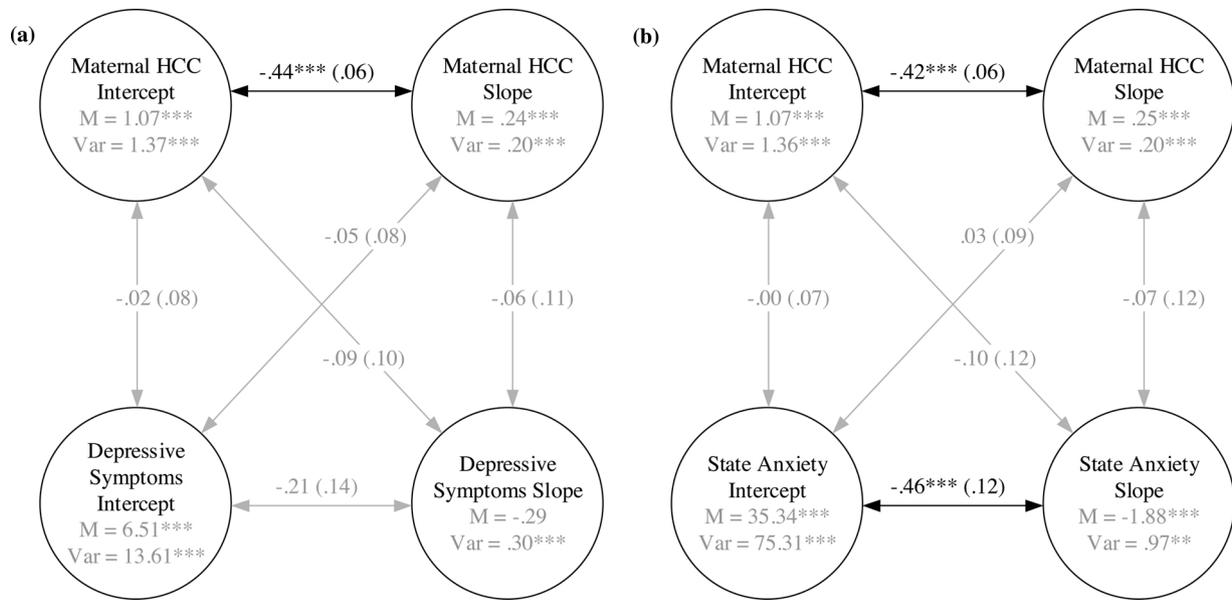


Fig. 1. Parallel Process Models for (a) maternal depressive symptoms and HCC, and (b) maternal state anxiety and HCC. Path coefficients represent correlations (and standard error). Greyed-out paths and parameter estimates are not significant. M, Mean; Var, Variance. Although a quadratic factor was estimated for maternal HCC and depressive symptoms in (a) and for maternal HCC and state anxiety in (b), all correlations with quadratic terms were constrained to zero in both models, and are, thus, not presented graphically. ** $p < .01$, *** $p < .001$.

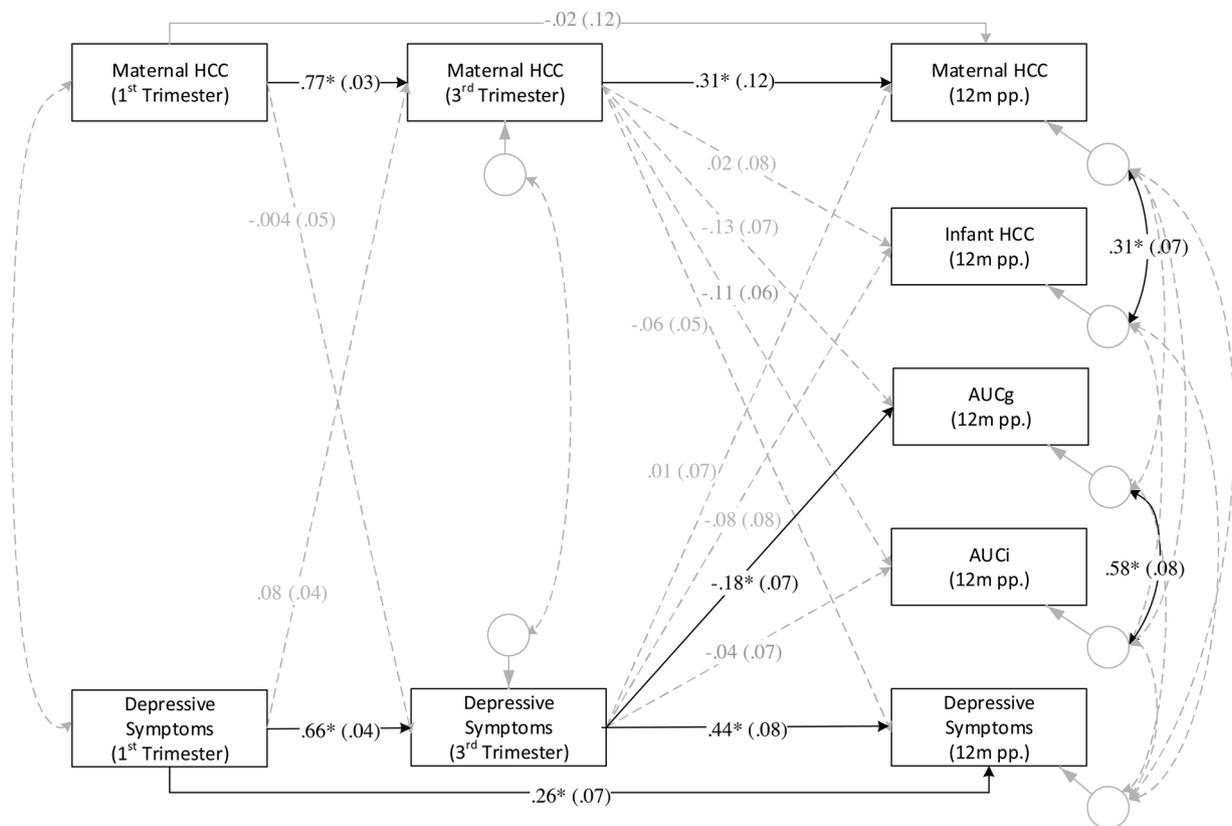


Fig. 2. Cross-lag panel model results (standardised coefficients and standard error parenthetically) for Maternal HCC and Depressive Symptoms, including Infant Cortisol Outcomes at 12 months only ($N = 241$). Greyed-out, dashed lines denote non-significant coefficients (FDR-controlled). Double-headed arrows represent correlation coefficients. Model fit: $\chi^2(N = 241, df = 14) = 14.69, p = .400, CFI = .999, RMSEA = 0.014, SRMS = 0.030$. Although not depicted in the figure, infant sex (Male = 1) controlled for in the infant cortisol outcomes at 12 months (i.e., Infant HCC, AUCg and AUCi).

*Benjamini-Hochberg FDR-controlled q -value < 0.10 .

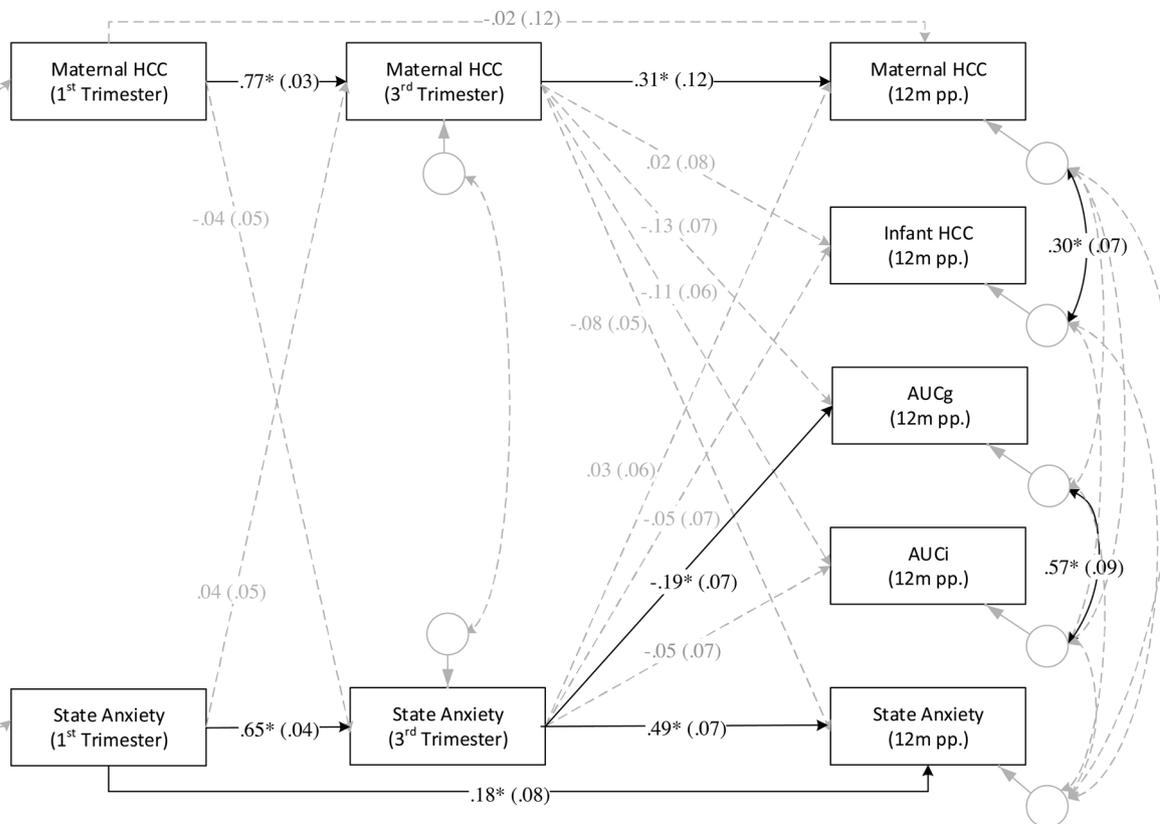


Fig. 3. Cross-lag panel model results (standardised coefficients and standard error parentetically) for Maternal HCC and State Anxiety, including Infant Cortisol Outcomes at 12 months only (N = 241). Greyed-out, dashed lines denote non-significant coefficients (FDR-controlled). Double-headed arrows represent correlation coefficients. Model fit: $\chi^2(N = 241, df = 14) = 14.07, p = .445, CFI = 1.000, RMSEA = 0.01, SRMS = 0.030$. Although not depicted in the figure, infant sex (Male = 1) controlled for in the infant cortisol outcomes at 12 months (i.e., Infant HCC, AUCg and AUCi). *Benjamini-Hochberg FDR-controlled *q-value* < 0.10.

regulation is likely to be underpinned by a range of psychological and biological influences across early life. These include in utero exposures to maternal stress regulation through cortisol, placental functioning with regards cortisol transmission from mother to fetus and the quality and security of the emerging mother-infant relationship, which is postulated to buffer and influence the development of infant stress regulation (Gunnar, 2017). Although within this study we did not assess attachment or the quality of the maternal-infant relationship, our findings did indicate an association specifically of late pregnancy depression and anxiety symptoms with lower overall infant cortisol response to a relational stress task. This suggests that a blunting of cortisol response to separation and reunion with their mother when there were increased maternal depressive and anxiety symptoms in late pregnancy, a response consistent with what is observed with chronic rather than acute stress exposure (Heim et al., 2000; Koss and Gunnar, 2018).

Intriguingly we also found a relationship between maternal and infant cortisol levels at 12 months postpartum. However, maternal antenatal HCC was only associated with infant cortisol reactivity measured through saliva samples and not with infant hair cortisol at 12 months. A previous study examining infant and maternal hair cortisol found an association between late pregnancy maternal cortisol and infant hair cortisol at 1 years of age (Karlen et al., 2013). While our study replicated this finding, it expanded by examining relationships between maternal and infant cortisol also at 12 months postpartum finding also a cross-sectional association within the dyad at this age. Synchrony and asynchrony of postpartum maternal and infant cortisol has been associated with infant sleep practices, breastfeeding and the quality of the dyadic relationship (Middlemiss et al., 2012; Neelon et al., 2015; Tarullo et al., 2017). Overall this may continue to support a

relationship between maternal perinatal cortisol and infant cortisol but this requires further elucidation and consideration of the potential genetic, epigenetic and environmental influences outside of mental health.

The decision for women and clinicians on antidepressant treatment in pregnancy is complex, however we found antidepressant use in pregnancy measured either as self-report use or maternal blood levels at delivery was not associated with maternal or infant cortisol levels. While this provides novel data as few studies have examined antidepressant exposure and cortisol across the perinatal period, future studies could also examine specific agents, dose and class of antidepressants.

Our study is limited by the lack of a diagnostic mental health outcome for offspring. For those women taking antidepressants it was not possible to examine specific agents. While powered for the analysis we undertook, a larger number of participants would allow greater number of variables and complexity of models. Furthermore, this study does not include data on fathers and given the importance of paternal mental health, parenting and support in early development this is a limitation of this study (Gentile and Fusco, 2017). While beyond the scope of this study we have previously found an association between childhood trauma experiences and current stressful life events and future research could explore this further (Galbally et al., 2019). This study did not collect a diagnostic measure of Posttraumatic Stress Disorder (PTSD).

5. Conclusions

If we are to progress our understanding of the intergenerational mechanisms that may underpin the association between maternal depression and child outcomes, future research needs to build on this

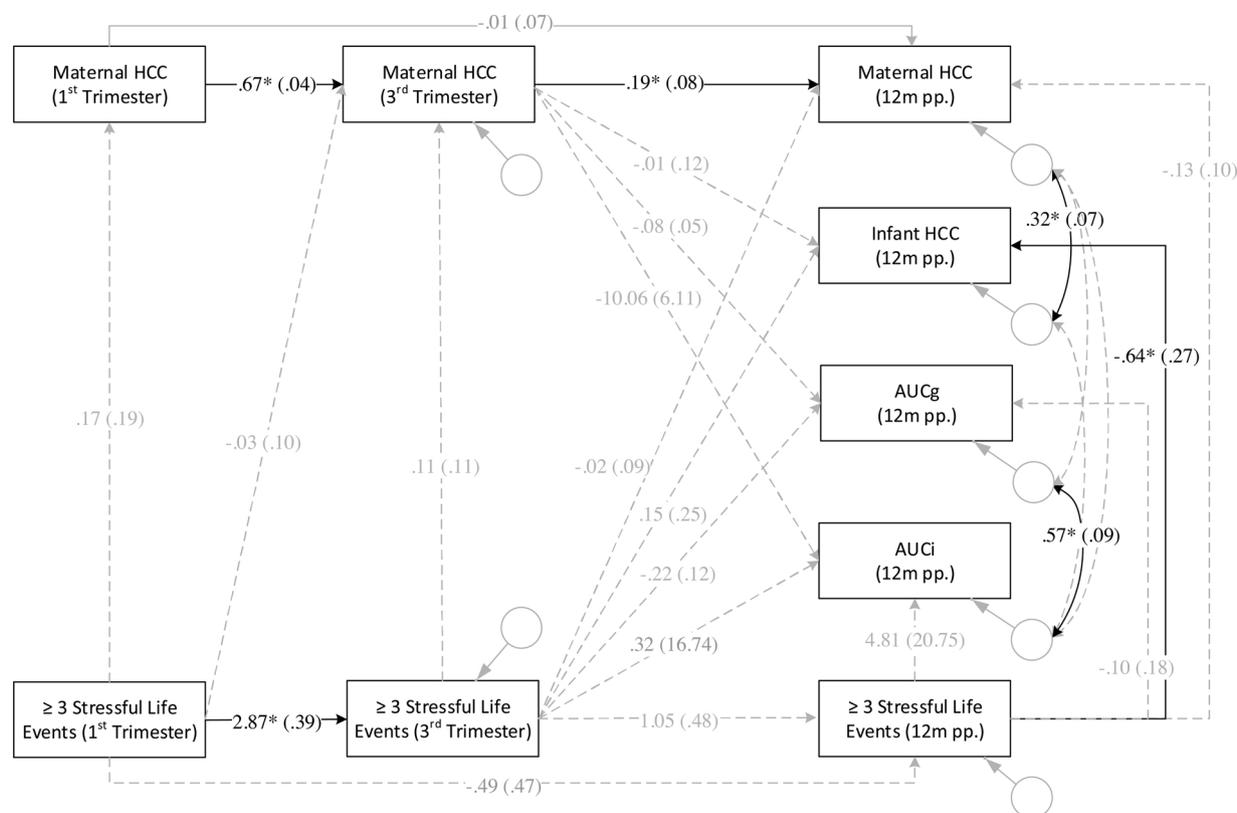


Fig. 4. Results of the Stressful Life Events effects panel model (unstandardised coefficients and standard error parentetically) for maternal HCC and binary stressful life events (0 = Less than 3 SLE's, 1 = ≥ 3 stressful life events), including Infant Cortisol Outcomes at 12 months only (N = 241). Pathways representing prediction of SLES represent the log of the MLR estimate; exponentiating these estimates result in an odds ratio. Greyed-out, dashed lines denote non-significant coefficients (FDR-controlled). Double-headed arrows represent correlation coefficients. This model was estimated using the Monte Carlo algorithm for parameter integration. Although not depicted in the figure, infant sex (Male = 1) controlled for in the infant cortisol outcomes at 12 months (i.e., Infant HCC, AUCg and AUCi). *Benjamini-Hochberg FDR-controlled *q-value* < 0.10.

study by robustly measuring mental health and cortisol to reflect the complexity of endocrinological systems that are dynamic and responsive to acute as well as chronic environmental influences. Our findings highlight the importance of study design that does not rely on a single measure for either mental health or biological outcomes. Finally, the largest gap is prospective research that includes robust and broad measures of mental health in pregnancy, potential risk and protective mechanisms and measures of mental health in children that include diagnostic as well as symptoms in children. Investing in this research is likely to uncover how we can move forward in our goal of preventing mental disorders into the next generation.

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Contributors

MG and AJL designed the original and overall study protocol and ethics application. EvR undertook the hair cortisol concentrations. RdK contributed to the interpretation of the data. SW undertook the statistical analysis. MG and SW drafted this manuscript and all authors critically reviewed and revised for content and gave approval to the final

to be published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.psyneuen.2019.104374>.

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