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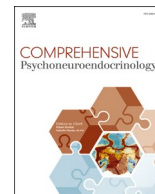
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Intergenerational impact of childhood trauma on hair cortisol concentrations in mothers and their young infants

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ABSTRACT

Background: Alterations in stress regulation and function of the hypothalamic-pituitary-adrenal (HPA) axis during infancy may be a risk factor for the development of psychopathology later in life. Maternal childhood trauma, depression, anxiety and stressful life events are individually associated with HPA axis dysregulation. Less is known about their interdependent influence on maternal and infant stress regulation in at risk populations. In a sample of mothers with a history of depressive-, and/or anxiety disorders and their infants we explored if a history of maternal childhood trauma, current depressive and anxiety symptomatology, and recent life events were associated with maternal and infant long-term cortisol levels three months postpartum.

Methods: Data were available of 89 mothers and 49 infants. All mothers fulfilled criteria for a lifetime depressive or anxiety disorder. Diagnosis was established with a diagnostic interview. Current depressive symptomatology was assessed with the Edinburgh Postnatal Depression Scale (EPDS), current anxiety with the State-Trait Anxiety Inventory (STAI), maternal childhood trauma with the Childhood Trauma Questionnaire (CTQ) and recent life events with the Everyday Problem Checklist (EPC). Maternal and infant hair cortisol concentrations (HCC) were quantified with liquid chromatography with tandem mass spectrometry (LC-MS/MS) three months after birth. Total scores of the CTQ and subscales, EPDS, STAI, and EPC were regressed on maternal and infant HCC using regression analyses. Differences in HCC regarding trauma history were tested with t-tests. Potential confounders were identified and adjusted for.

Results: In regression analyses, a positive curvilinear relationship was found between CTQ total score and maternal HCC ($n = 83$, $B = 0.076$, $SE 0.033$, $p = .021$), but not for current depression ($n = 88$, $B = -0.001$, $SE 0.011$, $p = .931$), current anxiety ($n = 88$, $B = 0.002$, $SE 0.004$, $p = .650$) or recent life events ($n = 89$, $B = 0.018$, $SE 0.032$, $p = .568$). Analyses were adjusted for confounders. A negative linear relationship was found between maternal CTQ score and infant HCC ($n = 49$, $\beta = -0.264$, $B = -0.006$, $SE 0.003$, $p = .052$), but not for current maternal depression ($n = 45$, $\beta = -0.182$, $B = -0.011$, $SE 0.008$, $p = .164$), current maternal anxiety ($n = 45$, $\beta = -0.209$, $B = -0.005$, $SE 0.003$, $p = .113$) or recent life events ($n = 46$, $\beta = -0.128$, $B = -0.022$, $SE 0.023$, $p = .325$). Analyses were adjusted for relevant infant hair characteristics. Specifically, maternal emotional and physical neglect were related to HCC in both mothers and infants.

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Conclusions: Results suggest that maternal childhood trauma is more prominent in altering maternal and infant long-term cortisol levels than perinatal depressive and anxiety symptomatology or recent life stressors in mothers with a history of depressive and/or anxiety disorders, and their infants. As infants of mothers with psychopathology are at increased risk for later psychiatric disease, future studies should investigate the interplay of possible risk factors for transgenerational transmission, intra-uterine programming of the HPA axis, including (epi-)genetic phenomena, of the HPA axis, and the influence of parenting impairment.

1. Introduction

Perinatal psychopathology is a risk factor for a range of psychiatric, somatic, and developmental disorders in offspring [1,2]. The pathways of transmission are not fully elucidated, but are perceived to stem from combined genetic and environmental vulnerability factors [3]. Accumulating evidence supports the hypothesis that the risk for negative outcomes in children is already prenatally transmitted [4,5]. Although not the only mechanism, dysregulation of the maternal stress response systems during pregnancy, specifically the HPA axis, is thought to play a key role in the process of intergenerational transmission [6]. In turn, this may cause perturbations of infant HPA axis functioning, which could explain the higher vulnerability for infants to future mental and physical illness [7].

The HPA axis is part of the stress system and its end product, cortisol, serves as a 'stress mediator' that affects different processes in the body in reaction to the stressor. Stressors can be emotional or physical in origin. Prolonged or repeated activation of the HPA axis is believed to trigger and maintain psychiatric disorders [8], and in turn psychiatric disorders can change HPA axis reactivity over time. HPA axis regulation is measured through cortisol quantification. Traditional methods include the assessment in bodily fluids like saliva, urine, and blood serum. Cortisol levels vary over the day, due to acute stress, diurnal rhythm and pulsatile secretion. Cortisol measurements in bodily fluids (serum, saliva) provide information about acute (serum, saliva) and short-term (urine) cortisol values, which offers insight in stress reactivity in psychiatric disorders [9]. But these methods are not always a reflection of long-term cortisol exposure. Lately, cortisol is analysed in hair, providing long-term systemic levels of cortisol retrospectively [10]. Hair cortisol concentrations (HCC) are a valid and reliable retrospective measure of mean cortisol and can provide information about chronic stress [11].

Depression, anxiety, and childhood trauma or life events have been linked to altered HPA axis activity, in which changes in cortisol reactivity can be both a cause and consequence of psychopathology ([12]; [13]). However, few studies have addressed the question to what extent the maternal and fetal HPA axis, by means of long-term cortisol output measured in hair cortisol concentrations (HCC), are impacted by maternal childhood trauma and by maternal psychopathology, such as

perinatal major depressive disorder (MDD) or anxiety disorder. In general study populations, patients with major depressive disorder tend to show higher HCC than controls ([14][15]; and patients with trauma-related disorders show a trend for lower HCC [16,17], although evidence is conflicting [18]. Regarding anxiety disorders, HCC findings show more inconsistency (i.e. higher, lower or no effect on HCC), although comorbid anxiety and depression have shown increased values [15]. These studies generally did not consider trauma history as an independent and pre-existing determinant of HPA axis functioning. Childhood traumatic experiences might be more prominent in chronic alteration of the stress system, by means of allostatic overload [19–21]. A detailed exploration yielded that lower HCC was more often associated with maltreatment beginning in childhood [22]. Regarding psychopathology, severity and duration of symptoms also appear to be important factors (besides the nature of the psychiatric illness), as different studies have shown blunting of the stress response over time [23].

Although mechanisms that influence infant HPA axis functioning when exposed to maternal psychopathology are probably a complex interplay of (epi-)genetic and environmental factors, different studies implicate maternal (prenatal) endocrine functioning is a possible mechanism of transmission from mother to child [24]. Studies on mutual influence of maternal-fetal HPA axis based on long-term HCC measurements are emerging. A first review of existing evidence suggests that maternal stress (i.e. perinatal depressive disorder) is inconsistently related to maternal and/or infant HCC [25]; weak associations are found specifically in populations with low levels of self-reported perinatal depression, where the associations appear to get stronger in populations with a greater variance or greater severity of symptoms. A recent larger study, not included in the review, found no association between a diagnosis of depression or anxiety and maternal HCC across pregnancy, nor with maternal and infant HCC at 12 months [26]. A previous study of our group in a small heterogenic sample of mothers with severe mental illnesses did find a positive association between maternal psychiatric symptom severity during pregnancy and infant HCC at 6 weeks ([27]). In this study maternal HCC also showed a strong association with infant HCC, but only in healthy women. This finding might reflect early physiological synchrony, which is defined as the matching of biological states between mother and child that develops via interactions among

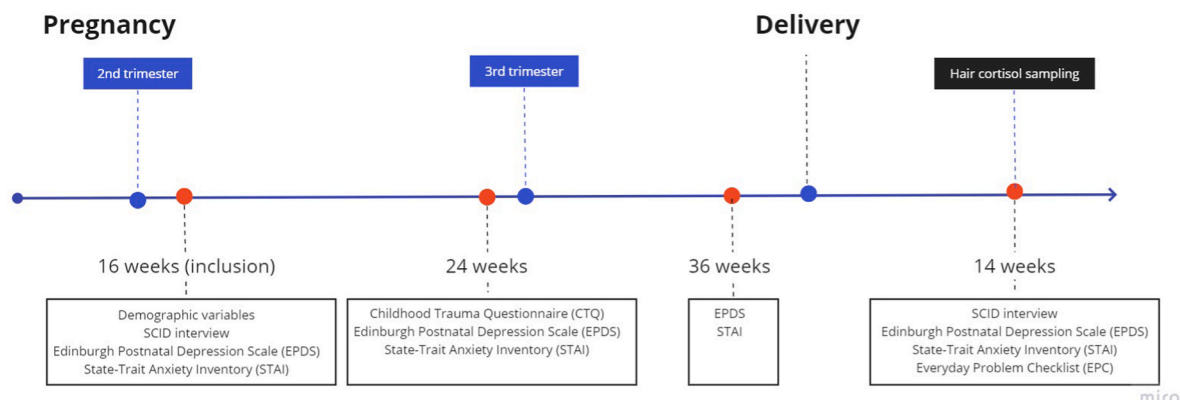


Fig. 1. Timeline of measurements of the Stop-or-Go study.

Table 1

Descriptive statistics of mothers (n = 89) and infants (n = 49) from the *Stop-or-Go* study with availability of hair cortisol measurements three months post-partum.

Demographic characteristics	N	%	M	SD	Range
Age, years ^a	89		32.5	4.2	23–43
Body mass index (BMI) ^b	88		25.1	5.0	18–42
Ethnicity	89	88.8			
• Native Dutch	79	4.5			
• European immigrant	4	6.7			
• Non-European immigrant	6				
Married/partnered	87	95.4			
• Yes	83	4.6			
• No	4				
Education level	85	40			
• Lower	34	60			
• Higher	51				
Parity	88	54.5			
• Primiparous	48	45.5			
• Multiparous	40				
Delivery	88	81			
• Vaginal	68	19			
• Cesarean	16				
Maternal smoking ^c	88	93.2			
• Yes	82	6.8			
• No	6				
Hair-related variables and HCC	N	%	M	SD	Range
Hair color	87	2.3			
• Black	2	39.1			
• Brown	34	55.2			
• Blonde	48	3.4			
• Red	3				
Hair wash frequency (times/w)	88		1.7	0.7	0–3
Hair treatment	88	48.9			
• None	43	51.1			
• Bleach, dye, perm	45				
Heavy transpiration	88	83			
• Yes	73	17			
• No	15				
Use of hair products	88	42			
• Yes	37	58			
• No	51				
Mean hair cortisol concentrations pg/mg (HCC) ^d	89		4.2	5.0	2.5–32
Clinical characteristics	N	%	M	SD	Range
Psychiatric disorder	89	86.2			
• Lifetime depression ^e	75	75.9			
• Lifetime anxiety disorder ^e	66	4.5			
• Current depression	4	23.6			
• Current anxiety disorder	21				
Medication use ^d	89	79.8			
• Antidepressants	71	27.0			
• Hormonal contraceptives	24				
Childhood Trauma Questionnaire (CTQ) ^f	83		8.9	4.4	5–22
• Emotional abuse ^g	35	5.6	1.6	5–13	
• Physical abuse	9	5.5	2.0	5–20	
• Sexual abuse	9	11.0	4.8	5–23	
• Emotional neglect	41	6.4	1.8	5–13	
• Physical neglect	18	45.2	13.6	28–87	
• CTQ total score					
Edinburgh Postnatal Depression Scale (EPDS)	88		6.5	3.9	0–19
• Pregnancy mean			6.7	5.1	0–27
• At the time of cortisol sampling					
State Trait Anxiety Inventory (STAI)	88		34.8	8.8	20–71
• Pregnancy mean			37.2	13.1	20–80
• At the time of cortisol sampling					
Everyday Problem Checklist (EPC) ^h	89	13.5	2.5	1.7	0–6
• No significant problems	12	19.1			
• Problems in one area of life	17	48.3			
• Problems in two areas of life	17				
• Problems in three or more areas of life	43				

Table 1 (continued)

Demographic characteristics	N	%	M	SD	Range
• Total number of problem areas					
Demographic characteristics	N	%	M	SD	Range
Age, weeks	45		14.3	1.7	11–19
Gender	49	57.1			
• Girl	28	42.9			
• Boy	21				
Gestational age, weeks	48		39.6	1.1	37–42
Birthweight, grams	48		3507.8	477.7	2428–4416
Hair-related variables and HCC	N	%	M	SD	Range
Hair wash frequency (times/w)	49		1.2	0.7	0–3
Heavy transpiration	49	10.2			
• Yes	5	89.8			
• No	44				
Use of hair products	49	10.2			
• Yes	5	98.8			
• No	44				
Hair cortisol concentrations (HCC) ^d	49		53.8	49.1	11–220

Note.

^a At time of hair sampling, 14 weeks post-partum.

^b BMI based on weight before pregnancy.

^c During at least two trimesters.

^d Reported in original units (pg/mg).

^e *Diagnosis of depression (incl. dysthymic disorder)/anxiety (incl. panic disorder, agoraphobia, generalized anxiety disorder, specific anxiety disorder, social anxiety disorder).*

^f CTQ was administered during pregnancy at 24 weeks.

^g Number of patients scoring above the cut-off on different CTQ subscales are reported.

genetic predispositions, prenatal programming and postnatal behavior; a synchronic effect that has been found more often between parents and children in different ages [28]. With regards to trauma, a negative association has been found between maternal childhood trauma and hair cortisol in infants on the day of birth [29]. Furthermore, studies indicate that parental trauma exposure could be associated with biological changes that render offspring more vulnerable to the effects of stressors and the development of psychopathology [3].

In the current study we try to delineate the influence of different influences on maternal and infant HCC three months postpartum. Therefore we assessed the influence of maternal childhood trauma, of maternal lifetime depressive and anxiety disorders, symptom severity throughout pregnancy and postpartum, and recent life events in an at-risk sample of women, while examining a variety of potential confounders. Based on previous studies [30], we hypothesize that maternal trauma history is more prominent in altering HCC in mothers and infants than symptom severity during pregnancy and at three months postpartum, as well as recent life events. As long-term longitudinal data did show that specifically emotional abuse and neglect are associated with a wide range of long-term adverse health outcomes (including psychiatric disorders) we hypothesize emotional abuse and neglect might have the greatest impact on HCC [31]. Furthermore we hypothesize a positive association between maternal and infant HCC.

2. Methods

2.1. Study design and sample

The present study is an exploratory analysis in an at-risk sample of 89 women with (a history of) depressive and/or anxiety disorders who used antidepressants at the start of the study (i.e. Selective Serotonin Reuptake Inhibitor (SSRI), Selective Serotonin and Noradrenalin Reuptake Inhibitor (SNRI), or Tricyclic Antidepressant (TCA)). This study was part of a larger nationwide research project on antidepressants, including both a randomized controlled trial, in which women were randomized to

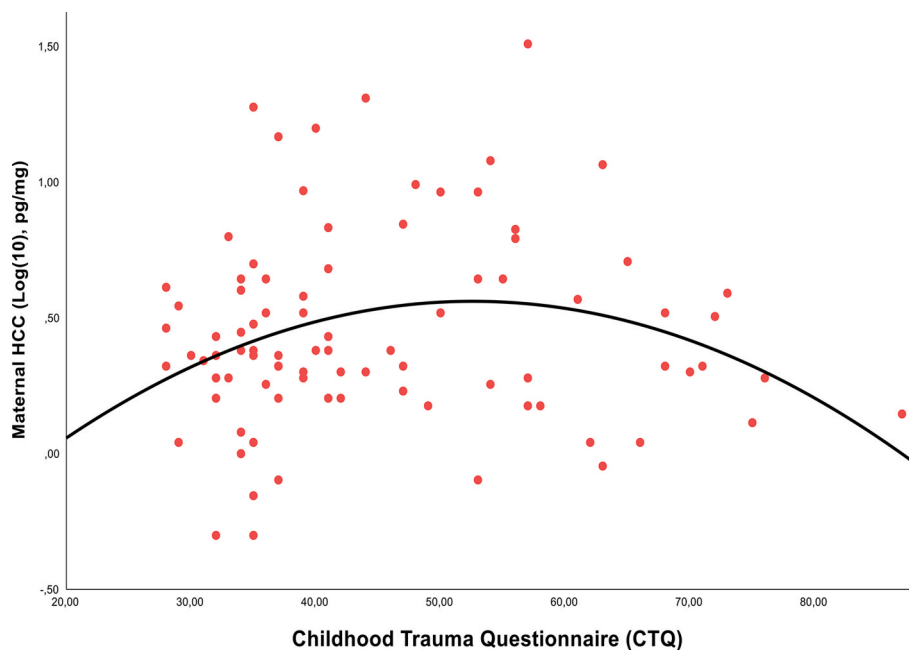


Fig. 2a. Scatterplot of the maternal hair cortisol concentrations (HCC) and the total score on the Childhood Trauma Questionnaire (CTQ) in mothers ($N = 83$). Average CTQ scores on community samples are 38.78 (SD 14.98) and 45.91 (SD 18.79) in patient samples [38]. Note: HCC below LLOQ ($=2.5$ pg/mg or $\text{Log}(10)$ 0.4 pg/mg) are considered censored.

continue or discontinue antidepressants during pregnancy combined with Preventive Cognitive Therapy [32], and an observational cohort [33,34]. The Medical Ethical Committee of the Erasmus Medical Center approved this research project (MEC-2014-505).

Women were recruited during their prenatal booking visit in midwifery practices and hospitals, through general practitioners, or through advertisement in (social) media. Written informed consent was necessary for participation. Women were regularly followed up both during pregnancy and up to three months after delivery. Maternal psychiatric diagnoses were assessed with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (SCID-IV) for all axis I psychiatric disorders (SCID-I) [35]. Interviews were administered by an independent trained interviewer at baseline around 16 weeks pregnancy, and at 14 weeks postpartum. For an overview of all measurements see Fig. 1.

2.2. Inclusion and exclusion criteria

Participants were eligible if they 1) were between 12 and 16 weeks pregnant, and 2) used a Selective Serotonin Reuptake Inhibitor (SSRI), Selective Serotonin and Noradrenalin Reuptake Inhibitor (SNRI), or Tricyclic Antidepressant (TCA) in their first trimester. For the present analyses, additional exclusion criteria for both mothers and infants were insufficient amount of hair necessary for analysis of cortisol, laboratory testing interference, use of locally administered and/or systemic corticosteroids and perinatal complications, including prematurity, as these influence HCC.

2.3. Measures

2.3.1. Dependent variable

2.3.1.1. Hair cortisol concentrations (HCC). HCC were determined from hair strands in both mothers and infants 14.3 (range 11-19) weeks postpartum. All samples were collected according to a similar protocol. In adults, scalp hair has a predictable growth rate of approximately 1 cm per month, making it possible to have an estimate of long-term exposure

to cortisol. When collected three months postpartum, HCC in the proximal 3 cm of maternal hair reflect the maternal HPA axis activity over the first three months after delivery. Most likely, HCC in infants collected at the same time, partly reflect the last part of the third semester during pregnancy and the first period after birth [36]. A small strand of hair was cut from the posterior vertex of the scalp, as close as possible to the scalp. Hair strands were taped to a piece of paper with the scalp end marked, and stored in an envelope at room temperature until further analysis. The proximal 3 cm of maternal hair samples were weighed and minced. For infants, the proximal 3 cm of hair were used; if less than 3 cm hair was available, the length was adjusted. For extraction of cortisol, LC-grade methanol was used at 25 °C, for 18 h, in the presence of labelled glucocorticoids as internal standard. The extraction was centrifuged and cleaned. Cortisol concentrations were quantified by liquid chromatography with tandem mass spectrometry (Waters XEVO-TQ-S system; Waters Corporation, Milford, MA, USA). Lower limit of the measurement interval (LLMI) was set at 2.5 pg/mg. Measurements were reported in picograms per milligram of hair, for the purpose of analysis values were log-transformed ($\text{Log}(10)$) to approach normality.

2.3.2. Primary independent variables

2.3.2.1. Childhood Trauma Questionnaire. Maternal childhood traumatization was assessed with the Childhood Trauma Questionnaire (CTQ-SF) [37], at 24 weeks of pregnancy. The CTQ-SF is a structured 28-item self-report questionnaire. It retrospectively assesses five different types of childhood trauma: emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse. Items are scored on a scale from 1 to 5, resulting in a score per CTQ subscale ranging from 5 to 25. The 3-item minimization/denial scale we did not use in our analyses, since it's mainly used to detect possible underreporting of maltreatment. For each subscale, (different) threshold scores indicate the severity of trauma (none, low, moderate, severe; "none" (Emotional Abuse ≤ 8 , Physical Abuse ≤ 7 , Sexual Abuse ≤ 5 , Emotional Neglect ≤ 9 , Physical Neglect ≤ 7 , CTQ ≤ 36), "low to moderate" (Emotional Abuse >8 and ≤ 12 , Physical Abuse >7 and ≤ 9 , Sexual Abuse >5 and ≤ 7 , Emotional Neglect >9 & ≤ 14 , Physical Neglect >7 and ≤ 9 , CTQ >36 and ≤ 51),

Table 2

Summary of Tobit regression analysis for variables predicting maternal hair cortisol concentrations (HCC).

A) Dependent variable: maternal hair cortisol concentrations (HCC), primary independent variable: Childhood Trauma Questionnaire (CTQ) total score and subscales (emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse); confounding variable: propensity score. N = 89.				
	Unstandardized coefficient	Std. Error	p-value	
1	CTQ total score	.002	.005	.492
2	CTQ total score	.077	.036	.033
	CTQ total score*2	-.001	.000	.040
3	CTQ total score	.076	.033	.021
	CTQ total score*2	-.001	.000	.021
	Propensity score	1.314	.378	<.001
4	CTQ Emotional neglect	1.134	.062	.031
	CTQ Emotional neglect*2	-.005	.002	.062
	Propensity score	1.237	.372	<.001
5	CTQ Emotional abuse	.025	.066	.704
	CTQ Emotional abuse*2	-.002	.003	.524
	Propensity score	1.413	.403	<.001
6	CTQ Physical neglect	.421	.241	.081
	CTQ Physical Neglect*2	-.028	.016	.081
	Propensity score	1.362	.392	<.001
7	CTQ Physical abuse	-.242	.281	.388
	CTQ Physical abuse*2	-.012	.017	.488
	Propensity score	1.381	.414	<.001
8	CTQ Sexual abuse	.717	.386	.063
	CTQ Sexual abuse*2	-.040	.024	.099
	Propensity score	1.103	.386	.004
B) Dependent variable: maternal hair cortisol concentrations (HCC), primary independent variables: Edinburg Postnatal Depression Scale (EPDS) total score, State-Trait Anxiety Inventory (STAI) total score and Everyday Problem Checklist (EPC) total score. N = 89.				
	Unstandardized coefficient	Std. Error	p-value	
1	EPDS (time of hair sampling)	.005	.012	.649
2	EPDS (time of hair sampling)	-.001	.011	.931
	Propensity score	1.337	.435	.002
3	EPDS (pregnancy mean)	-.003	.016	.843
4	EPDS (pregnancy mean)	-.009	.015	.538
	Propensity score	1.351	.399	<.001
1	STAI (pregnancy mean)	.005	.007	.493
2	STAI (pregnancy mean)	.002	.006	.798
	Propensity score	1.313	.400	.001
3	STAI (time of hair sampling)	.004	.005	.380
4	STAI (time of hair sampling)	.002	.004	.650
	Propensity score	1.303	.431	.002
1	EPC (time of hair sampling)	.035	.034	.312
2	EPC (time of hair sampling)	.018	.032	.568
	Propensity score	1.310	.399	.001

“moderate to severe” (Emotional Abuse >12 and ≤ 15, Physical Abuse >9 and ≤ 12, Sexual Abuse >7 and ≤ 12, Emotional Neglect >15 and ≤ 17, Physical Neglect >9 and ≤ 12, CTQ > 51 and ≤ 68), and “severe to extreme” (Emotional Abuse ≥ 16, Physical Abuse ≥ 13, Sexual Abuse ≥ 13, Emotional Neglect ≥ 18, Physical Neglect ≥ 13, CTQ ≥ 69). Participants with a sum score above the threshold of ‘low to moderate’ on one, two, and three or more CTQ subscales were grouped and used in the analyses a proxy of trauma severity besides the CTQ total score. The total CTQ severity score ranges from 25 to 125, with an average score of 38.78 (SD 14.98) in community samples and 45.91 (SD 18.79) in patient samples [38]. Psychometric qualities of the CTQ have been extensively validated, including in a Dutch sample [39].

2.3.2.2. Edinburgh Postnatal Depression Scale. Severity of current depressive symptomatology was assessed with the Edinburgh Postnatal Depression Scale (EPDS) [40], throughout pregnancy (16, 24 and 36 weeks) and postpartum around the time of hair cortisol sampling. The EPDS is a structured 10-item self-report instrument of depression during pregnancy and postpartum. Items have a score of 0-3, resulting in a total score of 0-30. Questions 1, 2 and 4 are scored 0, 1, 2 or 3 with top box scored as 0 (“very often”) and the bottom box scored as 3 (“not at all”); questions 3 and 5-10 are reverse scored, with the top box scored as a 3 (“most of the time”) and the bottom box scored as 0 (“not at all” or “never”).

Cut-off scores of 10-13 have been used in different studies; a value of 11 showed best combined sensitivity and specificity [41]. In this study we used the EPDS score as continuous measure. The Dutch version of the EPDS has been validated and has shown good psychometric qualities for measuring depressive symptoms, also during pregnancy [42,43].

2.3.2.3. State-Trait Anxiety Inventory. Anxiety was assessed with the State-Trait Anxiety Inventory (STAI) [44], throughout pregnancy (16, 24 and 36 weeks) and postpartum around the time of hair cortisol sampling. The original STAI is a 40-item self-report measure of anxiety, measuring both state and trait anxiety. In this study, the six-item short form of the STAI was used (“STAI-6”), containing six items from the state scale. This shortened version of scale utilizes a Likert scale in which each item has four response categories from 1 to 4 (from “not at all” to “very much”). Scores range from 6 to 24. Psychometric qualities of the STAI have been extensively studied and total scores were used in analyses [45].

2.3.2.4. Everyday Problem Checklist. Daily hassles and recent life events were assessed with an adaptation of the Everyday Problem Checklist (EPC) [46], around the time of hair cortisol sampling. The EPC is a self-report checklist, covering recent life events and day-to-day problems in the past two months. Items are rated on a scale from 0 to 4 (ranging from 0 (“I do not mind at all” to 3 “I do mind a lot”) and categorized in 8 subscales (personal, financial, work, family and health problems, time management problems, general concerns and recent life events). Two scores are derived from the EPC: 1) the total number of areas in which the participant experiences problems (scored as y/n in every of the 8 areas) and 2) the sum of the individual item scores. In this study we have used the total number of ‘problem’ areas in the analyses (ranging from 0 to 8).

2.3.3. Potential confounders

Based on theoretical and statistical criteria, the following confounders were included [47]. In mothers: age, marital status, parity, education level, ethnicity (European or Non-European origin), body mass index (BMI), psychotropic medication use, systemic and/or local use of glucocorticoids, use of hormonal contraceptives, smoking (yes or no), timing of cortisol sampling, and hair characteristics (hair color, hair wash frequency, use of hair products on the day of sampling, frequent heavy sweating of the scalp, and hair treatment in the past three months). In infants: timing of cortisol sampling, (gestational) age, birthweight, gender, type of delivery (vaginal/Cesarean), type of feeding (breastfeeding or formula feeding), topical use of glucocorticoids, and hair characteristics.

2.4. Analytic strategy

For all analyses we used the Statistical Package for Social Sciences version 28 (IBM, New York, USA). We presented median HCC for mothers and infants and analysed differences of distribution of HCC between mothers and infants of mothers with and without a lifetime and current depressive or anxiety disorder (based on the SCID-IV) with the Mann-Whitney *U* test and Kruskal-Wallis test. In these analyses, hair

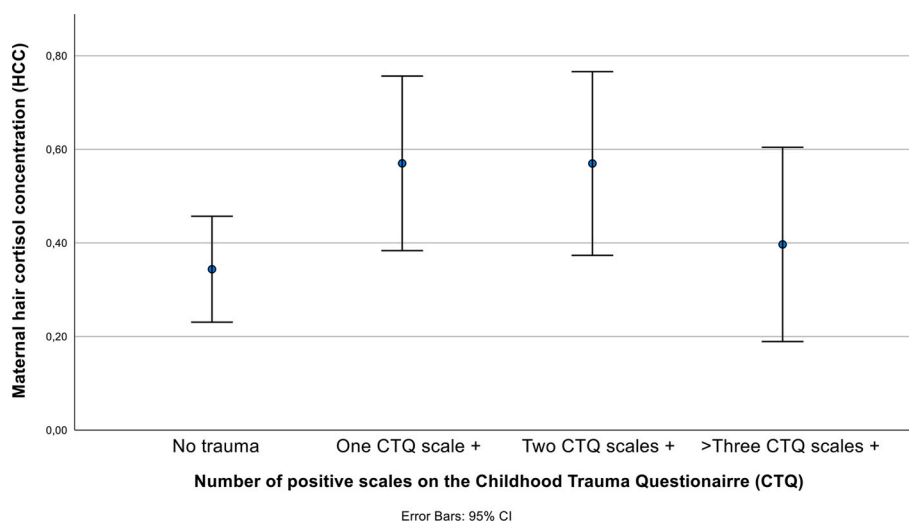


Fig. 2b. Mean hair cortisol concentrations (HCC) in women who reported no childhood trauma ($n = 32$), and women who scored positive on one ($n = 18$), two ($n = 15$) and three or more ($n = 18$) subscales (emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse) of the Childhood Trauma Questionnaire (CTQ) ($N = 83$). Note: HCC below LLOQ ($=2.5$ pg/mg or $\text{Log}(10)$ 0.4 pg/mg) are considered censored.

cortisol values below LLOQ ($= 2.5$ pg/mg) were replaced by value 2.49; sensitivity analyses were performed in which values below 2.5 pg/mg were treated as missing. Hair cortisol values were logtransformed to approach normality.

Maternal hair cortisol data were analysed using a censored regression model (Tobit regression analysis) with a Gaussian distribution. Data below lower limit (2.5 pg/mg) were considered censored. The coefficient in the Tobit regression should be interpreted as the combination of the change of those values below the limit, weighted by the probability of being below the limit; and the change in the probability of being below the limit, weighted by the expected value of HCC if below. Analyses were repeated in a linear regression model by means of a sensitivity analysis. Infant hair cortisol data were analysed using a linear regression model, as hair cortisol data were not censored (no data below LL). Assumptions (linearity, multivariate normality, absence of multicollinearity and homoscedasticity) were checked visually (scatterplots, histograms, Q-Q plots, P-P plots) and statistically (Mardia's test, tolerance, $>.2$ VIF <10 , Durbin-Watson between -2 and 2).

To test if the relationship between maternal and infant hair cortisol concentrations and Childhood Trauma Questionnaire (CTQ), Edinburgh Postnatal Depression Scale (EPDS), State Trait Anxiety Inventory (STAI) and Everyday Problem Checklist (EPC) scores were better characterized by a quadratic rather than a linear equation, all independent variables were regressed on maternal and infant HCC in separate regression models, with and without propensity scores. R-square change statistics were calculated to determine if model fit improved. Test statistics have been added as supplementary material. A significant increase in R-square was found with regards to maternal HCC and CTQ total score, indicating the quadratic (curvilinear) equation characterized the relationship better than the linear model. All other relationships (resp. EPDS, STAI and EPC scores) were better characterized by linear models. Regarding infant HCC all independent variables (CTQ, EPDS, STAI and EPC) were better described in a linear model. We have reported results accordingly.

Correlations between CTQ, EPDS, STAI and EPC were assessed with a Pearson correlation. Range and mean (SD) of all measures were reported. Continuous (total) scores of maternal CTQ, EPDS, STAI and EPC were regressed on maternal and infant HCC: for the EPDS and STAI both pregnancy mean and measurements at the time of cortisol sampling 14 weeks postpartum were regressed on maternal and infant HCC. For in depth analyses of the CTQ subscales continuous (total) scores of each of

five subscales (emotional, physical and sexual abuse and emotional and physical neglect) were regressed on maternal and infant HCC.

Furthermore, HCC of women who scored positive on one or more CTQ-scales (emotional neglect, physical neglect, emotional abuse, physical abuse and sexual abuse) were compared to women that reported no trauma history by comparison of mean HCC with independent T-tests. In infants these differences were not tested due to the smaller number of infants.

To adjust for the effects of other potential confounders, we calculated a propensity score for both mothers and infants including all available confounders as summarized in subheading 'Potential confounders', and included the propensity score as a single covariate in all analyses [48]. Both unadjusted and adjusted results were reported.

For mothers, we reported the coefficient and standard error (SE) of the Tobit regression model; for infants we reported standardized beta (β) and unstandardized B (B) with accompanying standard error (SE) of the linear regression model; for T-tests we reported the t-statistic value, the degrees of freedom (df) and the significance value of the test (p-value). Statistical significance was defined as $p < .05$.

3. Results

3.1. Background and clinical characteristics

Table 1 presents the demographic and clinical characteristics of the sample. In the total sample of 89 women, all mothers fulfilled criteria of a lifetime psychiatric disorder (resp. 75 depressive disorder, 66 anxiety disorder alone) and 53 (59.6%) mothers had comorbid psychiatric disorders (combined depressive and anxiety disorder). Regarding current diagnosis at the time of hair sampling, 4 women fulfilled criteria of a depression and 21 had an anxiety disorder (of whom 2 (2%) women had comorbid current depressive and anxiety disorder). Median HCC in mothers was 4.2 pg/mg (range <2.5 –32.3).

Maternal age at the time of hair sampling was 32.5 years and infant age was 14.3 weeks. At the time of cortisol sampling, 71 mothers used antidepressant medication. In infants, median HCC was 53.8 pg/mg (range 11–220).

3.2. Maternal psychiatric diagnosis and HCC

We did not find differences in distribution of hair cortisol

Table 3

Summary of linear regression analysis for variables predicting infant hair cortisol concentrations (HCC).

A) Dependent variable: infant hair cortisol concentrations (HCC), primary independent variable: maternal Childhood Trauma Questionnaire (CTQ) total score and subscales (emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse), with and without adjustment for propensity score. N = 49.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error				Beta	Lower Bound
1	CTQ total score	-,007	,004	-,289	−2092	,042	−,014	,000
2	CTQ total score	-,008	,003	-,298	−2195	,033	−,015	−,001
	Propensity score	,102	,060	,231	1700	,096	−,019	,222
1	CTQ Emotional neglect	-,023	,010	-,314	−2293	,026	−,043	−,003
	Propensity score	-,021	,010	-,297	−2233	,030	−,041	−,002
2	CTQ Emotional abuse	-,023	,010	-,304	−2211	,032	−,044	−,002
3	Propensity score	-,022	,010	-,291	−2174	,035	−,043	−,002
	CTQ Physical neglect	-,065	,028	-,321	−2344	,023	−,120	,009
	Propensity score	-,062	,027	-,310	−2310	,025	−,117	−,008
4	CTQ Physical abuse	,010	,038	,039	,269	,789	−,065	,086
	Propensity score	,019	,037	,073	,522	,604	−,055	,093
5	CTQ Sexual abuse	,022	,044	,073	,505	,616	−,067	,111
	Propensity score	,003	,045	,009	,059	,953	−,088	,094

B) Dependent variable: infant hair cortisol concentrations (HCC), primary independent variables: maternal hair cortisol concentrations (HCC); maternal Edinburg Postnatal Depression Scale (EPDS) total score during pregnancy and at the time of hair cortisol sampling (14 wks pp), State-Trait Anxiety Inventory (STAI) total score during pregnancy and at the time of hair cortisol sampling, and Everyday Problem Checklist (EPC) total score at the time of hair sampling. N = 49.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error				Beta	Lower Bound
1	Maternal hair cortisol concentrations	-,021	,109	-,029	−,194	,847	−,242	,199
2	Maternal hair cortisol concentrations	,014	,095	,019	,149	,882	−,177	,205
	Propensity score	1010	,250	,527	4047	<,001	,507	1513
1	EPDS (pregnancy mean)	-,006	,013	-,073	−,480	,633	−,032	,020
2	EPDS (pregnancy mean)	-,009	,011	-,101	−,788	,441	−,031	,014
	Propensity score	1034	,252	,534	4099	<,001	,525	1543
1	EPDS (time of hair sampling)	-,001	,010	-,015	−,107	,915	−,022	,019
2	EPDS (time of hair sampling)	-,001	,010	-,010	−,072	,943	−,021	,019
	Propensity score	,112	,063	,247	1786	,080	−,014	,238
1	STAI (pregnancy mean)	,005	,006	,135	,893	,377	−,007	,018
2	STAI (pregnancy mean)	,002	,005	,048	,363	,718	−,009	,013
	Propensity score	1008	,257	,520	3923	<,001	,489	1526
1	STAI (time of hair sampling)	-,003	,004	-,108	−,713	,480	−,010	,005
2	STAI (time of hair sampling)	-,005	,003	-,209	−1618	,113	−,011	,004
	Propensity score	1081	,247	,566	4384	<,001	,583	1578
1	EPC	-,030	,026	-,173	−1167	,249	−,083	,022
2	EPC	-,022	,023	-,128	−,996	,325	−,068	,023
	Propensity score	,985	,247	,514	3993	<,001	,488	1483

concentrations of mothers and infants based on current and lifetime diagnosis of depression (y/n) and anxiety disorders (y/n), nor for comorbid disorders. HCC were not significantly different in mothers with a current depressive disorder ($n = 4$, $U = 161.5$, $p = .871$) or a history of a depressive disorder ($n = 75$, $U = 660.5$, $p = .127$), nor in infants (current maternal depression $U = 25.0$, $p = .310$; maternal history of depression $U = 108.0$, $p = .541$). No differences were found between mothers with a current anxiety disorder ($n = 21$, $U = 762.0$, $p = .639$) and with a history of anxiety disorder ($n = 66$, $U = 708.0$, $p = .632$), nor in infants (current maternal anxiety disorder $U = 281.0$, $p = .170$; maternal history of anxiety disorder $U = 277.0$, $p = .633$). HCC were neither different across subgroups of depression alone, anxiety alone, and comorbid depression and anxiety (mothers $n = 89$, Chi square = 2.6, $p = .454$, $df = 3$; infants $n = 49$, Chi square 0.5, $p = .772$, $df = 2$). Sensitivity analyses did not show different results.

3.3. Maternal childhood traumatization, current depressive and anxiety symptoms, recent life events and HCC in mothers and infants

3.3.1. Mothers

Childhood Trauma Questionnaire (CTQ) total score was correlated with pregnancy mean of the Edinburgh Postnatal Depression Scale (EPDS) ($r(83) = 0.245$, $p = .026$), and showed a correlation at trend level with pregnancy mean of the State Trait Anxiety Inventory (STAI) ($r(83)$

$= 0.209$, $p = .058$). CTQ total score was correlated with EPDS total score ($r(82) = 0.392$, $p < .001$), STAI state score ($r(82) = 0.450$, $p < .001$) and Every Problem Checklist (EPC) total score ($r(89) = 0.325$, $p = .003$) at the time of cortisol sampling 14 weeks postpartum.

In mothers, a curvilinear (inverted U) association was found between maternal childhood trauma (CTQ total score) and HCC, both unadjusted and adjusted for identified covariates. Results are displayed in Fig. 2a. No association was found between depressive symptoms during pregnancy (EPDS pregnancy mean) and depressive symptoms at the time of cortisol sampling (EPDS total score 14 weeks after delivery), nor between anxiety symptoms during pregnancy (STAI pregnancy mean) and anxiety at the time of cortisol sampling (STAI total score at cortisol sampling). Recent life events (EPC total score at cortisol sampling) and HCC did not show an association. Table 2 presents Tobit regression analysis results for all variables (CTQ, EPDS, STAI and EPC) predicting maternal HCC.

3.3.1.1. CTQ subscales. Five different subscales of the CTQ were assessed in relationship to maternal HCC (Table 2A). In mothers, a curvilinear (inverted U) association was found between emotional neglect and HCC. For physical neglect and sexual abuse the same (inverted U) association was found at trend level. No relationship was found for emotional and physical abuse.

HCC of mothers who scored positive on one, two, three or more CTQ

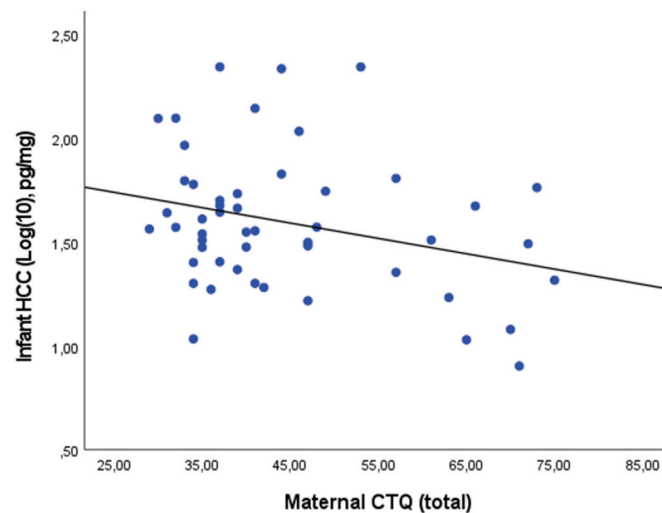


Fig. 3. Scatterplot of the hair cortisol concentrations (HCC) and the maternal total score on the Childhood Trauma Questionnaire (CTQ) in infants (N = 49).

subscales were compared to mothers that did not report childhood trauma. There was a significant increase of HCC in women that reported traumatic experiences on one CTQ subscale ($n = 18$, $M = 0.570$, $SD = 0.375$; $t(18) = -2.168$, $p = .019$) or two subscales ($n = 15$, $M = 0.569$, $SD = 0.354$, $t(15) = -2.111$, $p = .023$) compared to women that reported no trauma ($n = 32$, $M = 0.343$, $SD = 0.313$). In women that reported traumatic experiences on three or more CTQ subscales ($n = 18$, $M = 0.396$, $SD = 0.417$), no significant difference was found in HCC compared to women that reported no trauma ($t(18) = -0.469$, $p = .321$). Results are displayed in Fig. 2b.

3.3.2. Infants

Table 3 presents linear regression analysis results for all variables predicting infant HCC.

In infants, data revealed a negative linear relationship between maternal childhood trauma (CTQ total score) and HCC, when adjusted for potential covariates (Fig. 3). No associations were found with maternal prenatal and current depressive symptoms (EPDS pregnancy mean and EPDS total score at the time of cortisol sampling), prenatal and current anxiety symptomatology (STAI pregnancy mean and at the time of cortisol sampling) nor with recent life events (EPC total score). No association was found between maternal and infant HCC.

3.3.2.1. CTQ subscales. Analyses showed a significant negative linear relationship between maternal emotional neglect and infant HCC, and between emotional abuse and infant HCC at trend level (Table 3). No relationship was found between HCC and physical and sexual abuse and neglect.

4. Discussion

The aim of this study was to explore maternal childhood trauma, lifetime and current depressive and/or anxiety diagnoses and comorbidity, and recent life stressors in relation to long-term systemic cortisol levels, measured in scalp hair, in an at-risk group of mothers with lifetime depressive and/or anxiety disorders and their infants three months after birth. We found an association between maternal experiences of childhood trauma, on the one hand, and maternal and infant hair cortisol concentrations (HCC), on the other. No significant associations were observed between HCC and maternal depressive and anxiety symptoms throughout pregnancy and at the time of cortisol sampling after birth or with recent life events. Infant HCC was not associated with maternal HCC in this sample. Our results might suggest that a maternal

history of childhood traumatization is an independent transgenerational factor of HPA-axis functioning in both mothers and their offspring.

Maternal hair cortisol shows a positive curvilinear relationship with childhood trauma. In mothers who pass the threshold of significant trauma, we see that women subjected to mild to moderate childhood trauma show relatively higher cortisol concentrations, whereas women subjected to the most severe forms of trauma show lower hair cortisol, comparable to or slightly lower than women with no history of trauma. Although we have to be cautious given that this is a small sample size, it suggests that cortisol varies in relation to severity of traumatization. Our findings are in line with previous studies in adults, suggesting that childhood trauma and adversity probably contribute to environmental programming of the HPA axis and appear to be important factors associated with long-term cortisol secretion [49], although not all studies concur [50].

We speculate that the curvilinearity of the relationship between childhood trauma and HCC we found, might suggest that childhood trauma exposure is moderating the association between depression, anxiety, and recent life events, although we had insufficient power to perform a formal moderation analysis. Our findings are in line with ‘The Adaptive Calibration Model’ of stress reactivity, as has been extensively elaborated by Del Giudice and co-authors [51]. This is an evolutionary-developmental model, that distinguishes different stress reactivity profiles that are adaptive in different environmental contexts. The authors propose identify four patterns of reactivity: 1) a sensitive pattern (in which HPA reactivity is expected to be high, with moderate basal activity; as a highly responsive HPA promotes sensitivity to social feedback and the mobilization of metabolic and psychological resources; most often promoted by highly supportive environments); 2) a buffered pattern (with moderate HPA reactivity and moderate basal activity; which develops under conditions of moderate environmental stress, where they strike a balance between the costs and benefits of reactivity); 3) a vigilant pattern (with high HPA reactivity and moderate to high basal activity, which develops in stressful contexts, where people need to cope effectively with dangers and threats) and 4) the unemotional pattern (low HPA reactivity and low basal activity, which develops at the high-risk end of the environmental spectrum to respond in biologically adaptive ways to harsh and unsupportive (family) environments).

The finding that the most traumatized women in our sample showed lower HCC, could mean that reactivity to stress is diminished or absent (“the unemotional pattern”). This also corresponds with animal studies that found that severe and chronic stress by traumatization over time

leads to glucocorticoid receptor desensitization and ultimately to a relative hypocortisolism at the cellular level, caused by and causing exhaustion of the HPA axis [52]. In psychiatric populations the ‘sum’ of the (psychiatric) adversity, including childhood trauma, an early age of onset of psychiatric disease and more recurring episodes, can eventually lead to relatively lower cortisol output, no matter how stressful life circumstances might become [23]. We hypothesize this is prognostic for poorer clinical outcomes.

A relatively new observation is the negative association we found between maternal childhood trauma and HCC in three-month-old infants. As maternal depressive and anxiety symptoms nor recent life events affect infant HCC, this suggests that the transgenerational effect of trauma influences the (developing) infant HPA axis more prominently. This is in line with early findings in infant salivary cortisol from traumatized mothers [53] and more recently with findings in hair cortisol in newborns [54]. The latter study found a gene interaction (*FKBP5*, (modulating glucocorticoid receptor activity) × environment (maltreatment load)) on hair cortisol in mothers and newborn infants, showing a negative relationship between maternal childhood maltreatment and newborn HCC. The latter study was conducted in a community sample with relatively low trauma scores (mean CTQ sum score was <35; comparable to community means, whereas in our sample mean CTQ score was >45, in line with findings from clinical populations) [38]. Findings in infants concur with ours. In mothers, the authors describe a positive relationship between trauma and HCC, where we found a curvilinear (inverted U) relationship. These results are partly comparable, expect for the fact that we found a sharp decrease of cortisol values in individuals with the highest CTQ-scores. Probably, as mean CTQ-scores in the community sample were lower, the most severely affected women (with possibly lower HCC), were less represented in the community sample.

In depth analyses of the type of trauma in our study shows that specifically emotional and physical neglect seem to impact hair cortisol in both mothers and infants. This could mean that abusive ‘acts of omission’ (i.e., unmet basic emotional needs) have greater (transgenerational) impact. Emotional neglect and abuse are also the most prevalent forms of trauma in psychiatric populations [55], as well as in this specific sample. Long-term longitudinal data show that specifically emotional abuse and neglect are associated with a wide range of long-term adverse health outcomes (including psychiatric disorders) [31]. Other studies found a relationship between physical and sexual abuse and (adult) hair cortisol, mostly with increased values [56,57]. Possibly we did not have enough statistical power to find strong(er) relationships with other – less prevalent – forms of abuse in our sample, although sexual abuse showed a trend towards a positive association with maternal HCC.

The fact that different forms of abuse are related to another direction of cortisol values corresponds with a model proposed by McLaughlin and co-authors that aims to differentiate between childhood experiences of *threat* (e.g. threat, harm, physical abuse) and *deprivation* (involving the absence of expected needs from the environment), as they appear to disrupt (emotional) learning in different ways – possibly associated with other stress reactivity profiles - that are associated with different developmental outcomes [58].

Diagnosis of depression and/or anxiety disorders, both lifetime and current, as well as severity of depressive or anxiety symptoms, were not associated with maternal or infant HCC. This is in line with systematic reviews [25,59]. With regards to a history of a depressive disorder, we found a trend towards higher cortisol values; this was not supported by the sensitivity analyses. In a previous study of our group we found a positive relationship between maternal general symptom severity and infant hair cortisol shortly after birth ([27]), but psychopathology in that sample was more heterogenic and severe than in the current study and we were not able to correct for childhood trauma. A recent study on the effect of maternal perinatal depression and anxiety on infant HCC at 12 months of age did not find a direct effect of maternal

symptomatology either [26]. The authors did find a correlation with decreased infant cortisol reactivity during a separation task, which is in line with a previous study of our group ([60]). One of the proposed causal mechanisms is that parental psychopathology influences infant stress reactivity by parental care, as psychopathology has often been identified as a risk factor for parenting impairment and infant attachment disorganization [61,62]. In animal studies, it has been shown that differences in maternal care behavior can result in alterations of DNA methylation in rat pups, providing evidence for environmental programming of the HPA axis in offspring [63].

In our sample, childhood trauma, depression, anxiety and recent life events did show a mutual positive association. It has often been established that childhood trauma is a risk factor for the development of psychopathology [64]. This is in line with the sensitization hypothesis which proposes that childhood adversity can increase the consequences of exposure to adversity in adulthood, by disrupting stress physiology and consequently increase the risk for development of psychiatric disorders ([65]. But childhood trauma and psychopathology do not seem to affect HPA axis function to the same extent, as we did not find a relationship between current psychopathology and HCC.

4.1. Strengths and limitations

Strengths of our study include the clinical sample that allowed us to assess the influence of different risk factors in an at-risk population of (formerly) depressed and anxious woman and their infants. Other strengths include the availability of detailed and reliable diagnostic information and information about different sources of influence (childhood trauma, current depressive and anxiety symptoms and recent life events), as well as the non-invasive measurement of (chronic) stress in hair performed with the state-of-the-art liquid chromatography with tandem mass spectrometry, and the availability of information about a wide range of covariates. Our study also had several limitations. A majority of women used antidepressant medication which we could not properly control for. Also, a relatively small group of women met criteria of a current depressive or anxiety disorder, in comparison to lifetime disorders. Additionally, we could not control for the presence of personality disorders. Second, LC-MS/MS analysis of hair cortisol resulted in a (left) truncated dataset, which might have affected hair cortisol results in mothers, but not in infants. Sensitivity analyses did not reveal significant difference of results. Third, experiences of maternal childhood trauma were assessed with the CTQ, which is a retrospective self-report measure; it does not assess recent or ongoing trauma so we cannot rule out their influence. Fourth, within the scope of the current study it was not possible to assess consequences on parent child-interaction or infant behavior. Fifth, there might be confounders (measured and unmeasured) we could not control for because of the sample size. It is possible analyses were underpowered. Additionally, curvilinear models are more susceptible to outlying data in a smaller samples. Studies in larger samples have to make clear if the results can be replicated. Lastly, we present an exploratory analysis, therefore we were not able to justify the sample size *a priori*. A post-hoc power analysis showed that the sizes of our samples enabled us to show small to medium sized effects of the relationship between childhood trauma and HCC in mothers ($f^2 = 0.09$), and medium effect sizes in infants ($f^2 = 0.17$) taking confounding variables into account (5% significance level, power of 80%, two-sided test).

4.2. Conclusion

To our knowledge, this study represents a unique combination of parameters of maternal mental health in the peripartum period. This allowed us to examine prospectively the influence of different possible influences impacting the (developing) HPA-axis in mothers and infants. Our explorative study suggests that a history of maternal childhood trauma is of influence on HPA-axis functioning in both mothers and young infants, whereas we did not see the same for current and lifetime

depressive and anxiety disorders or recent life events. As infants of mothers with psychopathology are at increased risk for later psychiatric disease, Future studies are needed to elucidate the effect of (epi-)genetics, psychopathology, parenting, and other risk factors on cortisol metabolism.

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CRediT author contribution statement

Carlinde W. Broeks: Conceptualization, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. Nina Molenaar: Conceptualization, Data curation, Methodology, Conceptualization, Data curation, Methodology, Writing - review & editing. Marlies Brouwer: Writing - review & editing. Erica L.T. van den Akker: Methodology, writing - review & editing. Elisabeth F.C. van Rossum: Methodology, writing - review & editing. Rien Van: Writing - review & editing. Sjoerd A.A. van den Berg: Methodology, writing - review & editing. Manon Hillegers: Writing - review & editing. Witte Hoogendijk: Writing - review & editing. Huibert Burger: Writing - review & editing. Claudi Bockting: Writing - review & editing. Astrid Kamperman: Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing - review & editing. Mijke Lambregtse-Van den Berg: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Writing - review & editing.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cpnec.2023.100167>.

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