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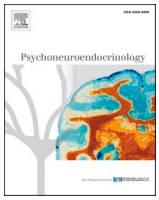

The association between maternal symptoms of depression and hair glucocorticoids in infants across the perinatal period

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ABSTRACT

Background: Maternal symptoms of depression constitute an early adversity for infants that is considered to exert its effects via the maternal-placental-fetal neuroendocrine axis. Previous research implicates associations between maternal prenatal symptoms of depression and infants' glucocorticoid (GC) levels shortly after birth. To date, associations have not been investigated in the early postnatal period. The current study aimed to investigate the influence of maternal perinatal symptoms of depression on infants' neonatal and postnatal hair GCs providing a retrospective reflection of integrated cortisol secretion in the intrauterine and early postnatal period, respectively.

Methods: As part of a prospective cohort study, hair samples of infants were taken up to two weeks after delivery ($N = 152$) and again eight weeks after delivery ($N = 165$). Liquid chromatography-tandem mass spectrometry was used to determine hair cortisol and cortisone in scalp-near 2-cm hair segments. Maternal symptoms of depression were assessed during pregnancy and eight weeks postnatally based on the Edinburgh Postnatal Depression Scale.

Results: Higher maternal prenatal symptoms of depression showed a significant association with higher infants' neonatal hair cortisol, when controlling for confounding variables (i.e., gestational age, mode of delivery, parity, storage time, pregnancy complications). A non-significant trend for this effect was found for the hair cortisol-to-cortisone ratio while no effect occurred for hair cortisone. No association of maternal postnatal symptoms of depression with infants' postnatal hair GCs was observed. Further exploratory analyses revealed no relationship between a change of maternal prenatal to postnatal symptoms of depression with the change from infants' neonatal to postnatal hair GC levels or postnatal hair GCs.

Conclusion: Our results suggest that maternal prenatal symptoms of depression are associated with dysregulated infants' hair cortisol levels mainly incorporated in the intrauterine period which, in turn, might contribute to increased susceptibility for later diseases. However, no relationship was observed in infants' hair samples additionally reflecting hair GCs of the early postnatal period. Future studies should consider research on associations between maternal symptoms of depression and infants' hair GCs also later in life and take into account additional risk factors with potential impacts on GC secretion during early infancy.

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1. Introduction

Prevalence rates for maternal depressive disorders during pregnancy range from 4% to 20%, with a symptom peak at the end of the third trimester (Melville et al., 2010; Smith et al., 2020). Depressive symptoms not merely have a major impact on the mother, but on the infant as well. Exposure to prenatal depression is considered a form of early adversity that is associated with birth-related outcomes (e.g., preterm birth, low birth weight: Jarde et al., 2016), and long-term behavioral, physiological, and biochemical outcomes in the offspring (e.g., Junge et al., 2017; Petzoldt et al., 2016; Stroud et al., 2014).

A large body of evidence indicates that symptoms of depression are associated with the functioning of the hypothalamic-pituitary-adrenal (HPA) axis including the secretion of glucocorticoid hormones (e.g., cortisol, cortisone) as its end products, in both pregnant and non-pregnant samples (meta-analyses: Gelman et al., 2015; Kennis et al., 2020). In expectant mothers, symptoms of depression seem to exert its effects on the fetus via the maternal-placental-fetal neuroendocrine axis (Glover, 2015; Wadhwa, 2005), affecting the offspring's long-term HPA axis regulation (Hollanders et al., 2017; Laurent, 2017). Specifically, it is assumed that exposure to stress or high levels of glucocorticoids (GCs) in the perinatal period or during early stages of life might "programme" HPA axis activity in offspring (Welberg and Seckl, 2001). Research suggests different pathways by which the fetal programming effects of elevated maternal cortisol may be regulated (review: Entringer et al., 2015). One plausible pathway is increased production of the placental corticotrophin-releasing hormone (CRH), which is known to affect the fetal HPA axis and thus the biosynthesis of adrenal steroids. Another plausible pathway constitutes the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) that converts cortisol in its inactive form cortisone and serves as a partial barrier for maternal cortisol to pass the placenta (review: Entringer et al., 2015).

Previous prospective research on the association between perinatal depression and neonatal cortisol is predominantly based on traditional cortisol measurements via plasma, urine, or saliva (Meyer and Novak, 2020). Specifically, previous results indicate that second and third trimester depressive symptoms are associated with elevated urinary baseline cortisol levels in the newborn within few days after delivery (Diego et al., 2004; Field et al., 2004; Lundy et al., 1999). Furthermore, Brennan et al. (2008) found a positive association between retrospectively assessed maternal prenatal depression and infant salivary cortisol reactivity in response to induced stress six months after birth. Additionally, research suggests maternal postnatal depression as a potent predictor of infant's cortisol levels at a later developmental stage. Specifically, positive associations with infants' cortisol levels were found in childhood (Ashman et al., 2002), adolescence (Halligan et al., 2004), as well as adulthood (Douglas and Harmer, 2011), suggesting that early adverse experiences might affect GC levels later in life (Hollanders et al., 2017). However, traditional cortisol assessment methods are highly vulnerable to situational and physiological factors (e.g., food intake, illness), show typical daily fluctuations, and thus are considered mainly useful for short-term measures of cortisol (meta-analysis: Stalder et al., 2017). In contrast, the analysis of hair GCs constitutes a valuable tool for the retrospective assessment of cumulated GC secretion over an extended period of time (Meyer and Novak, 2020; meta-analysis: Stalder et al., 2017) and initial research supports the unique potential of this method to reflect GC regulation across the perinatal period in offspring. Specifically, levels of neonatal hair cortisol were observed to mainly reflect the third trimester increase of maternal cortisol while some weeks after childbirth, neonatal hair cortisol was found to decrease sharply and have been shown to mirror both intra- and extrauterine periods of GC regulation (Hollanders et al., 2017).

To date, only few studies have been conducted on the association between perinatal depression and infants' hair GC levels. In a study based on a clinical sample, Broeks et al. (2021) found a positive association between the severity of maternal perinatal symptoms of depression and infants' hair cortisol levels at six weeks postnatally reflecting a combination of the last trimester of pregnancy as well as the early postnatal period. In contrast, van der Voorn et al. (2018) found a negative association between maternal prenatal symptoms of depression and infants' neonatal hair cortisol levels after birth based on a predominantly clinical sample. Interestingly, the highest decrease in hair GCs was found in newborns being persistently exposed to maternal stress associated with chronic depressiveness. Another study based on a community-sample did not find a relationship between prenatal symptoms of depression and infants' neonatal hair cortisol after birth (Romero-Gonzalez et al., 2018).

Besides focusing on the relationship between prenatal maternal depressive symptomatolgy and GC levels mainly reflecting the intrauterine period, the association between maternal depressive symptoms and offspring' GC levels may persist after delivery and might be additionally influenced by the extrauterine period (Hollanders et al., 2017). Specifically, it is conceivable that postnatal factors that are related with depressive symptoms such as caregiving behavior (e.g., lack of maternal sensitivity and responsiveness, lower positive engagement synchrony: Bleker et al., 2020; Maughan et al., 2007; Tarullo et al., 2017) and physiological factors (e.g., breastfeeding, sleep) might be related to infants' HPA axis activity (Flom et al., 2017). Therefore, it is conceivable that maternal depressive symptoms in the postnatal period may additionally affect the newborn which may contribute to altered long-term integrated GC secretion. Promising evidence for this notion stems from one study showing a positive correlation between mothers' postnatal depressive symptoms four weeks and one year after delivery and hair cortisol in their 1-year-old infants in a community-based sample (Palmer et al., 2013).

This study aims to extend previous knowledge on the associations between prenatal and postnatal symptoms of maternal depression and corresponding long-term integrated GC levels in offspring by using hair analyses. In addition to cortisol and cortisone we included the hair cortisol-to-cortisone ratio as an estimate of 11β-HSD2 activity that converts cortisol into cortisone. We hypothesize a relationship between maternal prenatal symptoms of depression and infants' neonatal hair GCs, reflecting mainly the intrauterine period. No direction of association is postulated given heterogenous results in prior literature (Broeks et al., 2021; Palmer et al., 2013; van der Voorn et al., 2018). Furthermore, we assume a relationship between maternal postnatal symptoms of depression and infants' postnatal hair GCs additionally reflecting the extrauterine period including the potential influence of a depression-affected environment. Since this is one of the first studies focusing on the early postnatal period, no direction of association is postulated. Finally, we set out to exploratively investigate associations between the change in maternal symptoms of depression from pregnancy to the early postnatal period and change in hair GCs in infants.

2. Methods

2.1. Study design and participants

The present study is part of the prospective cohort study "Dresden Study on Parenting, Work, and Mental Health (**DREAM**; "**DR**esdner Studie zu **E**lternschaft, **A**rbeit und **M**entaler Gesundheit") that aims to investigate the interplay between work, stress, and health-related factors as well as intergenerational influences on somatic and mental health. The DREAM study examines (expectant) mothers as well as their partners and the offspring with currently six measurement points from pregnancy up to at least 4.5 years postnatally (T1 DREAM – T6 DREAM). Using a multi-method approach, the DREAM study comprises additional sub-studies. The sub-study $DREAM_{HAIR}$ aims to investigate the complex relationships between psychological stress, long-term steroid hormone levels, and mental health-related outcomes during pregnancy up to 4.5 years postnatally (T1 $DREAM_{HAIR}$ – T6 $DREAM_{HAIR}$). For further details regarding the DREAM study, see Kress et al. (2019). Study data are

collected and managed using Research Electronic Data Capture (REDCap; Harris et al., 2009, 2019). REDCap is a secure, web-based application designed to support data capture for research studies, hosted at the "Koordinierungszentrum für Klinische Studien" at the Faculty of Medicine of the Technische Universität Dresden, Germany. Ethical approval of the DREAM study was received by the Ethics Committee of the Faculty of Medicine of the Technische Universität Dresden (No: EK 278062015). During the recruitment process, participants had to sign a declaration of consent for DREAM and $DREAM_{HAIR}$ separately.

The present study focuses on data of mothers and newborns with the following measurement points: Questionnaire-derived data from T1 DREAM (during pregnancy) and T2 DREAM (eight weeks after the anticipated birth date) as well as hair samples and an additional hair-related questionnaire from T1 $DREAM_{HAIR}$ (during pregnancy), T1 $DREAM_{HAIR\text{-}BABY}$ (within the first two weeks after birth), T2 $DREAM_{HAIR\text{-}BABY}$ (eight weeks after the anticipated birth date; for details, see Fig. 1).

For the basic DREAM study, eligible families were recruited mainly in obstetrical clinics or midwife practices. Participants received T1 DREAM questionnaires during pregnancy. Expectant mothers, who were enrolled in the basic DREAM study and had completed T1 DREAM, were recruited for $DREAM_{HAIR}$ via a telephone screening. For T1 $DREAM_{HAIR}$ hair samples of eligible expectant mothers were taken shortly before the anticipated date of birth (4 ± 2 weeks prenatally). The aim was to take infants' hair samples up to two weeks after delivery, mainly reflecting intrauterine hair GCs (Hollanders et al., 2017). Eight weeks after the anticipated birth date, mothers received T2 DREAM questionnaires. Likewise, for T2 $DREAM_{HAIR}$, hair samples of mothers as well as newborns were taken eight weeks after the anticipated birth date. At the respective first measurement point, hair samples were taken by trained staff. At the respective second measurement point, hair samples were taken by participants.

General inclusion criteria for the basic DREAM study were a current pregnancy, sufficient German skills to complete the questionnaires, and being a resident in the area in and around Dresden. For the present investigation, infants were excluded due to maternal conditions, considering potential intrauterine effects on newborns' HPA axis activity (e.g., Stroud et al., 2014). Specifically, inclusion criteria were not being pregnant with twins or multiples, no intake of psychotropic drugs (including alcohol consumption on a regular basis), no serious physical disease over the last five years (e.g., multiple sclerosis or cancer), and no use of GC containing medication in the last three months as well as no smoking during pregnancy (Wells et al., 2014). In line with this, our final sample for each hair GC consisted of two sub-samples for either the neonatal or postnatal investigation depending on the availibility of usable hair samples (for details, see Fig. 2).

Additionally, we only included infants without serious diseases (e.g., brain bleeding), when hair samples were collected in time (current study: T1 $DREAM_{HAIR\text{-}BABY}$ = within the first 2 ± 1 weeks after delivery; T2 $DREAM_{HAIR\text{-}BABY}$ = 9 ± 3 weeks after delivery), hair samples had been sent to the laboratory by then, and laboratory analyses were possible (e.g., due to sufficient hair mass). For the sub-sample including hair samples at T2 $DREAM_{HAIR\text{-}BABY}$ we further only included infants whose mothers returned T2 DREAM and completed the relevant questionnaires. The samples for hair cortisol consisted of $N = 154$ infants for the sub-sample including T1 $DREAM_{HAIR\text{-}BABY}$ and $N = 167$ infants for the sub-sample including T2 $DREAM_{HAIR\text{-}BABY}$. N varied slightly between different analyses and different hair GCs due to missing data.

Dropout analyses were conducted for sociodemographic characterisics, hair-related characteristics, and predictor variables, using Welch-Test and Fisher's exact test. Completers were defined as mother-infant dyads that fulfilled inclusion criteria and participated at T1 DREAM, T1 $DREAM_{HAIR\text{-}BABY}$, T2 DREAM, and T2 $DREAM_{HAIR\text{-}BABY}$. They were compared to non-completers, who fulfilled inclusion criteria as well and participated only at T1 DREAM and T1 $DREAM_{HAIR\text{-}BABY}$. Except for maternal education, completers and non-completers did not differ (p's $> .32$). Specifically, completers were more likely to go to school for more than 10 years compared to non-completers (87.8% vs. 68.2%, Fisher's exact test, $p = .02$).

2.2. Measures

2.2.1. Sociodemographic, psychological, and hair-related measures

Sociodemographic characteristics relevant for the current investigation were derived from the basic DREAM study. Regarding mothers, we included information on age, marital status, parity, education, gestational week, and lifetime depression. In terms of infants' sociodemographic characteristics, we included information on sex, birth weight, and gestational age at birth.

Mode of delivery was assessed at T2 DREAM by means of maternity records ("Mutterpass"; Gemeinsamer Bundesausschuss, 2015). Based on six categories (i.e., spontaneous vaginal birth, vaginal birth induced by drugs, vaginal operative birth, planned caesarean section for personal reasons, planned caesarean section for medical reasons, unplanned caesarean section) we computed a dichotomous variable specifying whether a caesarean section had occurred or not.

Within the sub-study $DREAM_{HAIR}$, hair characteristics as well as health-related factors were assessed using an in-house questionnaire in order to identify potential confounding variables on hair GCs (e.g., hair treatments, washes per week, medication; meta-analysis: Stalder et al., 2017). Mothers had to complete the hair protocol at each of the measurement points for themselves as well as for their infant.

In order to assess maternal depressive symptoms prenatally (T1 DREAM) as well as postnatally (T2 DREAM) the German version of the Edinburgh Postnatal Depression Scale (EPDS; Bergant et al., 1998; Cox et al., 1987) was used. The EPDS is a 10-item self-report scale that evaluates depressive symptoms during the past seven days on a four-point scale from *zero* to *three*, with a total score ranging from 0 to

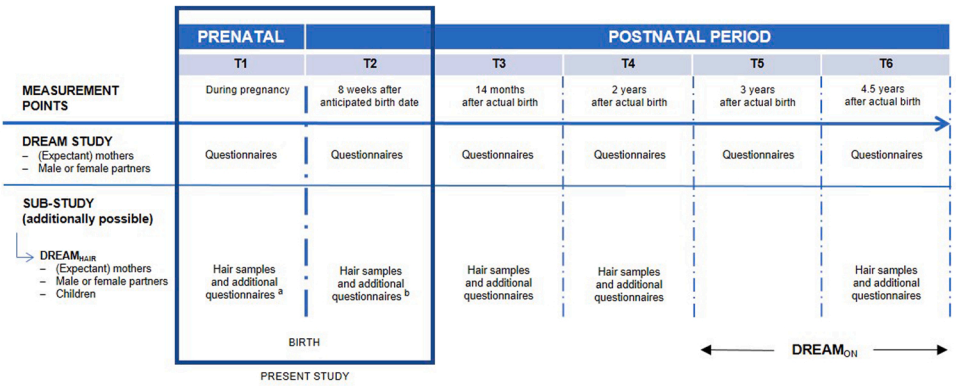

Fig. 1. Assessment waves of the DREAM study. At T1 $DREAM_{HAIR}$ hair samples and additional questionnaires (e.g., sociodemographic data, EPDS) were obtained 4 ± 2 weeks before the anticipated birth date for the mothers and within the first two weeks after birth for the babies (i.e., T1 $DREAM\text{-}_{HAIR\text{-}BABY}$). At T2 $DREAM_{HAIR\text{-}BABY}$ hair samples and additional questionnaires were obtained for the babies. T2 $DREAM_{HAIR\text{-}BABY}$ aligned with the DREAM study measurement point and questionnaires (e.g., birth-related questions, EPDS) eight weeks after the anticipated birth date. .

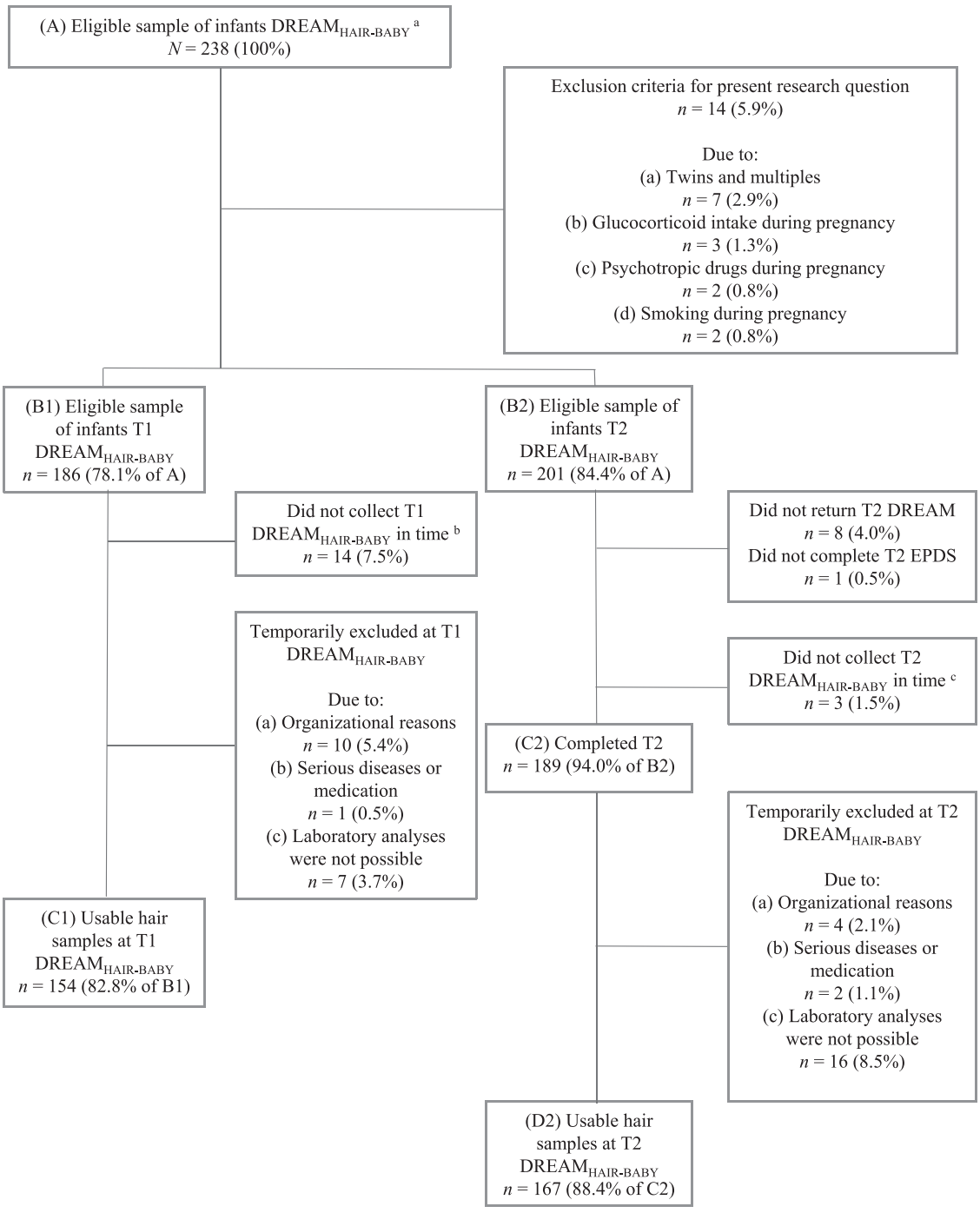

Fig. 2. Flowchart of retention rate and exclusion criteria resulting in the final hair cortisol sample. *Note.* T1 DREAM$_{HAIR-BABY}$ = within first two weeks after birth; T2 DREAM & T2 DREAM$_{HAIR-BABY}$ = eight weeks after anticipated birth date. Data until end of February 2020 (prospective data collection ongoing). [a] T1 and/or T2 DREAM$_{HAIR-BABY}$ is potentially available. [b] Current study = within three weeks after delivery. [c] Current study = 9 ± 3 weeks after delivery.

30. Higher symptoms indicate stronger symptom severity. For the sample description, we used the most frequently used cutoff score of ≥ 10 for minor and ≥ 13 for major depression (Bergant et al., 1998; Cox et al., 1987). Originally developed to assess postnatal depressive symptoms, the EPDS has been validated as an instrument for prenatal depression as well (e.g., Bergink et al., 2011). Within the current investigation, the EPDS revealed good reliabilities of α ≥ 0.80 for the measurement points T1 DREAM and T2 DREAM in both sub-samples.

2.2.2. Hair steroid analyses

Hair strands were taken scalp-near from the posterior vertex of the head, if possible. Hair samples were stored in a dry and dark place at room temperature in aluminum foil and were sent to the Institute of Biological Psychology of the Technische Universität Dresden in two batches (storage time: *M* = 45.75 weeks, *SD* = 15.76, Range = 16–77). Besides hair cortisol (HairF), hair cortisone (HairE) was determined as a more robust estimate of GC regulation (Perogamvros et al., 2010; Stalder et al., 2013) and the HairF/HairE ratio was calculated.. Laboratory analyses were performed via liquid chromatography-tandem mass spectrometry (LC–MS/MS analysis) according to the published protocol provided in Gao et al. (2013), demonstrating high sensitivity, reliability, and specificity.

Table 1
Sample characteristics of the sub-sample for investigating associations with postnatal HairF ($N = 165$).

Variables	*n* (%) or Mean ± *SD* (Range)
Infant	
Sociodemographic characteristics	
Sex[c]	
Male (*n, %*)	74 (44.80)
Female (*n, %*)	91 (55.20)
Birth weight (g; *M, SD*, Range)[c]	3451.45 ± 470.24 (2400–4890)
Gestational age at birth (weeks; *M, SD*, Range)[c]	39.99 ± 1.06 (36.71–42)
Hair GCs	
HairF (T1; pg/mg; *M, SD*, Range)[b]	384.49 ± 223.18 (59.85–1498.50)
HairF (T2; pg/mg; *M, SD*, Range)[c]	132.35 ± 83.22 (23.99–544.01)
HairE (T1; pg/mg; *M, SD*, Range)[b]	183.30 ± 104.15 (30.58–561.42)
HairE (T2; pg/mg; *M, SD*, Range)[c]	165.91 ± 116.6 (22.57–657.47)
HairF/HairE ratio (T1; pg/mg; *M, SD*, Range)[b]	1.16 ± 0.13 (0.80–1.56)
HairF/HairE ratio (T2; pg/mg; *M, SD*, Range)[c]	0.97 ± 0.19 (0.63–1.43)
Maternal	
Sociodemographic characteristics	
Age, years (*M, SD*, Range)[a]	30.4 ± 3.70 (21–42)
Marital status[a]	
Married/registered same sex partnership (*n, %*)	74 (51.10)
Unmarried (*n, %*)	85 (51.08)
Divorced (*n, %*)	5 (3.00)
Parity[a]	
Primiparous (*n, %*)	128 (77.60)
Multiparous (*n, %*)	37 (22.40)
Graduation[a]	
≤10 years (*n, %*)	22 (13.30)
>10 years (*n, %*)	143 (86.42)
Hair GCs	
HairF (T1; pg/mg; *M, SD*, Range)[a]	10.32 ± 14.66 (0.54–129.05)
HairF(T2; pg/mg; *M, SD*, Range)[c]	10.24 ± 9.80 (.73–57.25)
HairE (T1; pg/mg; *M, SD*, Range)[a]	31.11 ± 32.80 (4.12–277.98)
HairE (T2; pg/mg; *M, SD*, Range)[c]	22.33 ± 15.11 (0.99–98.94)
HairF/HairE ratio (T1; pg/mg; *M, SD*, Range)[b]	0.58 ± 0.16 (−.01–.88)
HairF/HairE ratio (T2; pg/mg; *M, SD*, Range)[c]	0.65 ± 0.27 (−.1.91–1.17)
Psychological variables	
Prenatal symptoms of depression (T1; EPDS total score; *M, SD*,Range)[a]	5.11 ± 4.28 (0–21)
Postnatal symptoms of depression (T2; EPDS total score; *M,SD*,Range)[c]	5.37 ± 3.76 (0–23)
Lifetime Depression (*n, %*)[c]	
Yes	21 (12.70)
No	144 (87.30)
Measurement points	
T1 DREAM (gestational week; *M, SD*, Range)[a]	27.48 ± 4.91 (12–36)
T2 DREAM (weeks after birth; M, SD, Range)c	8.32 ± 1.51 (5–12)
T1 $DREAM_{HAIR\text{-}(BABY)}$ (gestational week; *M, SD*, Range)[b]	40.00 ± 1.06 (36.71–42.00)
T2 $DREAM_{HAIR\text{-}(BABY)}$ (weeks after birth; *M, SD*, Range)[c]	8.23 ± 0.96 (6–12)

Note. EPDS = Edinburgh Postnatal Depression Scale. HairF = hair cortisol concentrations. HairE = hair cortisone concentrations. HairF/HairE = ratio hair cortisol concentrations – hair cortisone concentrations.
[a] T1 $DREAM_{(HAIR)}$ (during pregnancy). [b] T1 $DREAM_{HAIR\text{-}BABY}$ (within first two weeks after birth). [c] T2 $DREAM_{(HAIR)}$ (eight weeks after anticipated birth date).

2.3. Statistical analysis

All analyses were conducted using IBM SPSS Statistics 27. Potential missing values in the EPDS were substituted with the individual's mean value if at least 80% of the scale's items were completed. Due to the expected lack of normality of GC data, log transformation was applied. Outlying values of more than three standard deviations above or below the mean were excluded resulting in the following final samples: T1-HairF: $n = 152$, T1-HairE: $n = 152$; T2-HairF: $n = 165$, T2-HairE: $n = 164$. For sociodemographic characteristics, descriptive analyses including frequency analyses were computed.

To reduce variance within the outcome, potential confounders were evaluated using Spearman correlations according to prior literature and theoretical considerations. In particular, potential confounding variables for hair GCs included storage time (e.g., Steudte-Schmiedgen et al., 2017), birth weight and infants' sex (Gray et al., 2018), gestational age at birth, infants' age at T1 and T2 $DREAM_{HAIR\text{-}BABY}$, maternal HairF at T1 and T2, mode of delivery, parity (e.g.,Hollanders et al., 2017; Stoye et al., 2021), breastfeeding (Flom et al., 2017), pregnancy complications (Obel et al., 2005), and birth complications of mother and child (Fuchs et al., 2020). Additionally, maternal hair GCs at T1 $DREAM_{HAIR}$ and T2 $DREAM_{HAIR}$ were included as a potential confounding variable due to the given association between maternal and offspring's hair GCs in prior studies (Bryson et al., 2021; Dauegaard et al., 2020; Hollanders et al., 2017; Karlén et al., 2013).

First, correlational analyses without adjustment for confounding factors were performed to detect cross-sectional associations between maternal depressive symptoms (T1 DREAM or T2 DREAM, respectively) and infants' hair GCs (T1 $DREAM_{HAIR\text{-}BABY}$ or T2 $DREAM_{HAIR\text{-}BABY}$, respectively). Given potential differences in self-report depressive symptoms over the course of pregnancy, we repeated the analyses only for women who filled in the EPDS within the third trimester of pregnancy.

To investigate whether maternal depressive symptoms prenatally (T1 DREAM), postnatally (T2 DREAM), or the change in prenatal to postnatal depressive symptoms (EPDS T2 DREAM - EPDS T1 DREAM) have differential impacts on offspring neonatal and postnatal hair GCs, multiple regression analyses were conducted with infants' neonatal and

Table 2
Spearman correlations between HairF, HairE, and HairF/HairE ratio (T1 & T2 $DREAM_{HAIR\text{-}BABY}$) and potential confounding variables.

	HairF		HairE		HairF/HairE ratio	
Variable	T1	T2	T1	T2	T1	T2
Gestational age[a]	**.35****	**.18***	**.20***	.14	.13	−.04
Birth weight[d]	.11	.07	.15	.05	−.01	.03
Maternal prenatal HairF[b]	.04	.05				
Maternal prenatal HairE[b]			.03	.10		
Maternal prenatal HairF/HairE ratio[b]					−.13	−.05
Infant's neonatal HairF[c]		**.45****				
Infant's neonatal HairE[c]				**.47****		
Infant's neonatal HairF/HairE ratio[c]						**.51****
Maternal lifetime depression[a]	−.00	−.05	.04	−.02	.00	.03
Measurement point[c]		−.13	−.04	.00		−.05
Mode of delivery[d]	**−.16**	−.08	.05	.03	**−.20***	−.07
Parity[a]	**−.32****	−.07	**−.16***	.12	−.13	−.10
Sex[d]	.10	.02	**.17***	.09	−.07	.05
Storage time[c]	**−.17***	−.14	**−.17***	−.14	.02	.05
Pregnancy complications[d]	**−.25****	**−.16***	.01	.00	**−.23****	−.09
Birth complications mother[d]	.11	−.12	.10	−.09	−.01	.02
Birth complications child[d]	−.06	.15	.03	−.00	−.09	.10
Breastfeeding[d]	−.12	−.01	.05	−.01	**−.17***	0.2

Note. [a] T1 DREAM (during pregnancy). [b] T1 $DREAM_{HAIR}$ (4 ± 2 weeks prior to anticipated birth date). [c] T1 $DREAM_{HAIR\text{-}BABY}$ (within two weeks after birth). [d] T2 DREAM (eight weeks after anticipated birth date).
Significant associations *$p < .05$, * * $p < .01$ are presented in bold.

postnatal GCs, as well as the change in infants' neonatal to postnatal hair GCs (T2 $DREAM_{HAIR\text{-}BABY}$ - T1 $DREAM_{HAIR\text{-}BABY}$) as dependent variables.

According to Field (2017), model assumptions were checked prior to all analyses. Because further assumptions including homoscedasticity and normality of residuals were not met, bias-corrected and accelerated (BCa) bootstrap confidence intervals (CI) were calculated ($N = 2000$). Moreover, using the Preacher and Hayes PROCESS macros (Hayes, 2018), we conducted mediation analyses (model 4 with neonatal GCs as mediator), one for each GC estimate.

3. Results

3.1. Descriptive statistics

Sample characteristics of the sub-sample for investigating associations with HairF are summarized in Table 1. For the sub-samples investigating associations with HairE and the HairF/HairE ratio comparable descriptive results were revealed. For T1 $DREAM_{HAIR\text{-}BABY}$ $N = 152$ and for T2 $DREAM_{HAIR\text{-}BABY}$ $N = 165$ hair samples were analyzed for HairF data. Regarding prenatal symptoms of depression, 10 mothers met the cutoff for minor depression (6.1%) and an additional 12 mothers met the cutoff for major depression (7.3%). Similarly, 6.7% ($n = 11$) of mothers showed symptoms of minor postnatal depression and 4.8% ($n = 8$) of major postnatal depression.

Table 2 shows findings of Spearman correlations between hair GCs and potential confounding variables. Variables showing a significant association with HairF, HairE, and the HairF/HairE ratio were then included as confounding variables in further analyses, respectively.

3.2. The association of maternal prenatal symptoms of depression and infants' neonatal GCs

In the unadjusted analyses, no significant association between maternal prenatal EPDS and infants' neonatal HairF ($r = .10$, $p = .27$, 95% BCa CI [−.06,.25]) and HairE ($r = -.09$, $p = .28$, 95% BCa CI [−.24,.07]) were revealed, whereas the ratio showed a significant association ($r = .16$, $p = .046$, 95% BCa CI [.00,.31]). Furthermore, regression analyses with the above identified confounding variables were conducted to explore associations of maternal prenatal symptoms of depressions and infants' neonatal hair GCs (see Table 3). When considering the confounding variables of gestational age at birth, mode of delivery, parity, storage time, and pregnancy complications, a significant positive association between maternal prenatal symptoms of depression and infants' neonatal HairF emerged (β = .14, $p = .04$, 95% BCa CI [.00,.02]). The association between maternal prenatal symptoms of depression and HairF/HairE ratio revelaed by unadjusted analyses lost significance (β = .16, $p = .07$, 95% BCa CI [−.00,.01]) while no association with HairE was confirmed (β = −.06, $p = .41$, 95% BCa CI [−.01,.00]). When repeating the analyses within the subsample of women who filled in the EPDS within the third trimester, correlational analyses revealed a significant association between maternal prenatal symptoms of depression and the HairF/HairE ratio ($r = .22$, $p = .048$, 95% BCa CI [.00,.42]) and a marginally significant association with HairE ($r = -.19$, $p = .08$, 95% BCa CI [−.39,.03]). However, this was not the case for HairF ($r = .07$, $p = .52$, 95% BCa CI [−.15,.28]). Within regression analyses with the corresponding confounders a significant

Table 3
Regression analysis predicting infants' neonatal hair GCs (T1 $DREAM_{HAIR\text{-}BABY}$) from maternal prenatal depressive symptomatology, controlled for confounding variables.

	HairF				HairE				HairF/HairE			
Predictor	β	*p*	[95% BCa CI]	R^2 adj.	β	*p*	[95% BCa CI]	R^2 adj.	β	*p*	[95% BcCa CI]	R^2 adj.
				.29				.10				.08
EPDS at T1[a]	.14	**.04**	[.00,.02]		−.06	.41	[− .01,.00]		.16	.07	[− .00,.01]	
Gestational age at birth[b]	.27	**.00**	[.03,.10]		.11	.17	[− .01,.06]					
Mode of delivery[b]	−.10	.07	[.19,.02]						−.19	**.02**	[− .15, − .02]	
Parity[a]	−.32	**.00**	[− .27, − .10]		−.14	.05	[− .17, − .00]					
Infant's sex[b]					.15	.05	[.00,.14]					
Storage time[c]	−.13	**.05**	[− .00,.00]		−.16	.02	[− .00,.00]					
Pregnancy complications[b]	−.26	**.00**	[− .14, − .04]						−.15	.07	[− .05,.01]	
Breastfeeding[b]									−.15	**.01**	[− .19, − .02]	

Note. β = Standardized beta coefficient. Bca CI = 95% bias corrected and accelerated bootstrap confidence interval (2000 iterations), Adj. R^2 = Adjusted coefficient of determination. EPDS = Edinburgh Postnatal Depression Scale. HairF = hair cortisol concentrations. HairF = hair cortisone concentrations. HairF/HairE = ratio hair cortisol / hair cortisone. [a] T1 DREAM (during pregnancy). [b] T2 DREAM (eight weeks after anticipated birth date). [c] T1 $DREAM_{HAIR\text{-}BABY}$ (within first two weeks after birth). Significant associations ($p < .05$) are presented in bold.

association emerged between maternal prenatal symptoms of depression and the HairF/HairE ratio (β = .27 p = .02, 95% BCa CI [.00,.01]) as well as a non-significant trend for HairE (β =−. 16 p = .08, 95% BCa CI [−.02,.00]). However, the association with HairF from the larger sample was not confirmed (β = .15 p = .14, 95% BCa CI [−.00,.02]).

3.3. The association between maternal symptoms of depression and infants' postnatal hair GCs

In the unadjusted cross-sectional correlational analyses, no significant association between maternal postnatal EPDS scores and infants' postnatal hair GCs were found (*ps* >.29). Findings of regression analyses including the identified covariates did not change the pattern of results (*ps* >.40; see supplementary material).

To examine a possible mediating effect of neonatal hair GCs on the association of prental symptoms of depression and infants' postnatal hair GCs, PROCESS model 4 was employed. In contrast to the linear regression analyses, maternal prenatal symptoms of depression were not predictive of infants' neonatal HairF, HairE, or the ratio (a-Path, *ps* > .05), whereas a significant association was observed for the effect of neonatal hair GCs for infants' postnatal hair GCs at eight weeks postnatally (*ps* = <.01, b-Path). There was no significant effect of maternal prenatal symptoms of depression on infants' postnatal hair GCs at eight weeks postnatally in all models (c-Path, *ps* > .05). Accordingly, none of the indirect effects were significant (*ps* >.05, for details see supplementary material).

3.4. Exploratory analyses: The association between the change in maternal perinatal symptoms of depression and infants' GCs

Correlational analyses between the change in maternal perinatal symtpoms of depression and infants' postnatal hair GCs revealed no significant relationship for all hair GCs (*ps* >.14). In addition, explorative multiple regression analyses with the corresponding confounders were performed (see supplementary material). Regression analyses between the change of maternal prenatal to postnatal symptoms of depression and infants' postnatal hair GCs showed no significant association (*ps* >.60), which was also confirmed within the sub-sample of women who filled in the EPDS within the third trimester of pregnancy. In addition, no association could be detected between the EPDS change score with the change score of infants' hair GCs neonatally to postnatally (*ps* >.69; see supplementary material), which was also confirmed within the within the sub-sample in the third trimester of pregnancy.

4. Discussion

The objective of the present study was to investigate the associations between maternal symptoms of depression and infants' hair GCs across the perinatal period. As the main result, we found that higher maternal prenatal symptoms of depression were associated with higher infants' neonatal HairF and the HairF/HairE ratio (non-significant trend), when controlling for confounding variables. No association was revealed between maternal postnatal depressive symptoms and postnatal GCs in infants. Neonatal hair GCs did not mediate the association of maternal prenatal symptoms of depression and infants' postnatal hair GCs. Finally, a change from maternal prenatal to postnatal symptoms of depression was neither associated with infants' postnatal hair GCs nor with the GC change across the perinatal period.

In line with our hypothesis, we found a relationship between maternal prenatal symptoms of depression and infants' neonatal HairF, when controlling for gestational age, mode of delivery, parity, storage time, and pregnancy complications. Specifically, we found that higher maternal prenatal symptoms of depression were associated with higher infants' HairF levels mainly incorporated in the intrauterine period. This is in line with findings based on research using traditional measurement methods revealing that higher symptoms of depression in the second and third trimester of pregnancy are predictive of infants' elevated urinary cortisol levels few days after delivery (Diego et al., 2004; Field et al., 2004; Lundy et al., 1999). In the context of hair GC research, our results match well with a recent transdiagnostic study based on a clinical sample (Broeks et al., 2021) showing a positive association between infants' HairF levels reflecting both the last trimester of pregnancy as well as the early postnatal period and maternal perinatal symptom severity. In contrast to our findings, van der Voorn et al. (2018) found a negative association between maternal prenatal depressive symptoms and infants's neonatal HairF, indicating a different nature of association between maternal prenatal depression and infants' neonatal HairF in clinical samples, potentially dependent on the chronicity of maternal symptoms as well as chronic stress (van der Voorn et al., 2018). Furthermore, our finding is in contrast to the only other study conducted on the association between maternal prenatal symptoms of depression and infants's neonatal HairF based on a community sample (Romero-Gonzalez et al., 2018). However, the authors did not consider mode of delivery and pregnancy complications as potential confounding variables, which proved to be important confounders in the present investigation. This is especially important since a recent study confirmed the finding that neonatal hair is associated with birth outcomes, with infants showing higher levels of hair GCs following spontaneous labor due to the biological process of labor, compared to no labor (e.g., caesarean section: (Stoye et al., 2021)). In general, the overall trend of studies suggests maternal prenatal symptoms of depression to exert their effect on the fetus via the HPA axis, with dysregulated maternal cortisol levels crossing the placenta (review: Entringer et al., 2015). Surprisingly, despite the detected positive association between maternal prenatal symptoms of depression and infants's neonatal HairF, maternal prenatal and infants's neonatal HairF were not related in the current investigation. This finding is in contrast to studies conducted on the association between maternal and infant HairF in the perinatal period (Hollanders et al., 2017; Romero-Gonzalez et al., 2018; van der Voorn et al., 2018). A possible explanation for our finding is the partially lacking correspondence of DREAM and $DREAM_{HAIR}$ measurement points in the present study, which makes it difficult to link maternal hair GCs with the occurrence of symptoms of depression and infant's hair GCs. Furthermore, the various confounding variables for maternal hair GCs were not considered in the correlational analyses. Finally, it should be noted that within the PROCESS model investigating the mediating role of neonatal hair GCs in the association between maternal prenatal symptoms of depression and infants' postnatal hair GCs, no relationship between prenatal symptoms of depression and neonatal hair cortisol was confirmed. It is conceivable that this might be due to a reduced sample size due to listwise deletion within the mediation analyses or the lack of considered confounding variables that were observed to influence hair GCs in the current sample.

To our knowledge, this is the first study investigating HairE as another relevant measure in addition to HairF and the HairF/HairE ratio in neonatal hair in the context of maternal perinatal depressiveness. Within our analyses, we showed associations within the unadjusted correlational analyses between maternal prenatal sympoms of depression and HairE (non-significant trend) and the HairF/HairE ratio within the subsample of pregnant women within their third trimester of pregnancy as well as a significant association between the HairF/HairE ratio and maternal prenatal symptoms of depression in the overall sample. The ratio has been succesfully applied as an estimate of hair GC regulation also in other research contexts (e.g., metabolic syndrome; Stalder et al., 2013) and initial evidence (Yehuda and Seckl, 2011) indicates that this long-term marker of cortisol metabolism may be altered by stress. Specifically, it was shown that maternal perceived stress in the postnatal period did increase the HairF/HairE ratio in a sample of non-depressed women (Lang et al., 2021). Our findings add to this approach and suggest that cortisol metabolism might be also altered in neonates as a function of maternal prenatal depressive symptoms and highlight the usefulness of this marker for future research in this context.

Regarding the postnatal period, to our knowledge, this was the first study investigating the nature of association between maternal perinatal symptoms of depression and infants' *postnatal* hair GCs based on a community sample. Against our hypothesis, a change in maternal prenatal to postnatal symptoms of depression was not associated with infants' hair GCs eight weeks after delivery as well as the change from infants' neonatal to postnatal hair GCs, respectively. Furthermore, mediation analyses did not provide evidence for the notion that neonatal hair GCs mediate the association of maternal prenatal symptoms of depression and infants' postnatal hair GCs. Prior literature indicates that maternal behavior associated with symptoms of depression in the postnatal period may potentially affect the infant (e.g., parenting behavior), resulting in a dysregulation of HPA axis activity (Essex et al., 2002; Tarullo et al., 2017). In a study by Palmer et al. (2013), maternal symptoms of depression one year after birth were negatively related to infants' HairF. In line with previously mentioned studies, the findings of Palmer et al. (2013) implicate complex relationships between a variety of factors in predicting infants' hair GCs. Thus, the nature of association between maternal symptoms of depression and infants' hair GCs might be variable due to differences in sociodemographic characteristics and psychological variables such as ethnicity and parenting stress (Palmer et al., 2013). In general, newborns are exposed to several new influences and impressions after birth, with potential effects on long-term HPA axis activity. For instance, breastfeeding and longer sleep duration as well as living in a house compared to an apartment are associated with lower HairF in early infancy (Flom et al., 2017; Karlén et al., 2013). It is conceivable that the potential interaction of various factors in predicting infants' postnatal hair GCs may have impeded the detection of an association with maternal perinatal symptoms of depression. Whereas maternal prenatal symptoms of depression affect the fetus mainly physiologically, maternal postnatal symptoms of depression have the potential to affect the infant indirectly in various ways and on different levels (review: Slomian et al., 2019). We assume that postnatal depression might exert its negative effects on the infant mainly indirectly during longer periods of exposure. For instance, such an indirect path could be a distorted mother-infant-interaction which, in turn, might have a long-term impact on the infant's HPA axis activity (Palmer et al., 2013). This hypothesis is in line with prior research suggesting that while depressed mothers are able to meet their children's needs in early life, they show more deficits as the children age and mature and require more involved parenting (Gjerde et al., 2021). Moreover, it is conceivable that there are specific sensitive periods of the infant during the postnatal period with a higher vulnerability to adverse maternal conditions, comparable to the proposed sensitive periods during pregnancy (Romero-Gonzalez et al., 2018; van der Voorn et al., 2018).

Additionally, in line with Hollanders et al. (2017), we found a strong association between infants' neonatal and postnatal hair GCs. Hence, it is conceivable that the potential influence of maternal symptoms of depression on infants' hair GCs in the postnatal period is partly masked by the contribution of the major event of birth on GCs among other factors mentioned above and that early exposure to maternal symptoms of depression might exert their effects rather later in life. This is in line with prior literature based on traditional measurement methods, implicating that maternal postnatal depressiveness is associated with infants' cortisol levels in childhood, adolescence, as well as adulthood (Ashman et al., 2002; Douglas and Harmer, 2011; Halligan et al., 2004). The current design of the $DREAM_{HAIR}$ sub-study with measurement points up to early childhood (see Fig. 1) will allow a detailed investigation of the impact of maternal perinatal symptoms of depression on long-term GC regulation of the offspring.

One major strength of the present study is the clear separation of prenatal and postnatal associations regarding maternal symptoms of depression and infants' hair GCs. Possible explanations for heterogenous results may include the characteristics of the study population in terms of prevalence and chronicity of maternal depressive symptoms with potential differences in infants' hair GC outcomes. The present investigation was based on a community sample. Based on the most frequently used cutoff scores, minor and major maternal perinatal symptoms of depression had a combined prevalence of 12.7–13.6%. Thus, despite the high level of education in the present sample, prevalence rates for maternal perinatal symptoms of depression are comparable to the overall pooled adjusted prevalence for community samples reported in a recent review (11.9%; Woody et al., 2017).

However, the present study has some limitations as well. The investigation was based on a rather homogenous community sample which might not be representative of the total population. Additionally, our sample included only few mothers with clinically relevant depression scores, resulting in a limited variance regarding symptoms of depression. To add to that, when repeating the analysis for the association of maternal T1 EPDS and neonatal hair GCs within a subsample of pregnant women who filled in the EPDS only in the third trimester, results including confounders were not significant for HairF, however, they showed a non-significant trend for HairE and a significant association for their ratio. This association was also revealed in unadjusted analyses. The statistical power of the analyses within the subsample might have been too low for this small effect on HairF or the smaller subsample resulted in a slighlty different pattern of findings. Future studies should consider a closer correspondence between self-report depression symptoms and hair sampling over the entire course of pregnancy in a larger sample to extend the data base for long-term GC estimates in this research context.

Furthermore, recent data indicate that external contamination (e.g., GC-containing cremes) may lead to elevated HairF (Wang et al., 2019). However, to control for such potential contaminations, we excluded mother-child dyads exposed to GC-containing medication so this is unlikely to have affected the current results. Moreover, we considered HairE as an additional robust GC estimate, which partly confirmed the pattern of HairF data. However, while HairF and HairE were moderatly correlated as suggested by previous research (Stalder et al., 2013), our data did not confirm a significant relationship with maternal prenatal symptoms of depression for HairE in the overall sample. The fact that an association was revealed in the subsample consisting of women who filled in the EPDS at the third trimester of pregnancy again suggests that differences in the sample size and outlying values may have contributed to differential findings.

Overall, our study has several important theoretical and clinical implications. As demonstrated, exposure to maternal symptoms of depression already starts in the womb with potentially long lasting effects on infants' HPA axis functioning (Molenaar et al., 2019). In turn, long-term dysregulated GCs may be a risk factor for the mental and somatic health later in life. Future studies should focus on the clear temporal separation between prenatal and postnatal associations between maternal perinatal symptoms of depression and infants' hair GCs as a basis for further research. In particular, the postnatal period is characterized by a variety of stressful circumstances with potential effects on infants' HPA axis functioning (review: Slomian et al., 2019). Hence, it appears crucial to identify additional risk factors and their potential interrelations with maternal symptoms of depression to clarify the associations with infants' hair GCs. In any case, research should take into account feasible treatments for perinatal depression and its consequences on mothers and their infants with special attention to biological mechanisms. Specifically, infants' dysregulated long-term integrated GCs could consitute a basis for the development of tailored approaches in the field of prevention and early intervention.

5. Conclusion

In the present investigation, higher maternal prenatal symptoms of depression were associated with higher infants's neonatal HairF and the HairF/Hair E ratio (non-significant trend), when controlling for confounding variables (i.e., gestational age, mode of delivery, parity, storage time, and pregnancy complications). However, no such effect was

revealed for HairE. It is likely that infants' dysregulated cortisol levels mainly incorporated in the intrauterine period, in turn, might constitute an early vulnerability factor for the development of physical and mental challenges later in life. Our explorative analyses did not observe an association between the change from maternal perinatal to postnatal symptoms of depression and infants' hair GCs eight weeks after delivery. A possible association of maternal prenatal symptoms of depression and infants' postnatal hair GCs was not mediated by infants' neonatal hair GCs. Future prospective research should focus on the proposed stability of an HPA axis dysregulation caused by the exposure to maternal symptoms of depression and take into account additional risk factors occurring in early infancy.

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Declaration of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105952.

References

Ashman, S.B., Dawson, G., Panagiotides, H., Yamada, E., Wilkinson, C.W., 2002. Stress hormone levels of children of depressed mothers. Dev. Psychopathol. 14, 333–349. https://doi.org/10.1017/S0954579402002080.

Bergant, A.M., Nguyen, T., Heim, K., Ulmer, H., Dapunt, O., 1998. Deutschsprachige Fassung und Validierung der "Edinburgh postnatal depression scale". DMW. Dtsch. Med. Wochenschr. 123, 35–40. https://doi.org/10.1055/s-2007-1023895.

Bergink, V., Kooistra, L., Lambregtse-van den Berg, M.P., Wijnen, H., Bunevicius, R., van Baar, A., et al., 2011. Validation of the Edinburgh Depression Scale during pregnancy. J. Psychosom. Res. 70, 385–389. https://doi.org/10.1016/j.jpsychores.2010.07.008.

Bleker, L.S., van Dammen, L., Leeflang, M.M., Limpens, J., Roseboom, T.J., de Rooij, S.R., 2020. Hypothalamic-pituitary-adrenal axis and autonomic nervous system reactivity in children prenatally exposed to maternal depression: a systematic review of prospective studies. Neurosci. Biobehav. Rev. 117, 243–252.

Brennan, P., Pargas, R., Walker, E., Green, P., Newport, J., Stowe, Z., 2008. Maternal depression and infant cortisol: influences of timing, comorbidity and treatment. J. Child Psychol. Psychiatry 49, 1099–1107. https://doi.org/10.1111/j.1469-7610.2008.01914.x.

Broeks, C.W., Choenni, V., Kok, R., Voorn, B., van der, Kruijff, I., de, Akker, E.L.T., et al., 2021. An exploratory study of perinatal hair cortisol concentrations in mother–infant dyads with severe psychiatric disorders versus healthy controls. BJPsych Open 7. https://doi.org/10.1192/bjo.2020.159 e28.

Bryson, H.E., Mensah, F., Goldfeld, S., Price, A.M., Giallo, R., 2021. Hair cortisol in mother–child dyads: examining the roles of maternal parenting and stress in the context of early childhood adversity. Eur. Child Adolesc. Psychiatry 30, 563–577.

Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of Postnatal Depression: Development of the 10-item Edinburgh Postnatal Depression Scale. Br. J. Psychiatry 150, 782–786. https://doi.org/10.1192/bjp.150.6.782.

Dauegaard, S., Olsen, N.J., Heitmann, B.L., Larsen, S.C., 2020. Familial associations in hair cortisol concentration: a cross-sectional analysis based on the Healthy Start study. Psychoneuroendocrinology 121, 104836.

Diego, M.A., Field, T., Hernandez-Reif, M., Cullen, C., Schanberg, S., Kuhn, C., 2004. Prepartum, postpartum, and chronic depression effects on newborns. Psychiatry Interpers. Biol. Process. 67, 63–80. https://doi.org/10.1521/psyc.67.1.63.31251.

Douglas, J.-L., Harmer, C.-J., 2011. Early morning cortisol response and emotional processing in adults exposed to postnatal depression in infancy. Eur. Psychiatry 26, 479–481. https://doi.org/10.1016/j.eurpsy.2010.01.015.

Entringer, S., Buss, C., Wadhwa, P.D., 2015. Prenatal stress, development, health and disease risk: apsychobiological perspective—2015 Curt Richter Award Paper. Psychoneuroendocrinology 62, 366–375. https://doi.org/10.1016/j.psyneuen.2015.08.019.

Essex, M.J., Klein, M.H., Cho, E., Kalin, N.H., 2002. Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. Biol. Psychiatry 52, 776–784. https://doi.org/10.1016/S0006-3223(02)01553-6.

Field, A., 2017. Discovering Statistics Using IBM SPSS Statistics. SAGE.

Field, T., Diego, M., Dieter, J., Hernandez-Reif, M., Schanberg, S., Kuhn, C., et al., 2004. Prenatal depression effects on the fetus and the newborn. Infant Behav. Dev. 27, 216–229. https://doi.org/10.1016/j.infbeh.2003.09.010.

Flom, M., John, A.M.S., Meyer, J.S., Tarullo, A.R., 2017. Infant hair cortisol: associations with salivary cortisol and environmental context. Dev. Psychobiol. 59, 26–38. https://doi.org/10.1002/dev.21449.

Fuchs, A., Dittrich, K., Neukel, C., Winter, S., Zietlow, A.-L., Kluczniok, D., et al., 2020. Hair cortisol moderates the association between obstetric complications and child wellbeing. Psychoneuroendocrinology 121, 104845.

Gao, W., Stalder, T., Foley, P., Rauh, M., Deng, H., Kirschbaum, C., 2013. Quantitative analysis of steroid hormones in human hair using a column-switching LC–APCI–MS/MS assay. J. Chromatogr. B 928, 1–8. https://doi.org/10.1016/j.jchromb.2013.03.008.

Gelman, P.L., Flores-Ramos, M., López-Martínez, M., Fuentes, C.C., Grajeda, J.P.R., 2015. Hypothalamic-pituitary-adrenal axis function during perinatal depression. Neurosci. Bull. 31, 338–350. https://doi.org/10.1007/s12264-014-1508-2.

Gjerde, L.C., Eilertsen, E.M., Hannigan, L.J., Eley, T., Røysamb, E., Reichborn-Kjennerud, T., et al., 2021. Associations between maternal depressive symptoms and risk for offspring early-life psychopathology: the role of genetic and non-genetic mechanisms. Psychol. Med. 51, 441–449.

Glover, V., 2015. Prenatal stress and its effects on the fetus and the child: possible underlying biological mechanisms. Adv. Neurobiol. 10, 269–283. https://doi.org/10.1007/978-1-4939-1372-5_13.

Halligan, S.L., Herbert, J., Goodyer, I.M., Murray, L., 2004. Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. Biol. Psychiatry 55, 376–381. https://doi.org/10.1016/j.biopsych.2003.09.013.

Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform. 42, 377–381. https://doi.org/10.1016/j.jbi.2008.08.010.

Harris, P.A., Taylor, R., Minor, B.L., Elliott, V., Fernandez, M., O'Neal, L., et al., 2019. The REDCap consortium: building an international community of software platform partners. J. Biomed. Inform. 95, 103208 https://doi.org/10.1016/j.jbi.2019.103208.

Hayes, A.F., 2018. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. Methodology in the Social Sciences, Second edition. ed.,. Guilford Press,, New York.

Hollanders, J.J., van der Voorn, B., Kieviet, N., Dolman, K.M., de Rijke, Y.B., de, Akker, E.L.T., et al., 2017. Interpretation of glucocorticoids in neonatal hair: a reflection of intrauterine glucocorticoid regulation. Endocr. Connect 6, 692–699. https://doi.org/10.1530/EC-17-0179.

Jarde, A., Morais, M., Kingston, D., Giallo, R., MacQueen, G.M., Giglia, L., et al., 2016. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. JAMA Psychiatry 73, 826–837.

Junge, C., Garthus-Niegel, S., Slinning, K., Polte, C., Simonsen, T.B., Eberhard-Gran, M., 2017. The impact of perinatal depression on children's social-emotional development: a longitudinal study. Matern. Child Health J. 21, 607–615. https://doi.org/10.1007/s10995-016-2146-2.

Karlén, J., Frostell, A., Theodorsson, E., Faresjö, T., Ludvigsson, J., 2013. Maternal influence on child hpa axis: a prospective study of cortisol levels in hair. Pediatrics 132, e1333–e1340. https://doi.org/10.1542/peds.2013-1178.

Kennis, M., Gerritsen, L., van Dalen, M., Williams, A., Cuijpers, P., Bockting, C., 2020. Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis. Mol. Psychiatry 25, 321–338. https://doi.org/10.1038/s41380-019-0585-z.

Kress, V., Steudte-Schmiedgen, S., Kopp, M., Förster, A., Altus, C., Schier, C., et al., 2019. The impact of parental role distributions, work participation, and stress factors on family health-related outcomes: study protocol of the prospective multi-method cohort "dresden study on parenting, work, and mental health" (DREAM). Front. Psychol. 10. https://doi.org/10.3389/fpsyg.2019.01273.

Lang, J., Stickel, S., Gaum, P.M., Habel, U., Bertram, J., Eickhoff, S.B., et al., 2021. Predicting hair cortisol and cortisone concentration in postpartum women through repeated measurements of perceived stress. Metabolites 11, 815.

Laurent, H., 2017. Early calibration of the HPA axis by maternal psychopathology. Psychoneuroendocrinology 78, 177–184. https://doi.org/10.1016/j.psyneuen.2017.01.034.

Lundy, B.L., Jones, N.A., Field, T., Nearing, G., Davalos, M., Pietro, P.A., et al., 1999. Prenatal depression effects on neonates. Infant Behav. Dev. 22, 119–129. https://doi.org/10.1016/S0163-6383(99)80009-5.

Maughan, A., Cicchetti, D., Toth, S.L., Rogosch, F.A., 2007. Early-occurring maternal depression and maternal negativity in predicting young children's emotion regulation and socioemotional difficulties. J. Abnorm. Child Psychol. 35, 685–703.

Melville, J.L., Gavin, A., Guo, Y., Fan, M.-Y., Katon, W.J., 2010. Depressive disorders during pregnancy. Obstet. Gynecol. 116, 1064–1070. https://doi.org/10.1097/AOG.0b013e3181f60b0a.

Meyer, J.S., Novak, M.A., 2020. Assessment of prenatal stress-related cortisol exposure: focus on cortisol accumulation in hair and nails. Dev. Psychobiol. https://doi.org/10.1002/dev.22021.

Molenaar, N.M., Tiemeier, H., van Rossum, E.F.C., Hillegers, M.H.J., Bockting, C.L.H., Hoogendijk, W.J.G., et al., 2019. Prenatal maternal psychopathology and stress and offspring HPA axis function at 6 years. Psychoneuroendocrinology 99, 120–127. https://doi.org/10.1016/j.psyneuen.2018.09.003.

Obel, C., Hedegaard, M., Henriksen, T., Secher, N., Olsen, J., Levine, S., 2005. Stress and salivary cortisol during pregnancy. Psychoneuroendocrinology 30, 647–656.

Palmer, F.B., Anand, K.J.S., Graff, J.C., Murphy, L.E., Qu, Y., Völgyi, E., et al., 2013. Early adversity, socioemotional development, and stress in urban 1-year-old children. e1 J. Pediatr. 163, 1733–1739. https://doi.org/10.1016/j.jpeds.2013.08.030.

Perogamvros, I., Keevil, B.G., Ray, D.W., Trainer, P.J., 2010. Salivary cortisone is a potential biomarker for serum free cortisol. J. Clin. Endocrinol. Metab. 95, 4951–4958. https://doi.org/10.1210/jc.2010-1215.

Petzoldt, J., Wittchen, H.-U., Einsle, F., Martini, J., 2016. Maternal anxiety versus depressive disorders: specific relations to infants' crying, feeding and sleeping problems. Child Care Health Dev. 42, 231–245. https://doi.org/10.1111/cch.12292.

Romero-Gonzalez, B., Caparros-Gonzalez, R.A., Gonzalez-Perez, R., Delgado-Puertas, P., Peralta-Ramirez, M.I., 2018. Newborn infants' hair cortisol levels reflect chronic maternal stress during pregnancy. PLoS One 13, e0200279. https://doi.org/10.1371/journal.pone.0200279.

Slomian, J., Honvo, G., Emonts, P., Reginster, J.-Y., Bruyère, O., 2019. Consequences of maternal postpartum depression: a systematic review of maternal and infant outcomes, 1745506519844044 Women's. Health 15. https://doi.org/10.1177/1745506519844044.

Smith, A., Twynstra, J., Seabrook, J.A., 2020. Antenatal depression and offspring health outcomes. Obstet. Med. 13, 55–61. https://doi.org/10.1177/1753495X19843015.

Stalder, T., Kirschbaum, C., Alexander, N., Bornstein, S.R., Gao, W., Miller, R., et al., 2013. Cortisol in hair and the metabolic syndrome. J. Clin. Endocrinol. Metab. 98, 2573–2580.

Stalder, T., Steudte-Schmiedgen, S., Alexander, N., Klucken, T., Vater, A., Wichmann, S., et al., 2017. Stress-related and basic determinants of hair cortisol in humans: a meta-analysis. Psychoneuroendocrinology 77, 261–274. https://doi.org/10.1016/j.psyneuen.2016.12.017.

Stoye, D.Q., Sullivan, G., Galdi, P., Kirschbaum, C., Lamb, G.J., Black, G.S., et al., 2021. Perinatal determinants of neonatal hair glucocorticoid concentrations. Psychoneuroendocrinology 128, 105223. https://doi.org/10.1016/j.psyneuen.2021.105223.

Stroud, L.R., Papandonatos, G.D., Rodriguez, D., McCallum, M., Salisbury, A.L., Phipps, M.G., et al., 2014. Maternal smoking during pregnancy and infant stress response: Test of a prenatal programming hypothesis. Psychoneuroendocrinology 48, 29–40. https://doi.org/10.1016/j.psyneuen.2014.05.017.

Steudte-Schmiedgen, S., Wichmann, S., Stalder, T., Hilbert, K., Muehlhan, M., Lueken, U., et al., 2017. Hair cortisol concentrations and cortisol stress reactivity in generalized anxiety disorder, major depression and their comorbidity. J. Psychiatr. Res. 84, 184–190.

Tarullo St., A.R., John, A.M., Meyer, J.S., 2017. Chronic stress in the mother-infant dyad: maternal hair cortisol, infant salivary cortisol and interactional synchrony. Infant Behav. Dev. 47, 92–102. https://doi.org/10.1016/j.infbeh.2017.03.007.

van der Voorn, B., Hollanders, J.J., Kieviet, N., Dolman, K.M., de Rijke, Y.B., van Rossum, E.F.C., et al., 2018. Maternal stress during pregnancy is associated with decreased cortisol and cortisone levels in neonatal hair. Horm. Res. Paediatr. 90, 299–307. https://doi.org/10.1159/000495007.

Wadhwa, P.D., 2005. Psychoneuroendocrine processes in human pregnancy influence fetal development and health. Psychoneuroendocrinology 30, 724–743. https://doi.org/10.1016/j.psyneuen.2005.02.004.

Wang, X., Busch, J.R., Banner, J., Linnet, K., Johansen, S.S., 2019. Hair testing for cortisol by UPLC–MS/MS in a family: External cross-contamination from use of cortisol cream. Forensic Sci. Int. 305, 109968.

Welberg, L.A., Seckl, J.R., 2001. Prenatal stress, glucocorticoids and the programming of the brain. J. Neuroendocr. 13, 113–128.

Wells, S., Tremblay, P.F., Flynn, A., Russell, E., Kennedy, J., Rehm, J., et al., 2014. Associations of hair cortisol concentration with self-reported measures of stress and mental health-related factors in a pooled database of diverse community samples. Stress 17, 334–342. https://doi.org/10.3109/10253890.2014.930432.

Woody, C.A., Ferrari, A.J., Siskind, D.J., Whiteford, H.A., Harris, M.G., 2017. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. J. Affect. Disord. 219, 86–92. https://doi.org/10.1016/j.jad.2017.05.003.

Yehuda, R., Seckl, J., 2011. Minireview: stress-related psychiatric disorders with low cortisol levels: a metabolic hypothesis. Endocrinology 152, 4496–4503.