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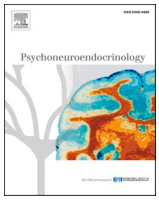

Longitudinal effects of maternal depressive and anxious symptomatology on child hair cortisol and cortisone from pregnancy to 5-years: The EDEN mother-child cohort

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ABSTRACT

Exposure to maternal depressive and anxious symptomatology in utero and after birth can affect child outcomes. One proposed mechanism is through changes in child stress hormone levels, however current studies present inconsistent findings, and further research is needed to better understand the impact of maternal mental health on child stress response. This study aims to add to the limited literature by analysing longitudinal data ranging from 24 weeks amenorrhea to 5 years postpartum among 281 mother-child pairs from the French EDEN mother-child birth cohort. Hair cortisol and cortisone data were collected from children at four time points: birth, 1, 3, and 5 years. Mothers reported depressive symptomatology via the Center for Epidemiologic Studies Depression Scale (CES-D) (at 24-weeks amenorrhea, 3-, and 5-year follow-up), and the Edinburgh Postnatal Depression Scale (EPDS) (at 4, 8 and 12 months postpartum). Prenatal anxiety symptomatology was measured via the State Anxiety Inventory (STAI) at 24 weeks amenorrhea. Group-based trajectory modelling indicated a 1-cluster classification of longitudinal child hair cortisol, cortisone and cortisol-to-cortisone ratio, as analyses did not reveal a classification by subgroups representing different child profiles. After inverse probability weighting, small effects showed prenatal depressive symptomatology was significantly associated to higher levels of child hair cortisone at one year. Prenatal anxiety symptomatology was significantly linked to higher levels of child cortisol measured at birth and cortisone at birth and at 1 year. Postpartum depressive symptomatology at 8 months was related to higher levels of cortisone among 3-year-olds. These effects were not moderated by child sex or maternal socio-economic status. Further research is needed to understand why there are associations at some time points and not others to determine any potential buffering factors.

1. Introduction

Maternal depression and anxiety are common mental health conditions both during and after pregnancy that significantly impact child outcomes, including their socio-emotional and cognitive development (Herba and Glover, 2013; Weissman et al., 2006). One hypothesized pathway through which exposure to maternal mental health problems may manifest their effect on development is through variations in

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children's stress hormone levels via changes in hypothalamic-pituitary-adrenal (HPA) axis function (Field, 2017; Monk et al., 2019; O'Donnell et al., 2014). Psychological or physiological stress activates the HPA-axis resulting in higher production of hair cortisol from the adrenal glands. Cortisol can then be metabolized into its inactive form hair cortisone. The assessment of hair cortisone in parallel to hair cortisol has been postulated to provide even more insight into the cumulative amount of active and inactive glucocorticoids in the body. For instance, higher levels of free cortisol could be due to a decreased conversion to cortisone rather than an increase in cortisol output, which can be measured via the ratio of cortisone compared to cortisol (CCratio) (Zhang et al., 2013).

Currently, studies in children have largely assessed individual HPA-axis dysregulation using plasma or saliva, which provides a measure of acute stress that fluctuates depending on diurnal cortisol release and factors such as sleep (Bates et al., 2017). On the other hand, hair samples provide a reliable, non-invasive, and retrospective measure of cortisol and cortisone levels and their ratio, which is important as chronic stress is associated with long-term changes in HPA-axis function (Khoury et al., 2023; Liu and Doan, 2019; Monk et al., 2019; Stalder et al., 2017).

Hair glucocorticoids (HGCs) represent a promising objective measure of chronic stress experiences in infants during early childhood that does not rely on adult-reported observations (Bates et al., 2017; Gray et al., 2018). However, further understanding of the determinants of HGC and how children's HGC concentrations fluctuate is needed to adjust for potential confounders and to determine guidelines for this biomarker of stress among children (Gray et al., 2018). In addition, substantial evidence from prospective studies shows that maternal prenatal stress, including high levels of anxiety and depressive symptomatology, contributes to long-term changes in child neurodevelopment (Glover, 2015). To provide a more complete picture of the child's long-term stress response it is important to establish the underlying mechanisms of these associations, such as the HPA axis, and to understand how they evolve longitudinally.

To our knowledge, only a few longitudinal studies currently exist exploring the effects of prenatal maternal depressive and anxiety symptomatology on child hair cortisol and cortisone levels from birth to 5 years (Broeks et al., 2021; Karl et al., 2023; Palmer et al., 2013; Romero-Gonzalez et al., 2018; van der Voorn et al., 2018). Yet, these remain limited in methodology and quantity, as they relied on clinical (van der Voorn et al., 2018) or small samples with fewer than 100 participants (Broeks et al., 2021; Romero-Gonzalez et al., 2018), use traditional techniques to control for confounding variables (Broeks et al., 2021; Karl et al., 2023; Palmer et al., 2013; Romero-Gonzalez et al., 2018; van der Voorn et al., 2018), and only measured child stress hormone levels at one or two time points (Broeks et al., 2021; Karl et al., 2023; Palmer et al., 2013; Romero-Gonzalez et al., 2018; van der Voorn et al., 2018). Possibly due to these limitations, the few studies using hair samples to explore the impact of maternal depressive and anxiety symptomatology on child stress hormone levels generally provide inconsistent findings. For instance, high levels of prenatal depressive symptomatology were associated with decreased levels of child hair cortisol at birth (van der Voorn et al., 2018), but in a different sample of mothers clinically diagnosed mainly with depression or anxiety, increased levels of child hair cortisol were found at 6 weeks postpartum (Broeks et al., 2021). Additionally, in a recent longitudinal study, associations were found between high levels of prenatal depressive symptomatology and high levels of child hair cortisol at birth, but not between postpartum depressive symptomatology and child hair cortisol at 8 weeks (Karl et al., 2023). Postpartum effects have also been found in a community-based sample, where lower levels of depressive symptoms measured at 4 weeks and 12 months postpartum were associated with higher levels of hair cortisol in 1-year old children (Palmer et al., 2013).

Studies that follow children from birth to early childhood can provide a more comprehensive understanding of how maternal mental health impacts both inter- and intra-person variability in child stress levels over time, especially when using repeated measures of child hair cortisol and cortisone at different time points. Moreover, it is possible that distinct subgroups of children follow a specific pattern of change or trajectory over time in their HGC levels. Membership in a particular subgroup may be differentially impacted by exposure to prenatal factors, such as maternal depressive and anxious symptomatology. It is important to assess whether various forms of stress, such as anxiety or depression, affect child outcomes in different ways. In that case, care can be personalized to the specific needs of these vulnerable subgroups. For example, prenatally and postnatally, maternal depressive symptomatology appears to have more effect on different types of child maladjustment compared to maternal anxiety, which was related to internalizing difficulties among children (Barker et al., 2011).

Furthermore, associations between both prenatal and postnatal anxiety and depression with child stress response are sometimes influenced by other factors, such as child sex (Kortesluoma, 2021), or low socio-economic status (SES) related to maternal education and income (Nolvi et al., 2022). These factors may modify cortisol or cortisone levels via direct or indirect effects. Regarding child sex differences, the intrauterine environment varies as the placenta reacts differently to maternal prenatal stress depending on child sex (Glover, 2014; Monk et al., 2019). In addition, maternal prenatal distress appears to be related to higher prevalence of certain mental health or neurodevelopmental outcomes depending on whether the child is male or female, with results indicating that males are more susceptible to the detrimental effects of maternal stress experience early in pregnancy (Matas-Blanco and Caparros-Gonzalez, 2020; Monk et al., 2019). Regarding low SES, mothers can be exposed to social adversity that can directly impact maternal prenatal stress hormone response levels (Monk et al., 2019), as well as heightening the risk of developing depression and anxiety (Field, 2017). After birth, child stress response may also be directly affected by SES (Tarullo et al., 2020), and indirectly by maternal mental health difficulties ensuing from these conditions (Zhu et al., 2019).

This present study adds to the literature by exploring the potential longitudinal impact of maternal depressive and anxious symptomatology on child stress response from birth to 5 years in a community-based sample while controlling for confounding variables and exploring the moderating effect of child sex and maternal SES. Study hypotheses posit that higher levels of anxious or depressive symptomatology are linked to higher levels of measured hair cortisol, cortisone and their ratio among children, and that these effects are moderated by child sex and maternal SES. Given the literature, it is hypothesized that the moderation effect will be stronger among mothers with male offspring and low SES. Moreover, using a community-based sample allows us to study these effects in women with varying levels of symptomatology. Findings from this study will identify areas for future investigation and intervention: an important step to support maternal mental health and promote beneficial child outcomes.

2. Methods

2.1. Participants

Ethical approval for the EDEN longitudinal cohort was provided by the Kremlin Bicêtre ethics committee and the French data privacy institution (CNIL: Commission Nationale Informatique et Liberté). The EDEN cohort was created between 2003–2006 from 2 university hospitals in France (Nancy and Poitiers) to study the pre- and early postnatal determinants of child health and development. Full information regarding cohort characteristics have been published by Heude et al. (2016). Cohort enrollment was proposed to 3758 eligible adult women before 24 weeks amenorrhea during prenatal visits in the Obstetrics and Gynecology departments of these hospitals. Women were not compensated for participation. No restrictions regarding women's maximum age or previous pregnancies were applied. Mothers were excluded from this cohort if they had multiple pregnancies, pre-pregnancy diabetes,

plans to relocate within the next 3 years, or French illiteracy. A total of 2002 women agreed to participate and provided written consent for themselves at inclusion. At birth, data was obtained from 1899 mother–infant pairs and maternal written consent was obtained for child inclusion. Over the past years, EDEN has gathered various data on mothers and children from medical records, face-to-face interviews with mothers, and parent self-report questionnaires at numerous time points (24 weeks amenorrhea; birth; 4 months; 8 months; 1 year; 2 years; 3 years; 4 years; 5 years).

From this cohort, all dyads for which hair samples were collected (at birth, 1, 3, 5 years) were included in the present study sample. This resulted in a total of 281 mother-child dyads, although sample size did vary depending on time points (see Table 1). Our study sample differed significantly from the overall EDEN cohort regarding type of delivery, as hair samples were obtained significantly less often from children born via caesarean section (11% of women gave birth via caesarean section compared to 17% in the overall EDEN cohort).

2.2. Measures

2.2.1. Depressive symptomatology

Maternal symptoms of depression were measured using 2 scales: (1) the French validated version of the Center for Epidemiologic Studies Depression Scale (CES-D) (Fuhrer and Rouillon, 1989; Radloff, 1977) at 24 weeks amenorrhea, as well as at the 3- and 5-year follow-up, and (2) the French validated Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) at 4, 8 and 12 months postpartum.

Regarding the CES-D (Fuhrer and Rouillon, 1989; Radloff, 1977), participants rated on a 4-point Likert scale (0 (never) - 3 (frequently)) 20 statements of how they perceived symptoms and behaviors related to mood in the previous week, such as “I felt lonely” or “My sleep was restless”. Overall scores ranged between 0–60 with some items reverse scored. A cut-off score of 16 or above was used in this study as a binary variable to indicate high levels of depressive symptomatology as recommended by Radloff (1977). In this sample, CES-D internal consistency was evaluated at $\alpha = .80$ (24 weeks amenorrhea), $\alpha = .76$ (3-year follow-up), and $\alpha = .84$ (5-year follow-up).

The EPDS is a 10-item questionnaire specifically designed to screen for postnatal depression as it is sensitive to mothers’ perinatal somatic experiences (Cox et al., 1987). Scores ranged from 0–30 with a cut-off score of 13 and above applied for this study as a binary variable to indicate whether mothers presented high levels of postpartum depressive symptomatology. Mothers rate statements (for example “I have blamed myself unnecessarily when things went wrong”) depending on how they felt over the past 7 days on a 4-point Likert scale (0 (never) - 3 (Most of the time)). In this sample, internal consistency was $\alpha = .84$ (4-months postpartum), $\alpha = .87$ (8-months postpartum), and $\alpha = .89$ (12-months postpartum).

2.2.2. Anxious symptomatology

The French validated State Anxiety Inventory (STAI) (Bruchon-Schweitzer and Paulhan, 1993; Spielberger, 1970) reported anxious symptomatology at 24 weeks amenorrhea. Mothers responded to 20 statements reflecting current emotional states (for example “I feel calm” or “I feel frightened”) on a Likert type scale (1: not at all to 4: very much). Scores ranged between 20 to 80 with a score of 38 or above indicating high levels of anxious symptomatology used as a binary variable in this study. In this sample, internal consistency was satisfactory at $\alpha = .96$.

2.2.3. Child hair glucocorticoids

Child hair included in this study was collected in one hospital (Poitiers) by a pediatrician or midwife at birth, 1 year, 3 years and 5 years. Professionals were instructed to: cut 3 cm of child hair with scissors from the occipital area, place hair in an envelope labelled with an ID number, and store it in a cabinet at room temperature. Only samples with sufficient hair quantity were sent for analysis to Dresden Lab Services GmbH (http://www.dresden-labservice.de/). High

Table 1
Child hair glucocorticoid characteristics.

	Cortisol (pg/mg)				Cortisone (pg/mg)				Cortisol-to-Cortisone ratio (pg/mg)			
	0 years	1 years	3 years	5 years	0 years	1 years	3 years	5 years	0 years	1 years	3 years	5 years
Data preparation												
Missing values	83	8	3	5	83	7	3	5	83	12	6	12
BLODs deleted[a]	0	4	3	7	0	0	0	1	0	0	0	0
Winsorized data	11	4	4	1	10	22	25	17	10	5	10	6
N	198	269	275	269	198	274	278	275	198	269	275	269
Descriptive statistics												
Before data cleaning												
Mean	66.90	5.56	2.29	1.65	20.43	8.04	6.80	4.89	0.36	3.16	4.18	5.57
Standard deviation	50.48	16.39	2.98	4.83	15.71	5.85	4.80	4.60	0.26	3.05	2.74	7.28
Median	64.93	2.64	1.65	0.92	18.58	6.76	5.70	3.47	0.30	2.80	3.74	4.28
Minimum	2.04	0.02	0.05	0.01	0.42	0.06	0.00	0.03	0.09	0.05	0.01	0.03
Maximum	415.30	210.82	29.05	75.92	125.03	27.39	24.27	29.50	2.85	34.10	28.92	82.12
Range	413.26	210.79	29.01	75.91	124.61	27.33	24.27	29.47	2.76	34.04	28.91	82.09
After data cleaning[b]												
Mean	1.67	0.36	0.15	-0.10	1.17	0.75	0.68	0.49	0.39	-0.50	0.55	0.61
Standard deviation	0.42	0.53	0.44	0.53	0.38	0.42	0.43	0.46	0.30	0.20	0.28	0.32
Median	1.81	0.42	0.22	-0.04	1.27	0.83	0.76	0.54	0.45	-0.52	0.57	0.63
Maximum	2.18	1.69	0.95	1.16	1.67	1.24	1.16	1.14	0.96	-0.11	0.91	1.34
Minimum	0.31	-1.61	-1.34	-1.97	-0.38	-1.25	-3.08	-1.48	-1.28	-1.04	-2.11	-1.46
Range	1.87	3.30	2.29	3.13	2.05	2.50	4.24	2.62	2.24	0.93	3.03	2.80
Coefficient of variation[c]	62.64	165.10	86.80	128.05	63.75	66.82	64.23	81.20	47.01	53.58	40.46	73.50
Mean differences[b]												
Male	1.66	0.36	0.15	-0.10	1.17	0.75	0.68	0.49	-0.50	0.39	0.55	0.60
Female	1.65	0.38	0.17	-0.22	1.17	0.79	0.68	0.34	-0.48	0.40	0.52	0.58
T-value[d]	-0.33	0.39	0.90	-3.47 ***	0.12	1.45	-0.15	-5.24 ***	1.35	0.28	-1.20	-1.22

[a] Below level of detection (BLOD);
[b] Winsorized, and log-transformed data;
[c] Winsorized not log-transformed data;
[d] Welch Two Sample t-test;
* < .05, ** < .01, *** < .001.

performance liquid chromatography tandem mass spectrometry (LC–MS/MS) was used to detect different corticosteroids, as it shows high sensitivity, reproducibility, and little cross reactivity (Gao et al., 2013). Child hair samples were analyzed as complete segments according to the following procedure: (1) washed in 3 mL isopropanol for 3 min (two times), (2) steroid hormones were extracted from whole, non-pulverized hair using 1.8 mL methanol for 18 h at room temperature, (3) 1.6 mL of the clear supernatant was transferred into a new 2 mL tube, (4) alcohol was evaporated at 50 °C under a constant stream of nitrogen and reconstituted with 225 μL double-distilled water and 20 μL of a mixture cortisol-d4, cortisone-d7, testosterone-d5, DHEA-d4, and progesterone-d9 as internal standards, (5) of this reconstituted extract, 100 μL were injected into a Shimadzu HPLC-tandem mass spectrometry system (Shimadzu, Canby, Oregon) coupled to an SCIEX API 5000 Turbo-ion-spray triple quadrupole tandem mass spectrometer (SCIEX, Foster City, California) with purification by online solid-phase extraction.

Hair cortisol and hair cortisone concentrations and their ratio were reported in pg cortisol/cortisone per mg sample weight and used as a continuous variable in these analyses. Inter- and intra-day variation were determined by calculating precision and accuracy estimates for hair samples with three replicates each on three separate days. The inter- and intra-assay coefficients of variance (CV) were below 10% for both cortisol and cortisone, and within the acceptable range (CV <15%) (Caruso et al., 2008; Gao et al., 2013).

The lower limit of quantification (LLOQ) is dependent on the weighted mass of hair used, which ranged from 0.10 to 5.00 mg. Following the current LC-MS/MS protocol, the LLOQ values correspond to 0.3 pg/mg for both cortisol and cortisone (Wang et al., 2019). Values below the level of detection (BLOD) were marked as "0" in the dataset by the laboratory. The lowest and highest detected concentrations of hair cortisol and hair cortisone in child hair samples of this study were 0.01 pg/mg to 415.30 pg/mg of cortisol and 0.03 pg/mg to 125.03 pg/mg of cortisone respectively.

2.2.4. Moderators

Maternal low SES or social disadvantage was determined by combining the following indicators measured at baseline: monthly family income below 1500€, at least one reported financial difficulty (any difficulties with clothing, feeding or utilities), unemployed during pregnancy and actively searching for a job, and no further studies after high school. Mothers presenting at least one of these indicators were placed in the low SES or social disadvantage group during moderation analyses. Child sex assigned at birth was also assessed as a moderator in this sample.

2.2.5. Covariables

Potential covariables and confounders were assessed via a literature review. Included binary covariables were premature birth (before 37 weeks of pregnancy), small for gestational age (underweight at birth), tobacco use before or during pregnancy, cannabis use before or during pregnancy, asthma during pregnancy (as an indicator for steroid-use), psychiatric medication before pregnancy (either antidepressants, anti-anxiety agents, sleeping pills, or tranquilizers). Included categorical covariables were mothers' body mass index (a BMI score above 25 before pregnancy was considered overweight and grouped into not above 25, between 25–30, or above 30), season of birth (January-March, April-June, July-September, or October-December), and type of delivery (vaginal, forceps/vacuum, or caesarean section).

2.3. Statistical analysis

2.3.1. Hair data preparation

Before any inferential analyses, hair GC data needs to be prepared with appropriate statistical methods. Following recommendations by Keizer et al. (2015), the "all data' method was used in the first instance. All detectable concentrations were included as continuous data, including points below the LLOQ (0.3 pg/mg). Concentrations below the level of detection were discarded. Secondly, it is important to winsorize the data to deal with outliers and extreme values. Any cortisol and cortisone values above 3 standard-deviations were winsorized, which in turn modified the cortisol-to-cortisone ratio. Third, data was then log10-transformed as it was highly skewed. See Table 1 for detailed information on child hair CG values before and after these procedures under the section "Data preparation".

2.3.2. Inferential analyses

First, longitudinal HGC data were explored via descriptive statistics, repeated measures ANOVAs, Paired-Samples t-tests, coefficient of variation (CV) and trajectory analyses after ensuring data fit specific requirements for each procedure. Repeated measures ANOVA determined whether there were significant changes in mean score over 3 or more time points. Pairwise comparisons were conducted via paired t-tests to verify whether these changes in HGC mean scores were significantly different between two specific time points. The Bonferroni adjustment was then applied to this analysis by multiplying the p-value for each test by the number of tests being carried out. The CV is calculated at each time-point to assess the level of dispersion around the mean. The higher the coefficient of variation, the greater the level of dispersion around the mean, indicating more heterogeneity among observations.

Second, trajectory analyses on the hair cortisol data were performed using Group-based trajectory modelling (GBTM) via the Proc Traj procedure on SAS software (version 9.4; SAS Institute, Inc., Cary, NC). GBTM uses maximum likelihood estimation (MLE) to identify groups of distinctive trajectories, which are summarized by a finite set of polynomial functions (Nagin, 2014). GBTM classifies individuals into meaningful subgroups that show statistically similar trajectories by estimating each individual's probability for membership in a trajectory and assigning them to the group for which they have the highest probability of belonging. Missing data is handled by GBTM by fitting a model using Maximum Likelihood Estimation (MLE) that assumes data are missing at random (MAR). Trajectory selection was assessed by (1) Bayesian information criterion (BIC) with a preference of $2 * \Delta BIC > 10$ (Bayes factor) between consecutive models, (2) adequate sample proportion in each group, (3) a parsimonious model, (4) a maximized average posterior probability (APP) value at > 0.75 for each group, (5) reasonably narrow confidence intervals, and (6) the odds of correct classification of above 5 for each group.

Third, alternatively, associations between depressive and anxiety symptomatology with HGC data at different time points were explored on R Studio (version 4.1.2) via linear regressions (unadjusted analyses) and weighted regressions (adjusted). Due to the lack of sample randomization, inverse probability weighting (IPW) was applied to control for confounding while exploring associations between exposures and outcomes (Chesnaye et al., 2021). The detailed methodology followed in this study for IPW is presented in a recent paper by Pishgar et al. (2021). Essentially, this consisted of first dealing with missing data via the Multiple Imputation by Chained Equations function in the MICE package on R that provided 5 imputed datasets. As a first step, all missing data were imputed (see Table 2 for amount of missing data per variable), except for GC hair data values at birth. Due to the large amount of missing child GC hair data at birth, data was not imputed for GC data at this time point for IPW analyses, which were run on a smaller sample size ($n = 198$). Scale internal consistency was calculated from imputed data. Multiple Imputed Datasets were weighted using the "within" approach and balance was achieved when the standardized mean difference (SMD) were below 0.20 and Kolmogorov-Smirnov (KS) means were under 0.10 (McCaffrey et al., 2013). All confounders in this study were sufficiently balanced and were included in weighted-logistic regression models. In these analyses, exposure outcomes are binary. For each time point, depending on whether anxiety or depressive symptomatology was being assessed, anxiety or depressive symptomatology

Table 2
Socio-demographic characteristics of the EDEN cohort participants included in analyses (n = 281).

	N[a]	N or mean	% or SD
Maternal characteristics			
Maternal age	281	30.6	4.8
Primiparous (yes)	281	137	48.8
BMI > 25	274	82	29.9
25-30		53	19.3
> 30		29	10.6
Socio-economic factors			
Household income < 1500 €/month	278	38	14.0
At least 1 financial difficulty (clothing, feeding, utilities)	278	28	10.0
Mother unemployed and not studying	277	60	22.0
Mothers with at least one indicator of low SES composite	281	98	34.9
Substances			
Asthma (indication of steroid use)	271	32	12.0
Psychiatric medication before pregnancy[b]	268	39	15.0
Cannabis before pregnancy	277	17	6.0
Cannabis during pregnancy	274	5	2.0
Tobacco use before pregnancy	279	95	34.0
Tobacco use during pregnancy	276	72	26.0
Depressive and anxiety symptomatology			
High prenatal anxiety symptomatology (STAI >38)	273	49	18.0
High prenatal depressive symptomatology (CES-D >16)	273	56	20.5
Comorbidity of prenatal anxiety and depressive symptoms	273	32	11.4
High depressive symptomatology at 4-months (EPDS >13)	273	17	6.2
High depressive symptomatology at 8-months (EPDS >13)	270	29	10.7
High depressive symptomatology at 12-months (EPDS >13)	263	31	11.8
High depressive symptomatology at 3-years (CES-D >16)	259	52	20.1
High depressive symptomatology at 5-years (CES-D >16)	263	36	13.7
Child characteristics			
Child sex	273		
Male		142	52.0
Female		131	48.0
Birth season	281	87	31.0
January-March		57	20.3
April-June		70	24.9
July-September		66	23.5
October-December			
Premature birth	273	14	5.0
Small for gestational age	281	22	8.0
Delivery type	273		
Vaginal		212	77
Forceps/vacuum		32	12
Caesarean section		29	11

[a] Variable total counts may vary due to missing values on individual variables
[b] Antidepressants, antianxiety agents, sleeping pills, tranquilizers.

were evaluated as a binary variable (based on their cut-off score) at each data point, compared to the rest of the sample (without anxiety or depressive symptomatology). Given that data was log10-transformed, Beta scores were exponentiated to facilitate interpretation. Results are presented as adjusted odd ratios (aORs). These weighted analyses were then moderated using the TWANG package in R (Griffin et al., 2022).

Statistical power for a sample size of 281 dyads with a log-normal distribution of effect size (d = .2; SD =. 2; α = .05) is as follows: (1) the power in the positive direction is .39 and the power in the negative direction is .00; (2) with study variation, the power in the positive direction is .44 and the power in the negative direction is .03 (Kenny, 2017).

3. Results

3.1. Mother and child characteristics

Maternal and child socio-demographic characteristics including missing data values are presented in Table 2. In this study sample, 48.8% (n = 137) of mothers were expecting their first baby, 34.9% (n = 98) had a low SES composite score, 18% (n = 49) presented high levels of prenatal anxiety symptomatology, 20.5% (n = 56) presented high levels of prenatal depressive symptomatology. High levels of postpartum depressive symptomatology varied between 6.2% to 20.1% at different time points. Regarding children, 52% (n = 142) were boys and 48% (n = 131) were girls.

3.2. Hair glucocorticoid characteristics and trajectory analyses

Concentrations of HGCs before and after data cleaning are presented in Table 1. Mean and median cortisol or cortisone hair levels decreased from birth to 5 years, whereas mean levels of cortisol transformed to cortisone increased. Repeated ANOVAs revealed statistically significant differences in mean levels of cortisol (F(3, 727) = 160.8, p < .001), cortisone (F(3, 741) = 101.2, p < .001), and cortisol-to-cortisone ratio (F (3, 726) = 734.7, p < .001), indicating that child HGC mean levels differed between the 4-time points. Furthermore, posthoc t-tests revealed that these mean HGC levels differed significantly between each time point (see supplementary material 1), except between 1-year and 3-year cortisone levels (t(270) = 1.8, p = .42), which indicates that cortisone does not increase or decrease significantly between the ages of 1- to 3-years among children in this sample. Cortisol and cortisone levels were correlated between succeeding points of measurement (0–3, 1–3, 3–5 years). Cortisol-to-cortisone ratios were correlated between 1–3, 3–5, as well as 1–5 years (see supplementary material 1).

As described in Table 1, the coefficient of variation showed greater levels of dispersion around the mean for cortisol at 1 and 5 years. Data seemed to be slightly more dispersed at 5 years with regards to cortisone and cortisol-to-cortisone ratio. HGC data was fairly similar among males and females, only cortisol (t(250) = −3.5, p = .00) and cortisone (t(262) = −5.2, p = .00) levels at 5 years differed significantly by child sex, with boys having lower concentrations.

Following model selection criteria, GBTM did not classify children into different trajectories for hair cortisol, hair cortisone, and CCratio data, as confidence intervals greatly overlapped and group sizes did not allow for meaningful interpretation. Any distinguishable groups remained very small (see supplementary material 2 for full results). Overall, the superior model remained the one with only 1 group, which was used for the following analyses presented below to assess outcomes at each time point separately.

3.3. Weighted regressions

After IPW adjustment, prenatal depressive symptomatology was significantly associated with higher levels of child hair cortisone at 1 year (OR_{IPW} [95% CI]: 1.1 [1–1.3]). They were also linked to higher CCratio levels measured at 5 years (OR_{IPW} [95% CI]: 1.1 [1–1.2]). No further significant associations were found between prenatal depressive symptomatology and child hair GCs (see Table 3).

Adjusted measures of prenatal anxiety symptomatology were significantly linked to higher levels of child cortisol measured at birth (OR_{IPW} [95% CI]: 1.2 [1–1.3]; and to higher levels of child cortisone at birth (OR_{IPW} [95% CI]: 1.2 [1.1–1.3]; and at 1 year (OR_{IPW} [95% CI]: 1.2 [1.1–1.3]. No further significant associations were found between prenatal anxiety symptomatology and child hair GCs at the 3-year and 5-year follow-ups (see Table 3).

Regarding maternal depression in the first year postpartum, depressive symptomatology at 8 months postpartum were linked to higher levels of cortisone in child hair at the 3-year follow-up when

Table 3
Associations between maternal prenatal depressive or anxious symptomatology and child cortisol, cortisone, cortisol-to-cortisone ratio from ages 0 to 5 years (n = 198).

		Depression (*n*= 56)				Anxiety (*n* = 49)			
Child hair glucocorticoids(pg/mg)	Child age	Unadjusted		IPW		Unadjusted		IPW	
		OR	95% CI	aOR	95% CI	OR	95% CI	aOR	95% CI
Cortisol	0	1.09	(0.94-1.26)	1.08	(0.93-1.27)	1.19	(1.02-1.39)*	1.16	(1.02-1.32)*
	1	1.07	(0.89-1.29)	1.12	(0.95-1.31)	1.15	(0.95-1.40)	1.15	(0.99-1.33)
	3	0.97	(0.83-1.14)	0.98	(0.84-1.15)	0.95	(0.80-1.12)	0.93	(0.80-1.07)
	5	1.04	(0.87-1.25)	0.98	(0.81-1.18)	1.01	(0.83-1.22)	0.86	(0.70-1.06)
Cortisone	0	1.09	(0.96-1.25)	1.10	(0.99-1.24)	1.19	(1.04-1.36)*	1.17	(1.05-1.32) **
	1	1.09	(0.95-1.26)	1.14	(1.00-1.29)*	1.19	(1.02-1.38)*	1.17	(1.05-1.30) **
	3	1.08	(0.93-1.26)	1.03	(0.90-1.18)	1.03	(0.87-1.21)	0.96	(0.84-1.10)
	5	1.15	(0.98-1.36)	1.08	(0.90-1.24)	1.06	(0.89-1.26)	0.93	(0.78-1.11)
Cortisol-to-cortisone ratio	0	1.00	(0.93-1.07)	1.00	(0.93-1.07)	1.01	(0.94-1.08)	1.00	(0.94-1.08)
	1	1.02	(0.915-1.14)	0.99	(0.89-1.09)	1.00	(0.89-1.13)	1.03	(0.94-1.12)
	3	1.11	(1.00-1.24)	1.05	(0.96-1.15)	1.10	(0.98-1.23)	1.05	(0.97-1.13)
	5	1.09	(0.98-1.21)	1.11	(1.01-1.21)*	1.02	(0.91-1.15)	1.07	(0.93-1.27)

Unadjusted linear regressions and IPW-adjusted regressions (95% CI);
* < .05, ** < .01, *** < .001.

adjusted (OR_{IPW} [95% CI]: 0.9 [0.7–1]) (see Table 4). Additionally, depressive symptomatology at 12 months postpartum were related to higher levels of cortisol-to-cortisone at 5 years when adjusted (OR_{IPW} [95% CI]: 1.1 [0.8–1.4]). No significant associations were found between maternal depressive symptomatology measured at 3- and 5-year follow-ups and child GCs (see Table 5).

3.4. Moderated weighted regressions

Weighted moderation analyses were conducted to explore whether the significant associations found in the weighted regressions were moderated by child sex or maternal SES during pregnancy. Unadjusted analyses revealed one moderating effect: maternal SES moderated the association between 8-month postpartum depressive symptomatology and cortisone levels among 3-year-old children (OR [95% CI]: 0.5 [0.4–0.8]) (see supplementary material 3). However, adjusted analyses were not significant indicating that child biological sex or maternal SES during pregnancy did not interact significantly on the relationship between depressive and anxiety symptomatology with child hair GCs at those specific time points.

4. Discussion

The aim of this study was to explore in a community-based sample the effects of maternal depressive and anxiety symptomatology on child stress response from birth to age five, assessed through hair cortisol and cortisone levels. Overall, findings showed that children did not follow specific HGC trajectories from birth to the 5-year follow-up. After controlling for confounding variables, high depressive and anxiety symptomatology were only linked to increased levels of child cortisol, cortisone and cortisol-to-cortisone ratio at certain time points and these associations were small, with the exception of prenatal anxiety and HGC in the first year. These effects were not moderated by child sex or maternal SES. Furthermore, findings show a certain within person variation as HGC levels differed between time points and prenatal anxiety and depressive symptomatology were associated with child stress responses only at particular time points. It is possible that other factors occurring during early childhood may protect children by buffering or reversing prenatal stress effects, such as parenting, financial status of the family, or less exposure to stressors (Gray et al., 2018).

Trajectory analyses indicated that our sample could not be partitioned into subgroups following specific trajectories of child hair cortisol and cortisone from birth to 5 years. This is in contrast to recent results by

Table 4
Associations between maternal postpartum depressive symptomatology measured via the EPDS at 4, 8, and 12 months and child cortisol, cortisone, cortisol-to-cortisone ratio from ages 1 to 5 years (n = 281).

		Depression EPDS 4 months (*n* = 17)				Depression EPDS 8 months (*n* =29)				Depression EPDS 12 months (*n* =31)			
Child hair glucocorticoids (pg/mg)	Child age	Unadjusted		IPW		Unadjusted		IPW		Unadjusted		IPW	
		OR	95% CI	aOR	95% CI	OR	95% CI	aOR	95% CI	OR	95% CI	aOR	95% CI
Cortisol	1	0.98	(0.77-1.29)	1.01	(0.76-1.35)	1.11	(0.91-1.36)	1.01	(0.76-1.32)	0.99	(0.82-1.20)	1.01	(0.79-1.27)
	3	0.81	(0.66-0.98) *	0.81	(0.65-1.01)	0.89	(0.76-1.05)	0.90	(0.77-1.05)	0.92	(0.79-1.08)	0.90	(0.77-1.06)
	5	1.05	(0.82-1.35)	0.99	(0.73-1.36)	0.88	(0.72-1.07)	0.94	(0.73-1.20)	0.97	(0.81-1.17)	0.92	(0.76-1.35)
Cortisone	1	1.00	(0.82-1.23)	1.01	(0.86-1.89)	1.12	(0.96-1.32)	1.10	(0.94-1.29)	1.02	(0.87-1.19)	1.06	(0.91-1.24)
	3	0.91	(0.74-1.12)	0.83	(0.64-1.06)	0.77	(0.65-0.90) **	0.85	(0.74-0.98)*	0.83	(0.71-0.98) *	0.87	(0.73-1.05)
	5	0.88	(0.71-1.10)	0.81	(0.53-1.24)	0.85	(0.71-1.01)	0.99	(0.77-1.25)	0.99	(0.84-1.17)	1.01	(0.85-1.21)
Cortisol-to-cortisone ratio	1	1.04	(0.90-1.20)	1.03	(0.87-1.21)	0.99	(0.88-1.11)	1.04	(0.94-1.15)	1.10	(0.99-1.22)	1.07	(0.98-1.17)
	3	1.02	(0.89-1.16)	0.99	(0.87-1.15)	0.89	(0.80-0.99) *	0.98	(0.89-1.08)	0.91	(0.83-1.10)	0.99	(0.88-1.10)
	5	0.93	(0.80-1.08)	0.95	(0.76-1.20)	1.02	(0.90-1.15)	1.07	(0.96-1.12)	1.06	(0.94-1.19)	1.14	(0.76-1.35) *

Unadjusted linear regressions and IPW-adjusted multinomial regressions (95% CI);
* < .05, ** < .01, *** < .001

Table 5
Associations between maternal depressive symptomatology measured via the CES-D at 3- and 5-years postpartum and child cortisol, cortisone, cortisol-to-cortisone ratio from ages 3 to 5 years (n = 281).

		Depression CES-D 3 years (n = 52)				Depression CES-D 5 years (n = 36)			
Child hair glucocorticoids (pg/mg)	Child age	Unadjusted		IPW		Unadjusted		IPW	
		OR	95% CI	aOR	95% CI	OR	95% CI	aOR	95% CI
Cortisol	3	0.94	(0.82-1.06)	0.91	(0.75-1.11)				
	5	1.06	(0.91-1.23)	1.06	(0.90-1.24)	0.93	(0.78-1.11)	0.92	(0.77-1.09)
Cortisone	3	0.89	(0.76-1.03)	0.89	(0.76-1.03)				
	5	0.98	(0.85-1.13)	0.98	(0.85-1.13)	0.90	(0.77-1.05)	0.93	(0.79-1.08)
Cortisol-to-cortisone ratio	3	0.93	(0.86-1.00)	1.06	(0.90-1.24)				
	5	0.96	(0.88-1.06)	0.96	(0.87-1.05)	0.97	(0.87-1.08)	1.01	(0.89-1.13)

Unadjusted linear regressions and IPW-adjusted regressions (95% CI);
* < .05, * *< .01, * ** < .001.

Rovnaghi et al. (2021), who assessed longitudinal trajectories of hair cortisol at 1-, 2- and 3-years of age. They found that cortisol declined among children in low-risk families (favorable demographic and psychosocial factors), whereas other children presented mixed trajectories which seemed to indicate dysregulated profiles of HPA-axis function linked to early life stressors (Rovnaghi et al., 2021). The high representation of families with favorable demographic and psychosocial factors in the EDEN cohort might thus be one reason why we were not able to differentiate between children's HGC trajectories. Another explanation could be that at certain time points, notably at 1 and 5 years, HGC concentration levels varied too much between individuals to assign children to specific meaningful trajectories.

As found in other studies, there exists a certain intra-individual stability as cortisol and cortisone levels were correlated to each succeeding measure as the child grew older (Karlén et al., 2013; Liu et al., 2016). The patterns of HGC concentrations differed significantly between time points: cortisol and cortisone levels decreased over time, whereas the level of cortisol transformed to cortisone increased. A previous study assessing HGC cross-sectionally at different time points also found that child hair cortisol concentrations declined over time (Karlén et al., 2013). Possibly, high levels of cortisol at birth may reflect maternal cortisol levels during the last trimester of pregnancy that are transmitted to the fetus (Monk et al., 2019; Rakers et al., 2017; Stoye et al., 2021).

Contrary to other community-based studies, our study failed to show that maternal prenatal depressive symptomatology predicts child hair cortisol or cortisone levels at birth (Karl et al., 2023) or at a 1-year follow-up (Romero-Gonzalez et al., 2018). This may be due to methodological differences, for example Karl et al. (2023) found that prenatal depressive symptomatology was linked to higher neonatal HGC only in the adjusted analyses when they controlled for covariables (gestational age, mode of delivery, parity, storage time, and pregnancy complications) in the overall sample. This significance was not maintained when assessing a subsample of mothers who only completed the EPDS questionnaire during the third trimester and not postpartum. This suggests that findings may be sensitive to the analysis adjustment, sample size and characteristics. Additionally, Karl et al. (2023)'s findings suggest that the time of assessment of depressive symptomatology may play a role, which also seems to be confirmed by our study as there were less associations between child HGCs and postnatal depressive symptomatology compared to prenatal symptomatology.

High levels of prenatal anxiety symptomatology were linked to higher levels of child cortisol at birth, and cortisone at birth and at 1 year. Other studies did not find these results, as prenatal anxiety symptomatology did not predict hair cortisol at birth in a study with a smaller sample size of 88 dyads that used a different scale for measuring anxiety (Romero-Gonzalez et al., 2018), nor at the 1-year follow-up in a study using the STAI with a similar sample size (Galbally et al., 2019). Furthermore, our study findings were the same among adjusted and unadjusted analyses, indicating that high prenatal anxiety seemed to present a strong independent effect on child GCs in this sample, which was not the case for prenatal depressive symptomatology. This could suggest that different mechanisms may underlie the intrauterine effects of depression compared to anxiety on child stress responses (Glover, 2014). High levels of comorbid symptoms of depression and anxiety in the perinatal period could also play a role (Milgrom and Gemmill, 2020), as 63% of mothers with prenatal anxious symptomatology also presented prenatal depressive symptomatology in our sample. Mothers diagnosed with comorbid depression and anxiety in the third trimester have been found to present higher salivary cortisol levels than controls, which was not the case for mothers diagnosed with only depression or anxiety (Evans et al., 2008). These findings indicate a biological stress response among mothers with comorbid symptomatology during pregnancy that may affect certain underlying biological mechanisms of fetal programming (Glover, 2014).

Our results for the first postpartum year showed that maternal depressive symptomatology at 8 and 12 months postpartum were respectively linked to higher cortisone concentrations and more cortisol transformed to cortisone at age 3 in children. Despite these effects being small, it suggests the possible hypothesis that, beyond in-utero exposure, maternal psychological functioning in the first year postpartum might also impact children's stress response. No significant associations were found between postpartum depressive symptomatology and child hair cortisol levels. The limited literature shows mixed results, as one study did not find any associations between postpartum depressive symptomatology and child hair cortisol, when they measured these associations at 8 weeks via a cross-sectional statistical analysis (Karl et al., 2023). Contrarily to our study, Palmer et al. (2013) found associations with cortisol: 4-week and 1-year postpartum maternal depression scores measured via the Edinburgh Postnatal Depression Scale were positively correlated to 1-year-old children's hair cortisol among mother-child dyads in a community-based sample (Palmer et al., 2013). Their study had a large sample of over 1000 mothers, which may have helped distinguish a significant statistical effect.

Findings in this sample did not show a moderation effect for child sex, which is in line with other papers that did not find any sex-specific effects in the relationship between prenatal maternal stress and child hair cortisol (Romero-Gonzalez et al., 2018; van der Voorn et al., 2018). Female and male cortisol and cortisone levels only differed significantly at 5 years, with a slightly higher level of cortisol among girls. A recent systematic review reported that child hair cortisol was higher among males in 6 studies, however, this is not always the case as no significant sex differences were found in the other 11 studies (Gray et al., 2018) as well as in the present study.

In the present community-based cohort sample, when analyses were not adjusted for confounders, maternal SES moderated the association only between 8-month postpartum depressive symptomatology and cortisone levels among children at the age 3. Moderation by maternal prenatal SES was no longer significant when numerous confounders were adequately considered seemingly indicating a weak effect when not or minimally adjusted. Two previous studies also found HPA-axis alterations after birth with exposure to psychosocial vulnerability and low SES environment but only when adjusting for a couple of

covariables such as gender, age, and small for gestational age (Karlén et al., 2015; Vliegenthart et al., 2016).

4.1. Strengths and limitations

This study presents multiple strengths as it is a community-based sample with longitudinal child HGC data from birth to the age of 5. Assessing HGCs, allows us to explore chronic stress responses among children and are less affected by diurnal cycles than GCs measured via blood or saliva. Furthermore, the statistical methods adequately controlled for confounders and explored data longitudinally, as well as at different time points. Regarding limits, first, this study relies on maternal self-report measures to assess depressive and anxiety symptoms during pregnancy, which may be subject to reporting biases and may not accurately capture the full extent of maternal mental health difficulties (Seth et al., 2016). Studies should incorporate more objective measures of maternal mental health, such as clinical interviews combined with maternal biomarkers of stress, to reduce the potential for reporting biases and improve the accuracy of maternal mental health assessments. Furthermore, even though the cut-off scores of the instruments used in this study are generally reflective of a level of symptomatology corresponding to clinical diagnoses, caution is needed when making any inferences on clinical diagnoses as they were not directly assessed. Second, the use of hair cortisol and cortisone as biomarkers of stress exposure is a relatively novel technique, and there is still limited understanding of the factors that can influence hair cortisol and cortisone measurements (Bates et al., 2017; Gray et al., 2018). Especially as hair cortisol represents a measure of chronic stress that will be affected by multiple factors over time compared to using saliva to measure acute stress. Further research is needed to establish the validity and reliability of hair cortisol and cortisone measurements in children and to better understand the factors that can affect these measurements. Finally, this study was conducted with a sample from only one location in a high-income country with a cohort presenting an overall high SES compared to national standards in France in 2003. Thus, the results may not be generalizable to other contexts, such as low- and middle-income countries. The sample with hair data was also less representative of children born via caesarean section, which is important to note as preliminary evidence suggests that adversity and stressors at birth could impact child HGC levels (Gray et al., 2018).

4.2. Future research

Child hair GCs present a promising measure of stress response in early childhood. Future studies should aim to recruit larger and more diverse samples of mother-child pairs to improve the generalizability of findings to larger populations and to examine potential differences in the relationship between maternal depressive and anxiety symptomatology and child hair cortisol and cortisone across different populations, contexts, and time points. Given the small subsample sizes we were not able to analyze findings from the comorbid group in this paper. However, findings indicate that further research is needed to examine how comorbidity of prenatal maternal depressive and anxiety symptomatology may affect child hair cortisol and cortisone differently to only one classification. Furthermore, this study indicates certain postnatal associations between depressive symptomatology and child HGCs, which is line with the literature showing that child stress response can be impacted by other pathways such as maternal caregiving behaviors (Berg-Nielsen et al., 2002; Khoury et al., 2020; Letourneau et al., 2012; Möller et al., 2016; Bleker et al., 2020; Nolvi et al., 2022; Tarullo et al., 2017; Thomas et al., 2017). Postpartum depression and anxiety can affect parenting behavior, such as increased irritability, withdrawal, and decreased responsiveness, which has been shown to affect the child's stress response system (Berg-Nielsen et al., 2002; Khoury et al., 2020; Letourneau et al., 2012; Möller et al., 2016). These associations should be explored in more detail in future research with an approach that evolves from focusing solely on mother-child dyads and adopt a more systemic approach that accounts for the indirect and direct role of coparents and social support.

5. Conclusion

The present study adds to the currently limited literature with findings from a longitudinal community-based cohort study from pregnancy until the children reach 5 years of age. We can conclude that prenatal anxious symptomatology is associated with child hair cortisol and cortisone concentrations at birth. This was not the case for prenatal depressive symptomatology. Child cortisone levels at 1 year were related to prenatal depressive and anxious symptomatology. These findings suggest a certain intrauterine transmission of prenatal stress. Some evidence was also found for postpartum depressive symptomatology effects. However, contrary to our hypotheses, child hair cortisol and cortisone levels could not be classified into group-based longitudinal trajectories, and explored associations varied between exposure (anxious vs depressive symptomatology), outcomes (cortisol vs cortisone) and analyses (adjusted vs unadjusted). Future research is needed to provide further understanding of the relationship between prenatal maternal depressive and anxiety symptomatology and child chronic stress reactivity to identify potential targets for interventions to support the mental health and development of both mothers, children, and their families.

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CRediT authorship contribution statement

Tafflet Muriel: Data curation, Project administration, Writing – review & editing. **Kirschbaum Clemens:** Formal analysis. **Maguet Charlotte:** Project administration. **Marr Ketevan:** Data curation. **van der Waerden Judith:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Heude Barbara:** Data curation, Project administration, Resources, Supervision, Writing – review & editing. **Koehl Muriel:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. **Kallas Kadri-Ann:** Formal analysis, Writing – review & editing. **Moirangthem Simi:** Data curation, Writing – review & editing. **DOWNES Naomi:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Conflict of interest

We have no conflicts of interest to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.106957.

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