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RESEARCH ARTICLE

Maternal early life and prenatal stress in relation to birth outcomes in Argentinian mothers

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Abstract

Environmental influences before and during pregnancy significantly impact offspring development. This study investigates open research questions regarding the associations between maternal early life stress (ELS), prenatal psychosocial stress, prenatal hair cortisol (HC), and birth outcomes in Argentinian women. Data on ELS, prenatal life events, HC (two samples representing first and second half of pregnancy), and birth outcomes were collected from middle-class Argentinian women ($N = 69$) upon delivery. Linear mixed models indicated that HC increased from the first half to the second half of pregnancy with considerable variability in the starting values and slopes between individuals. Mothers who experienced more ELS, were taller, or more educated, tended to show lower increases in HC. Older age was positively related to HC increases. Our data did not suggest an interaction between ELS and prenatal life events in relation to HC. We found that the change in HC was most likely negatively associated with birth weight. Our data are most compatible with either a weak or the absence of an association between ELS or prenatal life events and absolute values of HC. Mothers with stronger increases in hair cortisol tended to have newborns with slightly lower birth weight. Hence, ELS and birthweight may either have been related to changes in cortisol exposure during pregnancy or to factors that influence accumulation or retention of cortisol in hair.

KEYWORDS
birth outcomes, early life stress, pregnancy hair cortisol, prenatal life events, prenatal programming

1 | INTRODUCTION

Environmental influences during the prenatal period can significantly impact offspring development. This is referred to as fetal programming (Barker, 1998). One critical prenatal environmental factor is maternal psychosocial stress. Prenatal stress has been associated with adverse outcomes in the neonate such as preterm delivery, lower birth weight, and altered stress reactivity in the infant (Ae-Ngibise et al., 2019; Beydoun & Saftlas, 2008; Bussières et al., 2015; Nesari et al., 2018). It furthermore might affect later mental health outcomes of the offspring (Ahmad et al., 2021; van den Bergh et al., 2020). Another important factor that can influence birth outcomes is early life stress of the mother (ELS). ELS refers to adverse childhood experiences (ACEs) under 18 years of age, such as emotional neglect and physical, sexual or

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emotional abuse by a parent, caregiver or other person in a custodial role, as well as other hardships like parental separation and loss of a close person due to death or being in jail (Centers of Disease Control & Prevention, 2021). In a recent review that focused on maternal prepregnancy stress including, but not limited to, ELS, maternal history of abuse occurring before pregnancy was associated with preterm delivery and low birth weight (Nesari et al., 2018). Specifically, studies reporting maternal history of childhood abuse were related to a 57% increase of the risk of low birth weight (Nesari et al., 2018). Furthermore, Appleton et al. (2019) found that more maternal adverse life events during childhood were associated with higher cephalization scores in the offspring. The infant cephalization index score (head circumference divided by birthweight) is considered a marker of asymmetric fetal growth (Leitner et al., 2007). The goal of this study was to investigate the relations between ELS, prenatal stress, and birth outcomes (i.e., gestational age, birth weight and cephalization index). Prenatal stress was assessed by means of life events and hair cortisol, and the study was carried out in a less-well studied population of Argentinian mothers. The following paragraphs will focus on the role of cortisol in relation to (early) life stress and birth outcomes as well as on the current knowledge gaps that we will address in this study.

The mechanisms underlying the relations between maternal ELS, prenatal stress and birth outcomes are poorly understood, although the stress hormone cortisol is thought to play an important role (Beijers et al., 2014; Cherak et al., 2018; Cherak et al., 2019; Epstein et al., 2021; Zijlmans et al., 2015). To ensure normal fetal organ development, cortisol levels normally increase two- to fourfold across pregnancy (Austin & Leader, 2000; Challis et al., 2001; de Weerth & Buitelaar, 2005; Sandman et al., 2006). A recent review analyzed the relationship between maternal ELS and prenatal cortisol regulation as measured by either the cortisol awakening response, diurnal cortisol slope, acute response and recovery to a stressor, or baseline cortisol (measured via blood, saliva, or hair cortisol, HC) (Epstein et al., 2021). ELS was associated with larger cortisol awakening responses as well as blunted, delayed and prolonged cortisol responses to stressors. According to another recent review (Cherak et al., 2018), increased (salivary) cortisol during pregnancy is in turn associated with lower birth weight.

Compared to blood or saliva sampling, which allow to measure more acute stress responses including cortisol reactivity to a stressor or circadian rhythms, hair sampling measures long-term exposure to cortisol. This is particularly interesting to measure the exposure throughout pregnancy. Studies that focused on long-term pregnancy cortisol exposure by measuring HC in relation to either ELS or prenatal stress are limited and remain inconclusive (Epstein et al., 2021; Mustonen et al., 2018; Rinne et al., 2023; Wang, 2021). A recent review found evidence that mainly ELS was associated with prenatal cortisol and that associations with more proximal measurements of stress were less consistent, pointing out the importance of the timing of the stress experience (Rinne et al., 2023). Some studies suggest a possible interaction between ELS and prenatal stress in relation to HC. For example, Bowers et al. (2018) found that anxiety symptoms and perceived stress during pregnancy were only related to prenatal HC among women who had experienced more than 2 adverse childhood events (ACEs) (Bowers et al., 2018). Similarly, Swales et al. (2018) reported that the positive relationship between exposure to trauma in adulthood and HC was stronger among pregnant women who had experienced childhood trauma. These findings call for more studies that investigate this possible interaction. Other open questions are whether ELS and prenatal stress are associated with changes in cortisol over pregnancy and whether these changes are, in turn, associated with birth outcomes (King et al., 2022). According to Marceau et al. (2020), only half the studies examining HC throughout pregnancy report a substantial increase in HC, and individual variability in trajectories is typically ignored.

In sum, previous studies suggest that ELS might alter cortisol regulation during pregnancy, which in turn may influence birth outcomes. It is unclear whether these associations also hold when measures of long-term cortisol (HC) are taken, whether ELS and prenatal stress interact in relation to HC, whether there is a general increase in HC during pregnancy and whether this increase is related to ELS, prenatal stress or birth outcomes. Based on the presented research we formulated the following research questions for our data: (1) Are ELS and prenatal stress (i.e., prenatal life events) associated with birth outcomes in line with previous research? (2) Does HC increase during pregnancy? (3) Are ELS and prenatal life events independently associated with HC or with change in HC over pregnancy? (4) Is there an interaction between ELS and prenatal stress such that the association between prenatal stress and HC is either stronger, or potentially only present, among women that encountered higher ELS? (5) How does HC and change in HC over pregnancy relate to the birth outcomes gestational age, birth weight and the cephalization index?

2 | METHODS

2.1 | Participants

Participants ($N = 81$) were recruited at the Hospital Español de Mendoza in Argentina between April 3, 2017 and April 28, 2017. Of these women, nine later decided against participation and three were discharged before having a chance to fill in the questionnaires, leaving 69 women with complete data in the study. Inclusion criteria were as follows: patient $\geq$ 14 years old, singleton pregnancy with delivery at gestational age $\geq$ 37 weeks, no major physical health issues, no synthetic glucocorticoid treatment during pregnancy, no drug or alcohol abuse during pregnancy, sufficient proficiency in the Spanish language and healthy term infants. Permission to carry out the project was given by the scientific/ethics boards of the hospital.

2.2 | Procedure

Mothers were invited to participate in the study one or two days after delivery, before their discharge from hospital. Mothers were approached by the researcher in the morning. After mothers were informed about the study and had given their written informed

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consent, they were asked to complete the questionnaires. All participants were re-approached one to two times during completion of the questionnaires for eventual clarifications. In the afternoon of the same day or in the morning of the next day, the questionnaires were collected by the researcher. In addition to that, a hair sample of around 100–150 hairs was obtained. Each sample was wrapped in aluminum foil and stored at room temperature. Finally, birth outcome information was collected from the hospital records by the researcher.

2.3 | Measures

2.3.1 | Maternal questionnaires

From the maternal questionnaires, for the present paper we extracted demographic information including age, height, weight, and education.

2.3.2 | Birth outcomes

The following birth outcomes of interest were obtained from the hospital birth records and used for further analyses: birth weight in grams, gestational age in weeks and the cephalization index (head circumference in centimeters divided by birth weight in grams).

2.3.3 | Early life stress of the mother

Childhood trauma was assessed with a combination of the 28-item Childhood Trauma Questionnaire (Bernstein & Fink, 1998) and items from the Adverse Childhood International Questionnaire (ACE-IQ, WHO, 2014). The three items of the CTQ's denial scale were not included as the denial scale has often been omitted in previous research and its variability as indicator of response bias is questionable (MacDonald et al., 2015). Questions of the CTQ (e.g., "I did not have enough to eat") were answered on a five-point scale ranging from "never" = 1 to "very often" = 5. From the ACE-IQ questions F1 through F8, V1 and V4 through V6 of the frequency version (e.g., "Did you live with a household member who was ever sent to jail or prison?") were used. Participants answered these questions with yes or no. Scoring was done according to WHO guidelines (WHO, 2014) which means that some questions of the ACE-IQ were grouped so that participants only received one point independent of whether they experienced one or all events of a certain category of questions (e.g., questions F6,F7 and F8). We calculated sum scores for the CTQ and ACE-IQ items independently. We performed the entire analysis independently for CTQ and ACE-IQ, as they correlated moderately (see Table 2), reflecting the underlying construct of ELS. Given the complexity of the statistical analysis and covariation of the variables, we then decided to simplify results by using the sum of the two standardized sum scores as a measure of ELS. Note that each of these analyses led to similar conclusions with minor fluctuations in effects sizes.

2.3.4 | Prenatal cortisol

The hair samples were split into 2 segments of 4.5 cm each, as measured from the scalp. It is generally assumed that 1 cm of hair reflects one month of cortisol exposure (Sauvé et al., 2007) and all samples were collected within 3 days of delivery. Thus, the segments each measure 4.5 months of cortisol exposure, roughly reflecting cortisol secretion in the first (distal segment) and second half (proximal segment) of pregnancy. HC samples were stored in closed envelopes in a cabinet and collectively sent to the laboratory (Dresden LAB Service GmbH). The Cortisol Saliva Luminescence Immunoassay by IBL International® was utilized in this study, with a lower limit of detection of 0.1 pg/mg. Quality control (QC) samples were included in each batch, and six were randomly dispersed to assess variability. Segmented hair samples were washed in 2.5 mL of isopropanol twice for 3 min each time, dried for 12 h, and then weighed out to 7.5 mg per segment. The hair samples were minced into small pieces and then incubated for 18 h in 1.8 mL high-grade methanol at room temperature. The methanol was evaporated off at 55°C using a steady stream of nitrogen for 30 min, and the residue was resuspended in 225 μL of distilled water with the addition of 20 μL of internal standard (cortisol-d4). The interassay and intra-assay coefficients of variation were calculated to be below 8%. Resulting values were analyzed on the log scale. Note that the underlying cortisol exposure over time that we attempt to measure is an unobserved variable. Hair cortisol can be seen as a proxy for this exposure over time. Previous literature suggested several variables that might cause the HC levels to deviate from this underlying true exposure, including hair washing, hair treatments, sun exposure, intake of corticosteroids, and natural hair color (Dettenborn et al., 2012; Moody et al., 2022). We used a data driven approach to identify variables that might contribute to a deviation of our proxy measure from the underlying cortisol exposure based on previous literature. Variables considered were categorical and included hair washing (<4 or ≥ 4 times per week), natural hair color, used hair products on day of sampling, used corticosteroids in the past 3 months and hair treatments in the past 6 months. Only variables that improved predictive performance in a robust regression based on leave-one-out cross-validation (Vehtari et al., 2017) were included in our main analyses (see below). In our data, only the number of hair washings per week and use of corticosteroids improved model fit and were included in our models according to graphical criteria (Cinelli et al., 2020).

2.3.5 | Prenatal life events

An adapted version of Spurgeon et al. (2001) was used to collect data on pregnancy life events. The questionnaire consisted of 50 (mostly unpleasant) life events. Mothers were asked to indicate for every event whether they had experienced it during pregnancy or not. In line with previous adaptations of stressor lists to specific populations and situations (e.g., for the Democratic Republic of Congo; Mulligan et al., 2012), the questionnaire was adapted to the Argentinian culture in a

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pilot study set up by the last author. To this end, and in consultation with Argentinean colleagues, 23 out of the 55 original items of the life events questionnaire were selected based on their relevance. They were put together with another 27 culturally relevant items relating to finances (e.g., "You had major money problems"), safety (e.g., "While you were at home, a burglar entered or attempted to enter"), and pregnancy/medical issues (e.g., "You received medical check-ups during pregnancy," reversed item). In addition to that, an extra item was added to the questionnaire in which the participants could describe an unpleasant life event that had happened to them and that was not stated in the questionnaire. To give weight to each of the 50 items in the adapted questionnaire, women of childbearing age (e.g., hospital staff and visitors, women in public areas; total $N = 51$, age range: 21–43) were asked to rate the severity of each item on a scale from 0 to 10. The average grade per life event was used as the severity weight. "A baby or child of yours died" was rated as most severe with a weight of 9.66 and "You were able to get enough clothes and things for the baby" (reversed item) was rated as least severe with a weight of 3.30. The list of all life events and corresponding severity weight is provided in Appendix A. We computed the total score for life events by adding the severity scores for the experienced life events. The final scores were highly correlated with the frequency of life events ($r > .99, p < .001$) and effects sizes of the results would not differ meaningfully depending on the choice of weighted sum or frequency (see Table S1).

2.4 | Statistical analysis

We carried out all analyses in R version 4.1.0 (R Core Team, 2021). The code is publicly available (https://doi.org/10.5281/zenodo.7660860). Across 11 out of 13 variables, there were 1.4%–21.7% missing values (Table 1). There was no indication to assume that data was not missing at random (MNAR) and we could not reject the null hypothesis that the data is missing completely at random (MCAR) using Little's MCAR test ($p = .353$). To address missing values, multiple imputation (predictive mean matching; 50 imputations) was applied using the *mice* package (Buuren & Groothuis-Oudshoorn, 2011). Predictive mean matching is a robust imputation method that has been shown to perform well in data sets with mixed variable types and low to moderately high sample sizes (Kleinke, 2017; Kleinke, 2018; Marshall et al., 2010). To answer our research questions, we used a Bayesian Network approach (Scutari & Denis, 2021) as follows: first, we created a directed acyclic graph (DAG; Figure 1) using the *dagitty* package (Textor et al., 2017). DAGs are graphical representations of the researcher's assumptions whereby dependencies between variables (nodes) are represented with arrows (edges). The construction of a DAG can be data and knowledge driven (Scutari & Denis, 2021). First, we drew edges based on prior knowledge. For example, we can exclude that maternal education causes maternal age. A relation in the opposite direction is possible, for example, the older a person the more chances and time to obtain a degree. Next, we added the suspected relations such that ELS influences all outcome variables with two potentially mediating or moderating variables (prenatal life events and HC). In the last step we tested implied conditional independencies using linear models and added missing edges accordingly. The final DAG is shown in Figure 1.

We estimated all relevant total and direct effects corresponding to our research aims using Bayesian robust linear models that utilize the Student's *t* likelihood such that for each node in our network we assume:

$$y_i \sim T(\mu_i, \sigma, \nu)$$

$$\mu_i = \alpha + \beta_1 x_{1_i} + \beta_2 x_{2_i} \ldots + \beta_n x_{n_i}$$

$$\alpha \sim N(0, 5)$$

$$\beta \sim N(0, 0.5)$$

$$\sigma \sim \text{Exp}(1)$$

$$\nu \sim \text{Gamma}(2, 0.1),$$

where the predictors are included according to graphical criteria (Cinelli et al., 2020) for all models. This means that different covariates are included per model, depending on which path coefficient and whether the direct or total effect and is estimated. The exact covariates can be derived from the final DAG (Figure 1) with the graphical criteria (Cinelli et al., 2020). We will report results using all participants (including three participants that used corticosteroids) to maximize power in the Bayesian Network for estimation of path coefficients unrelated to corticosteroid use. However, for our research questions, we performed sensitivity analyses without these three participants and report if results differed meaningfully. The models were fit using the *brms* package (Bürkner, 2018) using mildly informative priors as shown above. Results did not differ compared to using the even less informative default priors of *brms*. The package utilizes the probabilistic programming language *Stan* (Carpenter et al., 2017), which estimates parameters by Hamilton Monte Carlo (HMC) simulation. All continuous variables were standardized before analysis. We explored modeling maternal education as an ordinal variable (Liddell & Kruschke, 2018) using an ordinal regression approach (McElreath, 2020), which is implemented into *brms* with the functions *cumulative* and *mo*. The results did not differ compared to when we modeled it as a continuous variable. Therefore, for simplicity, we present the latter approach. To evaluate whether HC changed over time we fitted a robust hierarchical linear model, allowing the intercept and the effect of time to covary between individuals with covariates included according to graphical criteria. Finally, to estimate the association between change over time with ELS, prenatal life events and the birth outcomes, we either used the difference between the second and the first HC

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TABLE 1 Descriptive statistics of all study variables ($n = 69$).

Variable	Missing	Mean	SD	Median	MAD	Min	Max
Adverse Childhood Events	1.00	2.00	1.37	2.00	1.48	0.00	5.00
Birth weight	0.00	3289.57	475.94	3320.00	489.26	2135.00	4440.00
Cephalization index	1.00	0.01	0.00	0.01	0.00	0.01	0.02
Childhood Trauma Questionnaire	3.00	33.08	7.41	31.00	7.41	24.00	54.00
Educational Level	3.00	4.91	1.61	6.00	0.00	1.00	6.00
Gestational Age	1.00	38.62	1.08	38.50	0.74	36.00	41.00
Hair Cortisol 0–20 weeks	15.00	0.38	0.83	0.46	0.86	−1.61	2.76
Hair Cortisol 21–40 weeks	15.00	1.53	0.51	1.46	0.46	0.67	2.69
Hair washes per week	9.00	3.35	0.61	3.00	0.00	2.00	4.00
Head circumference	1.00	34.94	1.52	35.00	1.48	30.00	39.00
Life events	1.00	22.20	22.64	16.74	16.45	0.00	108.99
Maternal age	0.00	32.64	5.23	33.00	4.45	20.00	42.00
Maternal height*	10.00	162.03	5.69	162.00	5.93	151.00	176.00
Maternal weight*	10.00	64.29	13.60	63.00	13.34	44.00	130.50

MAD = median absolute deviation.
*Measured before pregnancy.

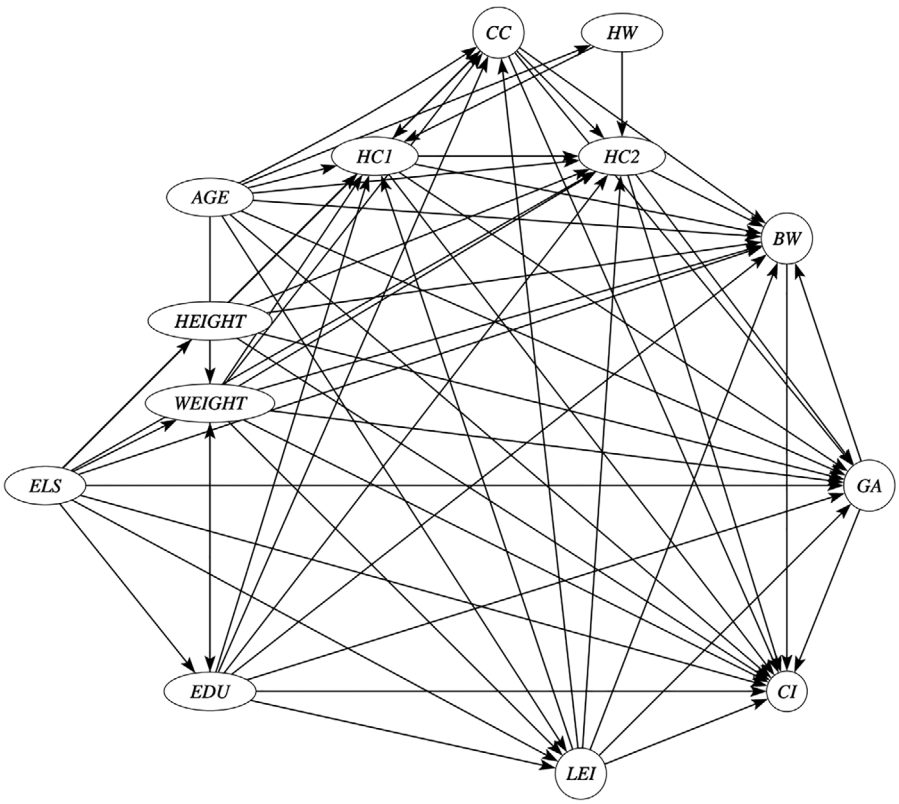


FIGURE 1 Knowledge and data driven directed acyclic graph (DAG) depicting the assumptions that underly the main analyses. BW = birth weight. CC = corticosteroids. CI = cephalization index. EDU = maternal education. ELS = early life stress. GA = gestational age. HC = hair cortisol. HW = hair washing per week. LEI = prenatal life events.

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TABLE 2 Correlation table of all study variables ($n = 69$).

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Life events	–												
2. Childhood Trauma Questionnaire	.25*	–											
3. Adverse childhood events	.24	.39**	–										
4. Hair cortisol 0–20 weeks	.26	.16	.11	–									
5. Hair Cortisol 21–40 weeks	.19	.08	.11	.73***	–								
6. Maternal age	−.20	−.06	−.27*	−.16	−.02	–							
7. Maternal height	−.10	−.17	−.12	−.17	−.31*	.07	–						
8. Maternal weight	.25	.00	.16	.10	.13	.10	.20	–					
9. Educational level	−.22	−.07	−.17	−.08	−.14	.39**	.06	−.27*	–				
10. Gestational age	−.14	.07	.12	.00	.02	−.16	−.01	−.20	.07	–			
11. Head circumference	−.12	−.10	.11	.02	−.06	−.04	.05	.06	.01	.40***	–		
12. Birth weight	.05	.04	.04	.24	.19	.01	.04	.30*	−.08	.53***	.58***	–	
13. Hair washes per week	−.04	−.13	.10	−.47***	−.33*	−.26*	−.06	−.19	.01	.17	.05	−.01	–
14. Cephalization index	−.04	−.05	.02	−.30*	−.22	.03	−.05	−.28*	.07	−.50***	−.38**	−.96***	.04

*$p < .05$.
**$p < .01$.
***$p < .001$.

measurement or the individual slope estimates from the hierarchical model.

For each model, to make a statement with confidence about the presence of an association between two variables, we defined that the 95% quantile-based Bayesian credible interval (CI) of the posterior distribution of the corresponding β parameter must exclude zero. For every β

parameter, we will furthermore report the proportion of the posterior distribution that is larger than zero. This proportion can be interpreted as a probability ($P(\beta > 0)$), given our model assumptions and data. For example, a value of $P(\beta > 0) = 0.04$ means that the corresponding association most likely is negative although it might not pass above criterion to state this with high confidence (the CI can overlap with zero).

3 | RESULTS

3.1 | Descriptive statistics

Table 1 shows descriptive statistics of all study variables including missing data. Correlations between all study variables are shown in Table 2.

3.2 | Research questions

To answer our research questions, we utilized a Bayesian Network (Figure 1) consisting of robust linear models. Direct and total effects derived from the network and relevant to our research questions are listed in Table 3. To model change in HC over pregnancy, we fit a robust linear multilevel model. Parameter estimates of the multilevel model will be mentioned in text. Next to the point estimate and the 95% CI of each β parameter, the table shows the proportion of the posterior distribution that is larger than zero. Figure 2 illustrates the main results of the Bayesian Network graphically by focusing on point estimates of the direct effects and the probability that the effect is positive or negative, respectively. Note that this path diagram (Figure 2) does not show the full DAG that guided our analysis (the full DAG is shown in Figure 1). In the following sections we will present the main results per research question.

(1) Are ELS or prenatal life events associated with birth outcomes in line with previous research?

Our results indicate no or potentially weak associations between ELS or prenatal life events on the birth outcomes (see direct effects in Table 3).

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TABLE 3 Summaries of the posterior distribution for all β parameters of interest (total and direct effect estimates).

Path	Effect	β	95% CI	$P(\beta > 0)$
EDU → LEI	Direct	−.02	−0.28:0.22	.57
ELS → BW	Direct	−.10	−0.3:0.1	.84
ELS → BW	Total	.02	−0.22:0.27	.58
ELS → CI	Direct	−.14	−0.47:0.15	.81
ELS → CI	Total	−.12	−0.38:0.12	.83
ELS → EDU	Direct	−.15	−0.56:0.27	.76
ELS → GA	Direct	.12	−0.13:0.38	.83
ELS → GA	Total	.11	−0.14:0.35	.80
ELS → HC1	Total	.16	−0.1:0.42	.88
ELS → HC1	Direct	.08	−0.15:0.33	.74
ELS → HC2	Direct	−.04	−0.17:0.09	.74
ELS → LEI	Direct	.18	−0.03:0.39	.96
GA → BW	Direct	.62	0.42:0.8	1.00
GA → CI	Direct	−.27	−0.55:0.01	.97
HC1 → BW	Direct	.22	−0.1:0.55	.91
HC1 → CI	Direct	.21	−0.23:0.65	.82
HC1 → GA	Direct	.06	−0.34:0.46	.61
HC1 → HC2	Direct	.45	0.29:0.59	1.00
HC2 → BW	Direct	.00	−0.46:0.47	.50
HC2 → CI	Direct	−.30	−0.97:0.36	.82
HC2 → GA	Direct	.18	−0.39:0.75	.74
LEI → BW	Total	.04	−0.2:0.28	.62
LEI → BW	Direct	.04	−0.17:0.25	.66
LEI → CI	Total	−.07	−0.35:0.19	.69
LEI → CI	Direct	−.19	−0.52:0.13	.88
LEI → GA	Total	−.13	−0.38:0.13	.84
LEI → GA	Direct	−.14	−0.42:0.13	.85
LEI → HC1	Direct	.12	−0.1:0.34	.86
LEI → HC2	Direct	−.02	−0.14:0.1	.66

(2) Does HC increase during pregnancy?

Figure 3a shows the log-transformed scores of HC in the first and second half of pregnancy. Using a hierarchical robust linear model with varying effects at the individual level, we found that, on average, HC increases over time ($\beta = 1.16$, 95% CI [1.01, 1.32]). Figure 3b shows variability in individual starting values (intercepts) and slopes. Intercepts and slopes varied considerably between individuals and were strongly negatively correlated ($r = -.86$, 95% CI [−0.99, −0.69]). Thus, individuals with lower starting values showed a stronger increase in HC over time than individuals who started with higher values. Only a single individual showed a slight decrease over time.

(3) Are ELS and prenatal life events independently associated with HC or change in HC over time?

Our data did not indicate an association between ELS or prenatal life events and the absolute HC measures. However, mothers who scored higher on ELS tended to increase less in HC during pregnancy ($\beta = -.20$, 95% CI [−0.41, 0.01]). Furthermore, older mothers showed a stronger increase ($\beta = .40$, 95% CI [0.17, 0.63]) whereas taller ($\beta = -.20$, 95% CI [−0.41, 0.02]) and highly educated ($\beta = -.21$, 95% CI [−0.43, 0.00]) mothers were more likely to show a smaller increase in HC during pregnancy. As expected, participants who washed their hair more frequently showed a stronger increase ($\beta = .53$, 95% CI [0.13, 0.93]) indicating that hair washing causes stronger wash-out effects in the distal part of the hair sample compared to the proximal part. Results did not differ meaningfully depending on whether we used raw difference scores or the slope estimates from the multilevel model.

(4) Is there an interaction between ELS and prenatal life events such that the association between prenatal life events and HC is

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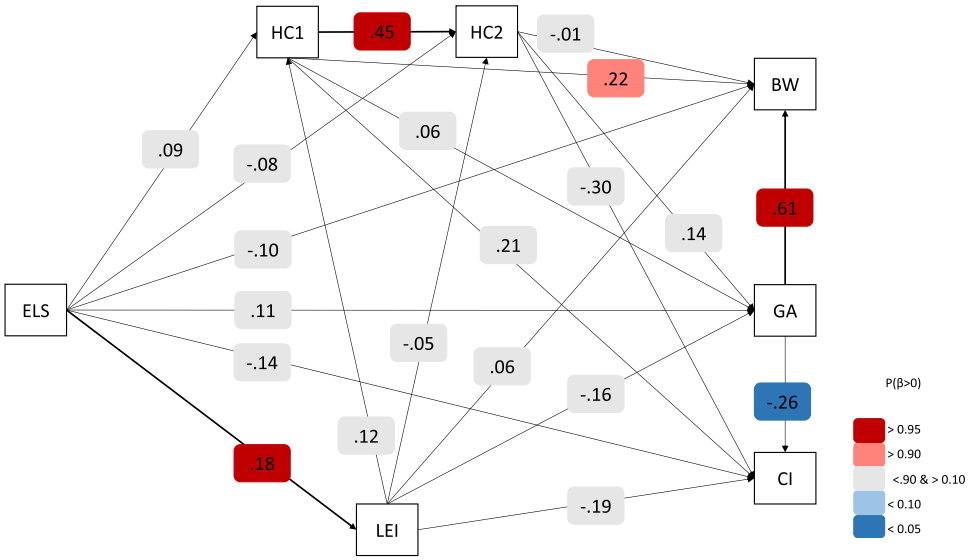


FIGURE 2 Path diagram of main findings. BW = birth weight. CI = cephalization index. ELS = early life stress. GA = gestational age. HC = hair cortisol. LEI = prenatal life events.

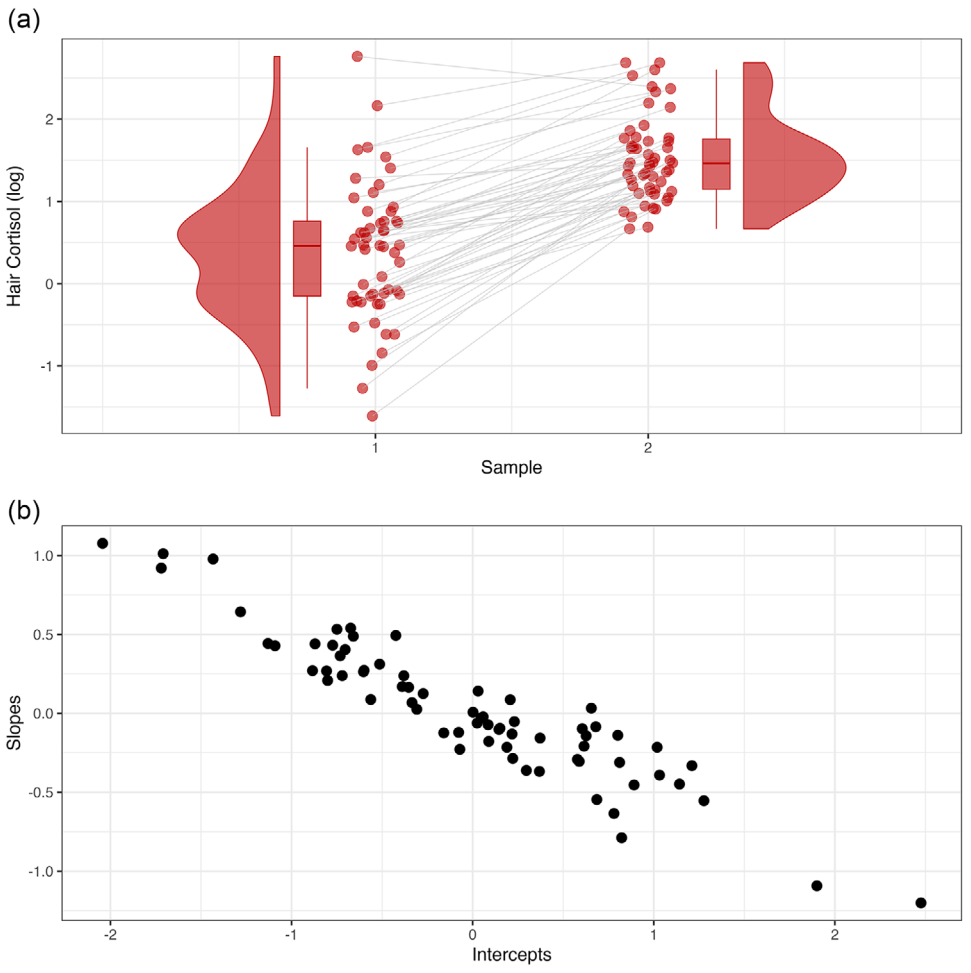


FIGURE 3 (a) Hair cortisol levels per time point on the log scale. (b) Covariation between random intercepts and slopes of the hierarchical model.

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either stronger, or potentially only present, among women that encountered higher ELS?

Our data did not indicate that ELS and prenatal life events interact in relation to HC ($\beta = .05$, 95% CI [−0.18, 0.28]). We further explored the data using a categorical variable where we divided our sample into higher ELS and lower ELS scores (4th quartile of ELS scores vs. remaining subjects). This led to similar results ($\beta = .15$, 95% CI [−0.26, 0.56]).

(5) How does HC and change in HC over time relate to the birth outcomes gestational age, birth weight and the cephalization index?

HC in the first half of pregnancy tended to be positively associated with birth weight (Table 3). We found that change in HC from the first to the second half of pregnancy most likely was negatively associated with birth weight ($\beta = -.20$, 95% CI [−0.41, 0.02], $P(\beta > 0) = .96$), possibly suggesting that mothers who have a higher increase in HC during pregnancy are more likely to have newborns with lower birth weight. Results did not change when using the individual slopes as outcome variable instead of the raw change scores.

4 | DISCUSSION

This study investigated the relations between maternal early life stress (ELS), prenatal psychosocial stress in the form of negative life events, prenatal hair cortisol (HC), and birth outcomes. Our data are most compatible with either a weak or the absence of an association between ELS or prenatal life events and the birth outcomes or absolute values of HC. We found that HC increased from the first to the second measurement with considerable variability in the starting values and slopes between individuals. Those individuals that had the lowest starting values increased the most. Mothers who experienced more ELS, were taller, or more educated, tended to show lower increases in HC. Older age and hair washing frequency were positively related to HC increases. Our data did not suggest an interaction between ELS and prenatal life events in relation to HC. Interestingly, we found that the change in HC was most likely negatively associated with birth weight. In the following, we will interpret and discuss these findings.

As opposed to previous studies, we did not find evidence for an association between ELS or prenatal life events and birth outcomes (Ae-Ngibise et al., 2019; Beydoun & Saftlas, 2008; Bussières et al., 2015; Nesari et al., 2018) when answering our first research question (RQ 1). We also did not find evidence for an interaction between ELS and prenatal life events (RQ 4) in relation to HC (Bowers et al., 2018; Swales et al., 2018). Note however, that our point estimates for the association between ELS and birth weight, prenatal life events, and gestational age, or for the interaction term are not in contrast with the results of previous studies who reported similar point estimates with narrower confidence intervals. Differences in other estimates may furthermore be due to the population studied, as most of the literature to date is based on European or North American populations. The combination of the Argentinian population, together with the specific instruments chosen for the study, may have determined the nature of these results. To measure ELS, mothers filled in two frequently used questionnaires (ACEs and CTQ) and a sum score was created for the analyses. We also explored using each measure separately, but this did not change the results meaningfully. With respect to prenatal stress, because of the retrospective nature of the maternal report (i.e., mother reporting about pregnancy stress in the days after giving birth) we chose to limit our questions to life events. This choice may however have led to a lack of associations between prenatal stress and outcomes. For example, Bussières et al. (2015) reported that pregnancy-related stress measures showed greater effect sizes in association with birth weight as compared to trait-based assessments, life event measures, or exposure to natural disasters. Their reported effect size for life events was extremely low ($d = -.03$; 95% CI [−0.05, −0.01]; $k = 55$). This would be compatible with our findings. Interestingly, our measures of ELS and prenatal life events were associated in this study, indicating that women that had suffered from more ELS reported more life events during their pregnancy, even after taking maternal education, as a proxy for social economic status, into account. Future studies in South American populations are needed, especially prospective longitudinal studies in which a greater diversity of pregnancy measures can be collected. Next to life events, information on pregnancy-specific stress, as well as on anxiety, depression, and daily hassles would be welcome.

We found that HC values increased over pregnancy (RQ 2) and that this increase was associated with maternal age, education, and hair washing. Furthermore, ELS (RQ 3), maternal height and birthweight (RQ 5) were related to this increase with high probability, although they did not pass our decision criterion to state this with high confidence (95% credible interval excluding zero). When interpreting these findings, the central question is: which factors explain the change in cortisol between the two measurements? Marceau et al. (2020) reported that increases in HC during pregnancy were only reported in studies (6/7) that sampled HC retrospectively while all studies that sampled prospectively (8/8) did not find an increase between the measurements. Their findings indicate that an increase in retrospectively sampled studies may arise due to less cortisol retention in the distal compared to the proximal part of the hair sample. In contrast, King et al. (2022) collected three 5 cm hair samples covering the time period from conception until > 24 weeks postpartum whereby they split each sample into 5 measurements, each reflecting 1 month. They found an increase throughout pregnancy as well as a decrease in the postpartum period. If a wash-out effect were dominating the signal in the data, they would not have been able to detect a decrease in the postpartum period. Furthermore, overlap in the time periods of the three hair samples allowed them to test how HC values of overlapping proximal and distal hair samples aligned. While distal hair samples showed indeed lower HC than proximal samples, the values showed high rank-order concordance. Note that our samples are expected to be more affected by wash-out effects as we collected a 9 cm long sample. In our data, strong covariation between highly variable starting values

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(random intercepts) and the increases (random slopes) are indicative of wash-out effects. Assuming that there is a constant accumulation of cortisol in hair over time and one hair sample has a much stronger wash-out effect than the other, we would expect that those with the strongest wash-out effects show the strongest difference between the proximal and the distal sample. Furthermore we would expect higher variability in the distal samples due to the additional variability in factors that influence or contribute to the wash-out effect (see Figure 3a). Nevertheless, despite this wash-out effect, part of that increased variability might reflect actual higher interindividual variability in cortisol levels in the first half of pregnancy in line with previous evidence (King et al., 2022). Furthermore, we did take hair washing, potentially the most important contributor to such wash-out effects, into account. And indeed, hair washing showed the expected negative association with HC with a much stronger effect on the distal compared to the proximal hair sample and a strong positive effect on change in HC. In sum, more research is needed to disentangle the magnitude of the contribution of wash-out effects and actual increase in cortisol throughout pregnancy to the observed increase in HC (King et al., 2022; Marceau et al., 2020). Hence, our findings that maternal education, age, and possibly ELS and birthweight were related to change in HC imply that these variables were either related to changes in cortisol exposure during pregnancy or that they were related to factors that influence accumulation or retention of cortisol in hair. For example, older or more educated or more traumatized women may differ in lifestyle behaviors compared to younger, less educated or less traumatized women. Also, time spent outdoors, as an example of a lifestyle behavior, is thought to influence cortisol accumulation or retention in hair (Moody et al., 2022), especially in the more distal hair sample.

With respect to our last research question (RQ 5), the Bayesian Network helps to extend the previous discussion by evaluating whether lower HC in the first or higher HC in the second half of pregnancy or both were responsible for our observation that change in HC is possibly related to birthweight. We reason that lower HC levels in the first half of pregnancy were responsible: we found that higher HC in the first half of pregnancy, accounting for HC in the second half of pregnancy, tended to be positively related to birth weight. In contrast, when we kept HC values of the first half of pregnancy constant within the model, increases in HC of the second half of pregnancy were most likely not associated with birth weight ($\beta = -.01$ [−.33, .31]). These results favor the idea that factors that drive the variability in the first half of pregnancy are related to birth weight. Thus, lower cortisol in the first half of pregnancy could be related to lower birth weight. Alternatively, third variables that are associated with lower hair cortisol, by influencing either cortisol production or retention in hair, may be related to lower birth weight. Note that there is prior evidence that prenatal salivary cortisol is negatively related to birth weight throughout all pregnancy trimesters (Cherak et al., 2018), making the connection via variables that influence cortisol retention in hair more likely.

Our study has several limitations and strengths. Our sample size is too modest to detect small effects with high confidence. Furthermore, although we collected recommended data on covariates of HC, noise introduced by wash-out effects remains a difficulty when using retrospective HC as a measure of chronic cortisol exposure. Future studies should limit wash-out effects by using an alternative sampling method to determine long-term cortisol exposure (see King et al., 2022 for an example). This would result in a more expensive and time-consuming data collection as well as in a higher burden on the study participants. Nevertheless, we believe that the alternative of identifying and accurately measuring all (or at least the most important) factors that cause wash-out effects is much less feasible. Furthermore, we did not ask mothers to indicate the stressfulness of their reported prenatal life events. However, using the frequency of life events instead of the weighted sum scores led to similar results (Table S1). Lastly, our results are only generalizable to a population of healthy mothers that delivered at term (≥ 37 weeks of gestation). HC concentrations may be very different in women delivering preterm or suffering from other complications of pregnancy (van Esch et al., 2020). Strengths of this study include the fact that we collected data of ELS, prenatal psychosocial stress, markers of chronic cortisol production covering the nine months of pregnancy (HC), several birth outcomes as well as many known covariates related to these variables. Moreover, the study was carried out in a rarely studied South American population of Argentinian mothers, hence aiding to increase our knowledge beyond that of studies in Western populations. The selection of variables allowed for a more accurate and comprehensive study of the associations between the variables compared to other studies. Combining several modeling approaches allowed us to disentangle the associations between these variables.

5 | CONCLUSION

Our results indicate either a weak or lacking association between early life stress or prenatal life events and absolute values of hair cortisol and the birth outcomes. Hair cortisol increased from the first to the second half of pregnancy and varied more in the first half of pregnancy. Individual increases strongly correlated with that variability indicating stronger wash-out effects in the distal part of the hair sample. Mothers with stronger increases in hair cortisol were more likely to score lower on ELS and tended to have newborns with slightly lower birth weight. Hence, early life stress and birthweight may either have been related to changes in cortisol exposure during pregnancy or to factors that influence accumulation or retention of cortisol in hair. Future studies should eliminate wash-out effects as far as possible by sampling shorter hair segments more frequently.

AUTHOR CONTRIBUTIONS

Henrik Eckermann: Data Analysis; manuscript. **Micaela Lugones**: Data collection; manuscript. **Daniel Abdala**: Manuscript. **Horacio Roge**: Manuscript. **Carolina de Weerth**: Study conceptualization and design; manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare to have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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