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Intergenerational effects of maternal childhood maltreatment on newborns' stress regulation: The role of maternal depressive symptoms

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ABSTRACT

Background: Maternal childhood maltreatment (CM) has been repeatedly associated with negative offspring's emotional outcomes. The dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis has emerged as the main underlying physiological mechanism.
Objective: To explore the association between maternal CM and newborns' physiological and neurobehavioral stress responses, considering the role of perinatal maternal depression and bonding.
Participants and setting: 150 healthy women were followed throughout pregnancy. 79 mother-infant dyads were included in the final analyses. Maternal CM was evaluated using the Childhood Trauma Questionnaire and depressive symptoms by the Edinburgh Postnatal Depression Scale (EPDS) at each trimester. At 7 weeks postpartum, the EPDS and the Postpartum Bonding Questionnaire were administered. Newborns' behavioral responses were assessed using "States Organization" (SO) and "States Regulation" (SR) subdomains of the Neonatal Behavioral Assessment Scale (NBAS). Newborns' salivary samples were collected before and after the NBAS to study cortisol reactivity.
Methods: A cross-lagged panel model was employed.

Abbreviations: CM, Childhood maltreatment; HPA-axis, Hypothalamic-Pituitary-Adrenal Axis; NBAS, Neonatal Behavioral Assessment Scale; SES, Socioeconomic status; CTQ-SF, Childhood Trauma Questionnaire – Short Form; EPDS, Edinburgh Postnatal Depression Scale; PBQ, Postpartum Bonding Questionnaire.

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Results: Infants born to mothers with higher CM presented more optimal scores on SO (β (0.635) = 0.216, p ⟨001) and SR (ß (0.273) = 0.195, $p = .006$), and a higher cortisol reactivity after NBAS handling (β(0.019) = 0.217, $p = .009$). Moreover, newborns of mothers with higher CM and postpartum depressive symptoms exhibited a poorer performance on SR (ß (0.156 = −0.288,p = .002). Analyses revealed non-significant relationships between mother-infant bonding, newborns' cortisol reactivity and SO.
Conclusions: Newborns from mothers with greater CM present higher cortisol reactivity and more optimal behavioral responses, which may reflect a prenatal HPA axis sensitization. However, those exposed to maternal postnatal depressive symptoms present poorer stress recovery.

1. Background

Childhood maltreatment (CM) represents one of the most pernicious forms of early life psychosocial stress for human beings. A comprehensive meta-analysis revealed that the worldwide prevalence of these experiences ranges from 7.6 % to 36 % depending on the type of CM, being emotional maltreatment the most common subtype (Stoltenborgh et al., 2014). Noticeably, exposure to maltreatment during childhood or adolescence is a well-recognized risk factor for the development of several medical conditions through the lifespan, including mental disorders (Lippard & Nemeroff, 2020). Moreover, these CM experiences have been also associated with emotional dysregulation, greater difficulties for managing stressful situations and other behavioral problems among individuals that have not received a categorical psychiatric diagnosis (Marques-Feixa et al., 2023). Unfortunately, the consequences of CM do not seem to be limited to individuals that suffer from it, but might also be transmitted to the next generations (Yehuda & Lehrner, 2018).

In the generation directly exposed to CM, the parental generation, maladaptive neurobiological and behavioral responses linked to psychosocial chronic stress seem to be a key mediator between CM and psychological maladjustment, especially by means of the dysregulation of the Hypothalamic - Pituitary-Adrenal (HPA) axis (Koss & Gunnar, 2018). The HPA axis, the main physiological stress response system in humans, is activated under acute psychosocial stress and ends up with the release of cortisol through the body, which then activates different mechanisms to cope with stress. The development of this system occurs already during the second half of the prenatal period (Glover et al., 2010), but continues postnatally in early infancy (Gunnar & Quevedo, 2008). In this regard, it has been clearly demonstrated that exposure to chronic stressors, such as CM, disrupts HPA axis functioning in a dose-dependent manner in infancy (Tarullo & Gunnar, 2006), childhood and adolescence (Marques-Feixa et al., 2021). Noticeably, the modifications on HPA-axis functioning induced by CM are long lasting and recognizable in adult populations (Bunea et al., 2017).

Regarding the subsequent generations, maternal history of CM has been linked to intergenerational adverse consequences in the offspring, including neurodevelopmental disorders, lifelong behavioral problems, and psychopathology (Plant et al., 2017; Su et al., 2022). Moreover, maternal exposure to CM seems to be associated with infant's abilities for handling stressful situations, including some temperamental traits such as the tendency to experiment fear, vigilance, sadness or irritability (Spry et al., 2022). As stated by Ellis and Del Giudice (2019), the transmission of these stress related traits or phenotypes between generations could be originally explained as an adaptive strategy to help the offspring cope with future harsh social conditions, although these adaptations may present some associated costs, as the increased lifelong vulnerability to mental disorders.

Despite several studies point out that the intrauterine and immediate postnatal environments may be especially relevant for this intergenerational transmission, the specific mechanisms are not fully understood (Buss et al., 2017). In this regard, it should be noted that pregnancy is a period of physiological changes associated with an especial emotional vulnerability, when the biological and psychological consequences of CM may become more evident. In that sense, previous studies have identified higher rates of perinatal mood disorders among pregnant women exposed to CM (Choi & Sikkema, 2016). However, less is known about the impact of these experiences on the development of subclinical symptoms among healthy women during the perinatal period. Additionally, recent studies suggest that women exposed to CM may also present alterations on endocrine, immune, metabolic gestational biology that may ultimately lead to a higher risk of alterations on fetal brain formation (Moog et al., 2022). Interestingly, a recent study by Kleih et al. (2022) described a proinflammatory profile among women exposed to CM who additionally presented depressive symptoms during pregnancy. Furthermore, history of maternal CM has also been related with suboptimal postnatal environmental conditions for the offspring through their development, including the more prevalent maternal postpartum depressive conditions (Alvarez-Segura et al., 2014), the worse mother-infant dyadic relationships (Khoury et al., 2022; Roubinov et al., 2021), and the repetition of abusive patterns to the child (Greene et al., 2020).

Although different studies have addressed the association between maternal history of CM and infant's stress regulation abilities, the methodological approaches are very heterogeneous and the results are not conclusive. Specifically, although some studies are focused only on the link between maternal history of CM and offspring's HPA-axis functioning (Barclay et al., 2023; Brand et al., 2010; Khoury et al., 2022), none of them include evaluations of newborns' neurobehavioral profiles. On the other hand, when researchers focused their attention on maternal CM consequences on offspring behavioral traits, as behavioral reactivity (Altemeier et al., 1986), temperament (Lang et al., 2010), or socioemotional development (Hipwell et al., 2019; McDonnell & Valentino, 2016), they did not report any information about physiological reactivity of the child.

To the best of our knowledge, the present study is the first to simultaneously analyze the association between maternal history of CM and both newborns' HPA axis functioning and neurobehavioral responses. The mediating role of maternal perinatal depressive symptoms and bonding on infant's outcomes was also analyzed. In accordance with previous literature, we hypothesized that newborns born to mothers with history of CM will present greater behavioral and physiological HPA-axis difficulties for responding to stress. We also hypothesized that mothers with more extensive histories of CM will present greater difficulties for managing daily stress and, in consequence, higher depressive symptoms. Finally, we believed that the association between maternal CM and offspring's outcomes will be mediated by maternal depressive symptoms during pregnancy and the postpartum period and mother-infant bonding.

2. Methods

2.1. Participants

150 mother-infant dyads were enrolled in the longitudinal "Intramural Maternal Epi-Project" study. Pregnant healthy primiparous women from the general Spanish population were recruited in the maternity units of two Spanish general hospitals: the Hospital Clínic de Barcelona (BCNatal Fetal Medicine Research Center) and the Hospital Universitario Central de Asturias. Recruitment took place from May 2016 to February 2020 and from July 2020 to June 2021. It was paralyzed during the COVID-19 pandemic period, when lockdown and mobility restrictions were mandatory in Spain. Participants were recruited according to the following inclusion criteria: (1) less than thirteen weeks of pregnancy, (2) age between 18 and 40 years, (3) first pregnancy, (4) no current diagnosis of physical, neurological, or mental diseases, (5) singleton pregnancy.

2.2. Study design

The "Intramural Maternal Epi-Project" is a prospective longitudinal study which aims to explore the effects of mild prenatal psychosocial stress on mother and infant health status, delivery characteristics and newborns' neurobehavioral traits in a cohort of healthy primiparous women. The study was approved by the medical ethics committee of the local hospitals and was conducted in full compliance with Helsinki declaration.

Firstly, pregnant women receiving care at regular obstetric units were contacted by telephone before their first ultrasound. In this first contact, we explained them the nature of the study and we assessed if they met the inclusion criteria for participation. After giving written informed consent, participants underwent a standardized face-to-face psychological interview, conducted by a trained psychologist, at each of the three trimesters of pregnancy. Interviews were preformed after the regulatory ultrasounds established by the Spanish public health services: between 11st-13rd weeks (first trimester: $\bar{X}$=12.3, SD = 1.2), between 20th-22nd weeks (second trimester: $\bar{X}$=20.8, SD = 1.6) and between 32nd-34th weeks (third trimester: $\bar{X}$=32.8, SD = 1.5). These face-to-face interviews had an approximate duration of one hour and were designed to evaluate maternal biographical and psychosocial aspects using several instruments (see Section *2.3*. *Measures*).

After delivery, mother-infant dyads were cited for a face-to-face appointment at approximately 7 weeks postpartum ($\bar{X}$=7.4, SD = 2.9; n = 111), in which we evaluated maternal psychological status and newborns' behavior. A second written informed consent for offspring's participation was obtained for that aim. Information regarding delivery and neonatal outcomes was retrieved from medical records and confirmed in the first postnatal appointment. In this arrangement, a trained professional administered the "Neonatal Behavioral Assessment Scale" (NBAS) (Brazelton & Nugent, 1995) to assess newborns' neurobehavioral outcomes. Additionally, newborns' salivary samples were collected before and after the NBAS assessment to study offspring's cortisol responses after NBAS handling. At the end of the project, participants were given a voucher of 50€ as a monetary compensation for their participation.

2.3. Measures and instruments

2.3.1. Maternal measures

Maternal sociodemographic information, socioeconomic status (SES), and general medical data were self-reported by the participants in each of the trimestral interviews. Specifically, SES was assessed using Hollingshead-Redlich Index of Socioeconomic Status (Hollingshead & Redlich, 1958), based on parental occupation and educational level.

2.3.1.1. Measures of childhood maltreatment. Maternal history of CM was assessed using the Spanish short version of the Childhood Trauma Questionnaire (CTQ-SF) (Hernandez et al., 2013) during the 2nd trimester interview. The CTQ-SF is a 28-item self-report questionnaire which retrospectively evaluates experiences of abuse and neglect during infancy and adolescence. The questionnaire includes 25 items evaluating five subtypes of CM (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect) and 3 items on the Minimization/Denial validity scale. Items are rated on a 5-point Likert scale (1 = never true, 2 = rarely true, 3 = sometimes true, 4 = often true, 5 = very often true). The scores from each subscale range from 5 to 25, with higher scores being indicative of greater maltreatment. CTQ-SF has been demonstrated to be valid and reliable, with Cronbach's α coefficients ranging from 0.66 for emotional neglect to 0.94 for sexual abuse in the original study (Hernandez et al., 2013).

Since the classification of CM on a continuum spectrum provides a deeper and more accurate understanding of each participant experiences, a novel composite continuous CM score was created considering both the subtype of CM and the severity. Firstly, the severity of CM for each subtype was classified as "none-to-low", "low-to-moderate", "moderate-to-severe", and "severe-to-extreme", according to the cutoff scores defined by Bernstein and Fink (1998) (See Section S1.1 of Supplementary Material; Table S1). Then, none-to-low experiences were assigned a score of 0; low-to-moderate experiences a score of 1; moderate-to-severe experiences a score of 2; and severe-to-extreme experiences a score of 3. Finally, the CTQ index score was obtained by summing up the scores from each subtype, being 0 the lowest possible score and 15 the highest possible score.

2.3.1.2. Measures of depressive symptoms. The Spanish version of the Edinburg Postnatal Depression Scale (EPDS) (Garcia-Esteve et al., 2003) was used to screen for depressive-like symptoms in women during the three trimesters of pregnancy and the postpartum period. This scale is composed of 10 items regarding women's emotions on the last 7 days. Items are rated on a Likert scale from 0 to 3 and the total score ranges from 0 to 30, with higher scores indicating higher depressive symptomatology. For descriptive data, we used the cutoff score for depression described by Bergink et al. (2011), being 11 in the first trimester and 10 in the second trimester, the third trimester and the postpartum period. The cutoff values defined in the Spanish validation show a sensitivity of 79 %, a specificity of 95.5 %, a positive predictive value of 63.2 % and a negative predictive value of 97.7 % (Garcia-Esteve et al., 2003).

2.3.1.3. Measures of mother-infant bonding. Mother-infant bonding was assessed using the Spanish version of the Postpartum Bonding Questionnaire (PBQ) (Garcia-Esteve et al., 2016) at the 7 weeks postpartum appointment. The PBQ consists on a hetero-administered scale which evaluates possible disturbances of mother-infant relationship during the postpartum period. The 25 items are rated on a Likert scale from 0 to 5. The Spanish validation of the scale revealed that the PBQ total score presented a good reliability ($\alpha = 0.90$) (Garcia-Esteve et al., 2016). For the purpose of this study, we considered the global score, which ranges from 0 to 125, being the highest scores indicative of greater bonding dysfunctions. For descriptive data, we employed the cutoff values established by Brockington et al. (2006), with scores above 26 determining "any type of bonding disorder" and scores 40 to being indicative of "severe bonding disturbances".

2.3.2. Newborns' measures

2.3.2.1. Neonatal outcomes. Information regarding infant's sex, gestational age at birth and birth weight was retrieved from medical records. Newborns' birth weight percentile for gestational age were calculated online using a tool based on the WHO growth charts (Kiserud et al., 2017). The cutoff-value for small weight for gestational age was established at percentile <10.

2.3.2.2. Newborns' behavioral stress responses. Newborns behavioral stress responses were evaluated using the 3rd Edition of the NBAS (Brazelton & Nugent, 1995). It had an approximate duration of 30 minutes and was administered by a trained certified expert at each hospital. The examiners were blinded to maternal history of CM and their distress status during pregnancy. Only basic information regarding the offspring was retrieved by examiners (e.g.: date of birth, gestational age at birth or breastfeeding). The NBAS has been demonstrated to be a valid and reliable tool in previous studies (Costas-Moragas et al., 2007).

This scale consists of an interactive evaluation of newborns' neurobehavioral responses, including the ability for interacting with the environment and responding to stimulation. NBAS comprises 35 behavioral items, scored on 9-point scale (from 1 to 9), and 18 items evaluating newborns' reflexes, rated on a 4-point scale (0 to 3). Behavioral items are usually regrouped in 6 subdomains: habituation, social-interactive, autonomous nervous system, motor system, state organization (SO) and states regulation (SR). Since the aim of the present study was to explore infant's behavioral stress regulation, only the SO and SR subdomains were included on the analyses. The SO subdomain is composed of 4 items and is indicative of newborns' arousal and the ability to change from consciousness states when exposed to stimulation. The SR subdomain is composed of 4 items and is indicative of newborns' ability to regulate its own states when faced with increasing levels of stimulation. These domains are the most representative of neonates' stress regulation since they assess the abilities for organizing their internal states to respond and recover from handling related stress and correlate with HPA axis activation (Gunnar et al., 1987).

For the present study, the items of the SO subdomain were recoded according to Lester et al. (1982) recommendations, since the optimal scores are gathered around the midpoint of the scale. A description of the items that comprise each subdomain and the criteria for recodification are provided in Section S1.2 of the Supplementary Material (Fig. S1).

2.3.2.3. Newborns' physiological stress responses. Salivary cortisol concentrations before and after NBAS were used as a measure of newborns' physiological stress responses. To that aim, saliva samples were collected by the professional who administered the NBAS right before and after the evaluation. In this regard, it is well known that the handling associated to the administration of the NBAS items produces moderate increases on newborns' cortisol levels (Gunnar et al., 2009).

Samples were collected employing cotton SalivaBio Children's Swabs (Salivette®, Sarstedt, Germany) and directly stored at the research center freezer at −20 °C. For cortisol determination, the tubes were thawed and centrifuged following manufacturer instructions. Cortisol concentrations were determined using Salimetrics® Cortisol Enzyme Immunoassay Kit, a high sensitivity enzyme-linked immunosorbent assay (ELISA) for cortisol (Salimetrics®, LLC, State College, PA). To avoid possible biases, samples were tested in duplicate and then the mean was calculated (μg/dL). When concentrations presented a coefficient of variation higher than 15 %, they were determined again. Cortisol values were log-transformed to reduce skewness. For studying the increase on cortisol levels during NBAS administration, we calculated the Area Under the Curve with respect to ground (AUCG), which indicates the total cortisol output between the two time points considering the effect of time.

2.4. Statistical analyses

Descriptive statistics were analyzed using SPSS 26 for Windows (IBM, Chicago, IL, USA). Missing scores on NBAS items were imputed using iterative imputation methods with the "MissForest" R package (Schweizer, 2010). Since we had to test a complex psychobiological scenario and the included variables presented higher interactions, structural equation modeling (SEM) was employed. Specifically, we ran a cross-lagged panel model using the path analysis package from EQS 6.4 for Windows.

We designed an initial overall theorical model in which the consequences of maternal CM on the offspring characteristics of interest would be mediated by maternal perinatal depressive symptoms and mother-infant bonding. Newborns' sex and percentiles of birth weight by gestational age were included as covariates for the analyses. Mardia's coefficient was used to assess data normality. Since Mardia's coefficient value was 38.36, we assumed that data followed a non-normal distribution and, in consequence, we used the Satorra-Bentler robust indexes (Bentler, 2006). Additionally, we employed different indexes to evaluate the model's goodness-of-fit, including Satorra-Bentler Chi-Square (S—B χ^2), Comparative fit index (CFI), Bollen's fit index (IFI), McDonalad's fit index (MFI) and the Root Mean Square Error of Approximation (RMSEA). According to standard criteria, we considered that the model presented a good fit to the data when values of S—B χ^2 were non-significant; CFI, IFI and MFI values were higher than 0.90 and values of RMSEA were lower than 0.05 (Barrett, 2007); (Schweizer, 2010). To respecify the initial model, Lagrange Multiplier test (LMT) and Wald test (WT) were used since they provide useful information about the associations that ensure the goodness-to-fit of the model (Bentler, 2006).

3. Results

3.1. Descriptive data of our sample

A total of 79 mother-infant dyads were included in the final analyses. Demographic and clinical descriptive statistics of the sample are summarized in Table 1. Maternal age at recruitment ranged from 22 to 40 years ($\bar{X}$ = 32.18, SD = 4.15). 79.5 % of pregnant women were from Europe and 20.5 % from South America. Approximately half of them were from a medium SES (49.4 %), 42.8 % were from high SES and only 7.8 % were from low SES.

Regarding depressive symptoms during pregnancy, 20.3 % of women presented scores above the cut off value for high risk of depression during the first trimester of pregnancy; 13.9 % during the second trimester; and 20.3 % during the third trimester. The percentage of mothers with depressive symptoms above the cutoff in the postpartum period increases to 24.1 %. Regarding mother infant-bonding, all the mothers except one presented an adequate bonding.

Data regarding maternal experiences of CM are presented in Table 2. From the 79 participants, 59.5 % reported no experiences of maltreatment and 35.44 % reported mild maltreatment during childhood. Only a 5.06 % of the participants presented moderate or severe CM. Among maltreated mothers, emotional neglect (11.4 %) and emotional abuse (10.1 %) were the most common type of maltreatment, followed by sexual abuse (9.1 %). The prevalence of the different CM experiences in our study is in great accordance with previous studies performed on Spanish population (Aguilera et al., 2009).

Table 1
Demographic and clinical descriptive data of the subsample of pregnant women of the "Intramural-Maternal-Epi-Project" included in this study (n = 79).

	% (n)	Mean (SD)	Range
Maternal characteristics			
Age (years)		32.18 (4.15)	22–40
Ethnicity (n = 78)			
European	79.5 (62)		
Latin-American	20.5 (16)		
Socioeconomic status (n = 77)			
Low	7.8 (6)		
Medium	49.4 (38)		
High	42.8 (33)		
Depressive symptoms: EPDS[a]			
EPDS 1st trimester		6.34 (4.24)	0–19
Scores ≥11	20.3 (16)		
EPDS 2nd trimester		5.76 (4.36)	0–24
Scores ≥10	13.9 (11)		
EPDS 3rd trimester		6.10 (4.58)	0–23
Scores ≥10	20.3 (16)		
EPDS postpartum		6.11 (5.27)	0–27
Scores ≥10	24.1 (19)		
Mother-infant bonding: PBQ[b]			
PBQ postpartum		9.23 (5.71)	0–28
Scores <26	98.7 (78)		
Scores ≥26	1.3 (1)		

Abbreviations: EPDS: Edinburg Postnatal Depression Scale; PBQ; Postpartum Bonding Questionnaire.

[a] EPDS cutoff scores for depression were 11 in the first trimester and 10 in the second trimester, the third trimester and the postpartum period.

[b] Lower PBQ scores are indicative of better mother-infant bonding. PBQ scores ≥26 are indicative of bonding disorders, and scores ≥40 are indicative of severe bonding disorders. In our sample, there were no mothers who presented scores ≥40.

Table 2
Maternal self-report of CM experiences in the subsample of the "Intramural-Maternal-Epi-Project" included in this study (n = 79).

	n	%
CTQ subdomains		
Emotional abuse		
None-to-low	68	86.1
Low-to-moderate	8	10.1
Moderate-to severe	2	2.5
Severe-to extreme	1	1.3
Physical abuse		
None-to-low	71	89.9
Low-to-moderate	5	6.3
Moderate-to severe	1	1.3
Severe-to extreme	2	2.5
Sexual abuse		
None-to-low	64	81
Low-to-moderate	7	8.8
Moderate-to severe	4	5.1
Severe-to extreme	4	5.1
Emotional neglect		
None-to-low	65	82.3
Low-to-moderate	9	11.4
Moderate-to severe	2	2.5
Severe-to extreme	3	3.8
Physical neglect		
None-to-low	73	92.4
Low-to-moderate	4	5
Moderate-to severe	1	1.3
Severe-to extreme	1	1.3
CTQ Index		
0	47	59.5
1	16	20.25
2–4	12	15.19
5–9	2	2.53
10–15	2	2.53

Abbreviations: CTQ, Childhood Trauma Questionnaire.

Newborns' characteristics are reported in Table 3. From the 79 newborns, 46.8 % were male and 53.2 % female. Mean gestational age was 39.2 weeks and mean birth weight was 3256 g. The majority of newborns (83.5 %) presented an adequate percentile of birth weight for gestational age and only 16.5 % of newborns were small for gestational age. Newborns' scores on the SO subdomain of the NBAS ranged from 7 to 20 ($\bar{X}$ = 16.35, SD = 3.06). Scores on the SR subdomain ranged from 6 to 36 ($\bar{X}$ = 25.55, SD = 8.10). Infants' cortisol reactivity values, evaluated by means of the AUC_G, ranged from −3.52 to 0.04.

Table 3
Descriptive data of the subsample of newborns of the "Intramural-Maternal-Epi-Project" included in this study.

	% (n)	Mean (SD)	Range
Newborns characteristics			
Sex			
Male	46.8 (37)		
Female	53.2 (42)		
Gestational age (weeks)		39.2 (1.52)	32–42
Birth weight (g)		3256 (506)	1800–4350
Birth weight percentile[a]		40.75 (29.44)	1–98
Appropriate for gestational age	83.5 (66)		
Small for gestational age	16.5 (13)		
NBAS scores			
States organization		16.35 (3.06)	7–20
States regulation		25.55 (8.10)	6–36
Salivary cortisol concentrations (μg/dL)[b]			
Pre NBAS levels		- 0.88 (0.44)	−2.44 - 0.35
Post NBAS levels		- 0.76 (0.41)	−2.12 - 0.28
Cortisol reactivity AUC_G		- 0.39 (0.47)	−3.52 - 0.04

[a] Small for gestational age refers to newborns whose birth weight is lower than the 10th percentile for their gestational age.
[b] Salivary cortisol values after log-transformation.

3.2. Results of the cross-lagged panel model

79 mother-infant dyads were included in the cross-lagged panel model analysis. From the 150 mothers recruited initially in the longitudinal "Intramural Maternal Epi-Project", 16 participants dropped-out from the study during pregnancy, 7 mothers dropped out after giving birth and 22 newborns could not be evaluated after birth due to restrictions derived from COVID-19 pandemic. Finally, due to the use of restrictive listwise deletion methods to treat missing data, 26 participants were removed for having missing information in, at least, one of the variables of the study. Thus, 71 mothers were skipped from the final analysis due to drop-out or to missing data. Analyses of attrition bias revealed no significant differences between pregnant women included and excluded in the present study in the following variables: maternal characteristics (age, SES, and ethnicity), mother-infant bonding, CTQ scores, newborns' percentile of weight for gestational age and EPDS scores on the 2nd and 3rd trimesters and postpartum. Only EPDS scores on the first trimester were higher among pregnant women excluded from the main analysis ($p = .037$). Thus, we can conclude that women in the final analysis are representative of the whole sample.

The analysis of goodness-to-fit of the initial model revealed that the model was not fitted ($\chi^2(13) = 34.09$, $p = .001$, CFI = 0.866, IFI = 0.894, MFI = 0.875, RMSEA = 0.144). Following indications of the LMT and WT to add and remove paths different from the ones hypothesized in the first model, we obtained a final model which presented a good fit to the data ($\chi^2(29) = 33.65$, $p = .25$, CFI =0.970, IFI = 0.975, MFI = 0.971, RMSEA = 0.045) (see Section S.2 of the Supplementary material; Figure S2).

3.2.1. Main direct effects of maternal CM

Fig. 1 represents statistically significant relationships between the variables included in the final model. Since we did not detect any significative interaction of the covariates (newborns' sex and percentiles of birth weight) with the main variables of the analysis, those were not represented in the figure.

As shown in Fig. 1, there is a direct positive relationship between maternal history of CM and infant's scores on the SO (β (0.635) = 0.216, $p < 001$) and SR (β (0.273) = 0.195, $p = .006$) subdomains. Therefore, newborns born to women with history of CM present higher scores on both NBAS subdomains, indicating a more optimal performance on the test. Additionally, maternal history of CM is directly positively associated with infant's cortisol reactivity (ß (0.019) = 0.217, $p = .009$). Thus, infants born to maltreated mothers present a higher cortisol increase when exposed to the mild psychosocial stress produced by NBAS handling.

3.2.2. Indirect effects of maternal CM

When exploring indirect associations, the analyses revealed that maternal CM is associated with higher rates of depressive symptoms during the second trimester of pregnancy (ß (0.107) = 0.129, $p = .011$), a higher prevalence of postpartum depressive symptoms (ß (0.255) = 0.265, $p = .009$), and better mother-infant bonding (ß (0.266) = −0.220, $p = .021$). It is worth mentioning that maternal depressive symptomatology during the first trimester correlates with the symptoms on the second (ß (0.123) = 0.644, $p < .001$) and third trimesters (ß (0.096) = 0.262, $p = .002$). Depressive symptoms during the second trimester were associated with the third trimester (ß (0.097) = 0.569, $p < .001$) and postpartum depressive symptomatology (ß (0.214) = 0.376, $p = .016$). With regard to infant outcomes, higher postpartum depressive symptoms seem to be associated with a poorer newborns' performance on the SR subdomain (ß (0.156) = −0.288, p = .002) and worse mother-infant bonding (ß (0.151) = 0.503, $p < .001$). Finally, the analyses showed that newborns' cortisol reactivity correlates with higher scores on SO (ß (0.635) = 0.268, $p = .003$) and SR (ß (2.736) = 0.343, $p = .017$) subdomains.

Among the variables tested in our final model (see Fig. S1 in Supplementary material), we found non-significant relationships between maternal depressive symptoms during both the third trimester of pregnancy and the postpartum and newborns' cortisol reactivity. Additionally, non-significant associations were found between mother-infant bonding and both newborns' cortisol reactivity and SO subdomain.

4. Discussion

The findings of the present study agree with previous literature suggesting the existence of an intergenerational origin of the early stress-reactive biobehavioral phenotypes.

Firstly, regarding the main effects detected in our model, maternal CM experiences seem to be associated with a more optimal behavioral performance under the psychosocial stress produced by NBAS handling, as observed by the scores of the SO and SR subdomains. Interestingly, to the best of our knowledge, this study is the first to report a positive effect of maternal CM on their offspring behavior, while previous articles state that it may be associated with children dysregulated emotional development. For instance, a study using also the NBAS suggested that newborns born to mothers with no history of CM presented higher levels of activity than the ones from exposed mothers (Altemeier et al., 1986). Moreover, maternal CM has been associated with worse infant temperamental outcomes (Lang et al., 2010), and poorer socioemotional functioning (McDonnell & Valentino, 2016) during the first year of life.

In this regard, the better newborns' performance may be explained by different aspects of maternal CM experiences that were not addressed in our analyses. For example, previous studies highlight that the different subtypes of CM suffered by the mother may generate differential consequences, being maternal emotional abuse a risk factor for blunted stress responses and maternal emotional neglect a risk factor for negative emotionality in the offspring (2019). Additionally, the severity of maternal CM experiences may also play a key role on maternal health and infants' outcomes. Since the participants in our sample mainly presented mild and moderate CM, it is possible that we could not detect the putative negative effects associated with more severe maternal CM. In this regard, it should also be highlighted that women in our sample present and atypical resilient profile since they have not developed severe

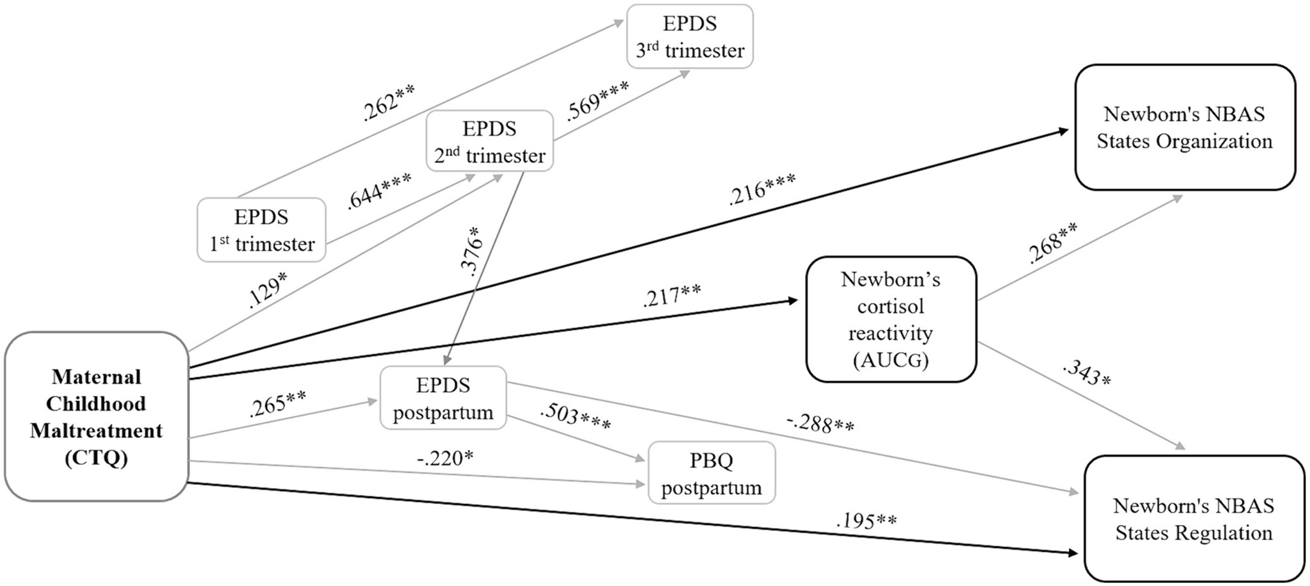

Fig. 1. Representation of the main statistically significant results obtained in the cross-lagged panel analysis. Wide black lines represent direct relationships between maternal CM and the main outcomes of the study: newborns' cortisol reactivity, and "states organization" and "states regulation" subdomains of the NBAS. Grey lines represent the indirect relationships between maternal CM, maternal perinatal depression, mother-infant bonding and newborns' outcomes.

psychiatric disorders, which may also be explicative of their offspring NBAS performance. Furthermore, the contradiction between our findings and previous studies could be also explained by infants age, since our study is focused on the first weeks of life. As it has been hypothesized by other authors, heightened stress responses may suppose a beneficial adaptation in the short-term, but could trigger maladaptive emotional outcomes later in life (Ellis & Del Giudice, 2019).

As it has been previously defined in the "Adaptive Calibration Model of stress responsivity" theory, stress reactive phenotypes may be the result of the prenatal modification of the developmental trajectories of the organism in order to adapt to the expected future environmental context (Del Giudice et al., 2011). In this regard, mothers exposed to more extensive experiences of CM could have developed biological strategies to cope with chronic stress that may be transmitted to the offspring. These adaptations could be related to the resilient prolife of the mothers in our sample and may underlie the more optimal stress response observed in the newborns. One of the mechanisms that might explain this better behavioral response is the increase of cortisol levels during the evaluation, as it has been previously correlated with self-quieting and social engagement in adequate and controlled environments (Gunnar et al., 1987).

Regarding the offspring physiological stress regulation, we observed that those newborns born to mothers with higher cumulative experiences of CM showed a significantly higher cortisol increase during NBAS handling, reflecting a greater activation of the HPA axis during a mild psychosocial stress situation. As suggested elsewhere, modifications on HPA axis functioning may be the result of a prenatal sensitization of the stress-response systems, inherited as a biological adaptation to cope with future harsh environments (Ellis & Del Giudice, 2019). For instance, a meta-analysis by Palma-Gudiel et al. (2015) demonstrated that pregnancy maternal stress generates specific epigenetic signatures in genes related with offspring's HPA axis functioning, as the *NR3C1* gene. Although further studies are needed to determine the role of epigenetic transmission, recent research proposes that methylation signatures acquired by the mothers may be directly transmitted to the subsequent generation (Takahashi et al., 2023). Additionally, those stress-related epigenetic changes in genes related with metabolic, neuroendocrine, and immune processes could generate an intrauterine environment that inform the fetuses about the nature of the future world and lead to fetal developmental adaptations (Bowers & Yehuda, 2016). However, the findings on the link between maternal CM and infant's cortisol are inconclusive. In accordance with our results, Khoury et al. (2022) found that 4-months old infants of mothers with history CM presented higher baseline cortisol levels, which remained higher during the Still Face Paradigm. Additionally, a study by Barclay et al. (2023) concluded that maternal CM was not directly associated with newborns' cortisol reactivity and recovery to the heel stick paradigm at 1-month old newborns; nor to the Still face paradigm in 6-months old infants. Finally, Brand et al. (2010) contended that infants born to mothers with a history of CM and not later trauma symptomatology presented lower baseline cortisol levels before a stress paradigm at 6 months postpartum.

With regard to the study of the indirect effects, our analyses suggest the existence of an association between maternal postpartum depressive symptoms and worse infants' abilities for recovering from stimulation. Previous research on the field indicates that the above mentioned prenatal sensitization of the stress response systems may represent a form of enhanced biological sensitivity to the environment (Belsky et al., 2007). In that sense, it has been suggested that children that may have undergone a prenatal HPA-axis sensitization are highly-reactive and present a higher sensitivity for environmental cues. Due to this dependence on the environment, they present poorer developmental outcomes when exposed to stressful nurturing conditions, but they present a more adequate development than low-reactive children when nurtured in optimal conditions (Boyce & Ellis, 2005). In line with our findings, when highly reactive children born to mothers with greater CM are exposed to maternal postpartum depressive symptoms, they seem to present higher problems for regulating their responses to environmental stress.

Additionally, several studies claim that CM may lead to a worse mother-infant relationship and less optimal parenting, which may constitute an adverse environment for child growth and development (Moog et al., 2022). However, in our study we could not replicate this association, probably due to the reduced variability of PBQ scores in our sample. Moreover, we could not replicate any mediating effects of maternal depressive symptoms nor bonding on newborns' cortisol responses. Interestingly, Barclay et al. (2023) reported that infants born to mothers exposed to CM who additionally presented depressive symptoms during pregnancy had lower cortisol reactivity after the heel stick test. Additionally, Brand et al. (2010) claimed that infants born to mothers with CM and later Post-Traumatic-Stress-Disorder had a higher cortisol reactivity. Thus, further studies are needed to examine how the interplay of prenatal sensitization and early postnatal environments contributes to the risk for mental health conditions in the offspring.

Altogether, the findings from the present study point out to the existence of intergenerational effects derived from early experiences of maltreatment. Notably, these effects seem to be already evident in mothers with mild and moderate experiences of CM that have a successful bonding with their offspring. Considering this, it is of crucial importance not to fault exposed mothers for the biobehavioral intergenerational transmission of the mentioned stress-related phenotypes.

4.1. Strengths and limitations

The greatest strength of the present work is that it is the first longitudinal study to examine the intergenerational effects of CM simultaneously on offspring behavioral and physiological stress responses during the first months of life. Moreover, we study perinatal maternal risk factors, thus providing a comprehensive understanding of the mechanisms of intergenerational transmission and the early environmental factors that influence newborns' development. Noticeably, we explored maternal experiences of CM as a continuum, which allowed us to study the severity and the accumulation of different CM subtypes. Unlike other studies, information regarding perinatal depression and bonding was collected prospectively in psychological interviews conducted by a trained professional. Furthermore, we administered the NBAS at 7 weeks postpartum, studying the contribution of prenatal and perinatal environments, and controlling for the impact of later postnatal factors that may influence offspring's biobehavioral responses.

However, this study presents some limitations. Firstly, due to the longitudinal nature of the study and the statistical treatment of missing data, a noticeable number of subjects were removed from the cross-lagged panel analysis. Specifically, pregnant women with higher depressive symptoms in the 1st trimester of pregnancy had higher rates of missing data. Thus, in our study we may have lost valuable information of the mothers at higher psychosocial risk, who may have supported even more the associations found in the final analysis. Furthermore, it should be also considered that our results may be difficultly generalizable to other populations due to the idiosyncratic characteristics of our sample. Firstly, our sample mainly comprises women from a medium-high SES, so, our results may not be generalizable to populations with lower SES. Additionally, our study is composed of mothers who are resilient to CM as they have not developed severe byproducts of this exposure. Thus, due to the recruitment strategy, the conclusions of our study may not be generalizable to those dyads in which mothers present a mental disorder or to the general population in which depression levels present a natural variation. Furthermore, it must be noticed that exclusion of participants with mental disorders was based on medical records and participants' self-report, which may be imprecise at times. Finally, with regard to CM experiences, our results may not be generalizable to mothers who present more severe experiences. Further studies are needed to determine if severe and extreme experiences of early life adversity are associated with poorer offspring outcomes. Additionally, the use of a new CTQ index may hinder the comparison with other studies that use different statistical approaches.

Regarding the mediating effect of maternal depressive symptoms and bonding, only one mother presented PBQ scores above the cutoff for bonding disorders. The reduced variance PBQ scores across our sample may have contributed to an underestimation of the effect of maternal postnatal bonding on infant's stress regulation. Additionally, it should be noticed that no variables with a potential positive effect against maternal CM were included in the model (e.g.: maternal social support, adaptive coping strategies, community services, etc.). These protective factors may contribute to mothers' resilience and moderate the association between maternal CM experiences and offspring's outcomes.

Regarding the behavioral evaluation, the main limitation is that the NBAS was administered by only one examiner and, thus, no inter-rater reliability ratings were available. Moreover, the recodification of the NBAS scores may entail a loss of information since it allows to study optimal and non-optimal performance, but do not discerns between hyperreactive and hyporeactive phenotypes. Finally, further analyses are needed to determine whether offspring's sex influences fetal vulnerability to maternal experiences of stress.

5. Conclusions

Newborns born to mothers with a more extensive history of CM presented a more optimal performance on the NBAS and a higher cortisol reactivity when exposed to handling. This performance may be indicative of better abilities to respond and recover from stress at two months of age. However, when those newborns were nurtured by mothers with higher levels of depressive symptoms they presented poorer abilities for regulating stress recovery. The biobehavioral performance of those infants may be explained by mechanisms of prenatal sensitization of the HPA axis.

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CRediT authorship contribution statement

Nerea San Martín-González: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jorge Moya-Higueras:** Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis. **Elisenda Eixarch:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Águeda Castro-Quintas:** Writing – review & editing, Conceptualization. **Laia Marques-Feixa:** Writing – review & editing, Visualization, Validation, Software, Methodology. **Fátima Crispi:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Maria Daura-Corral:** Writing – review & editing, Data curation. **Lorena de la Fuente-Tomás:** Writing – review & editing, Data curation. **José Luis Monteserín-García:** Writing – review & editing, Data curation. **María Paz García-Portilla:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Lourdes Fañanás:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Authors declare no conflict of interest.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chiabu.2024.106968.

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