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Placental corticotrophin-releasing hormone trajectories in pregnancy: Associations with postpartum depressive symptoms

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Abstract

Objective: Depressive symptoms following birth are common and can have adverse effects for mothers, children, and families. Changes in hypothalamic-pituitary-adrenal (HPA) axis regulation during pregnancy may be implicated in the development of postpartum depressive symptoms, particularly changes in placental corticotropin-releasing hormone (pCRH). However, few studies have tested how dynamic pCRH changes over pregnancy relate to postpartum depressive symptoms. This preregistered investigation tests associations of both pCRH levels and changes from early to late pregnancy with postpartum depressive symptoms.

Methods: The sample consists of 173 women studied in early, mid, and late pregnancy who later reported on depressive symptoms with the Edinburgh Postpartum Depression Scale during interviews at 1, 6 and 12 months postpartum. Blood samples were collected at each prenatal timepoint and assayed for pCRH using radioimmunoassay. Latent growth curve analysis was employed to identify distinct trajectories of pCRH during pregnancy.

Results: We identified three prenatal pCRH trajectories labeled as typical, flat, and accelerated. Each trajectory showed exponential increases in pCRH levels over the course of gestation but differed in overall levels and rates of change. pCRH levels were not associated with postpartum depressive symptoms. However, women with accelerated pCRH trajectories reported marginally higher depressive symptoms one month postpartum. Primary analysis models adjusted for marital status, income, prepregnancy BMI, parity, prenatal depressive symptoms, and gestational age.

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Declaration of Competing Interest

None

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.107030.

CRediT authorship contribution statement

Mary Coussons-Read: Funding acquisition, Investigation, Project administration, Supervision. **Christine Dunkel Schetter:** Conceptualization, Funding acquisition, Investigation, Project administration, Writing – original draft, Writing – review & editing, Supervision. **Isabel F. Almeida:** Conceptualization, Writing – original draft, Writing – review & editing, Investigation. **Gabrielle R. Rinne:** Formal analysis, Methodology, Writing – review & editing, Data curation.

Conclusions—These findings add to our understanding of dynamic changes to maternal HPA axis regulation during pregnancy and contribute to growing evidence on how pCRH changes relate to the development of postpartum depressive symptoms

Keywords

Postpartum depression; Hypothalamic-Pituitary-Adrenal (HPA) Axis; Pregnancy; Corticotrophin-releasing hormone (CRH); Maternal mental health

1. Introduction

One in 5 women report experiencing elevated depressive symptoms in the year after birth, representing a significant public health problem (O'Hara and McCabe, 2013). A growing body of research has investigated the implications of physiological changes during pregnancy for postpartum depressive symptoms. In particular, *corticotropin-releasing hormone (pCRH) levels*, which increase substantially during pregnancy due to the development of the placenta, have been implicated in the etiology of postpartum depression (Sandman, 2018).

During pregnancy, the placenta acts as an endocrine organ and secretes placental CRH (pCRH) into maternal and fetal circulation (Sandman, 2018). *Higher levels of* pCRH in maternal circulation during mid to late pregnancy have been associated with greater risk of developing postpartum depressive symptoms in prior studies (Glynn et al., 2014; Hahn-Holbrook et al., 2013; Yim et al., 2009). For example, Yim and colleagues (2009) indicate that higher pCRH at 25 weeks predicted PPD symptoms at eight weeks postpartum. Also, Hahn-Holbrook et al. (2013) found that pCRH at 37 weeks' gestation, but not 19 and 29 weeks, predicted depressive symptoms at eight weeks after birth. In a third study, maternal pCRH at 25, 31, and 36+ weeks' gestation predicted PPD symptoms three months postpartum (Glynn and Sandman, 2014). In contrast, two additional studies report conflicting results. Rich-Edwards et al. (2008) found that pCRH at 28 weeks was associated with *prenatal* depressive symptoms, but not symptoms at 6 months postpartum. Meltzer-Brody et al., (2011) reported no evidence for associations between pCRH at <20 weeks or 24–29 weeks with depressive symptoms three or 12 months after birth.

The differences among these findings may be due in part to the varying study designs and methodological approaches. Specifically, assessment of pCRH levels at any one timepoint does not capture the exponential increases in pCRH that occur across gestation (Kassotaki et al., 2021; Sandman, 2018). Notably, there is evidence that individuals vary in the degree of change in pCRH over pregnancy and that such individual variation holds implications for birth outcomes and child development (e.g., Ramos et al., 2020; Rinne et al., 2023). Growing evidence also suggests that pCRH *trajectories* influence postpartum depressive symptoms. For example, two prior studies found accelerated changes in pCRH levels from mid-pregnancy (23–26 weeks; Yim et al., 2009) to late pregnancy (29–37 weeks; Hahn-Holbrook et al., 2013) in women with depressive symptoms postpartum, suggesting that comprehensive HPA axis *changes* over pregnancy may be a risk factor for postpartum depression.

Collectively, this past work suggests that additional research comparing pCRH levels at different timepoints and trajectories over pregnancy may elucidate links between pCRH and symptoms of depression postpartum. Person-centered approaches that characterize comprehensive changes in pCRH across pregnancy may be especially useful in clarifying links with postpartum mental health (Peterson et al., 2020). Whereas variable-centered approaches elucidate links between pCRH with postpartum depressive symptoms at a *sample* level, person-centered approaches can identify subgroups of individuals based on pCRH changes over pregnancy and test whether these subgroups, in turn, differ in postpartum depressive symptoms (Jung & Wickrama, 2009). That is, rather than assuming that all individuals in a sample will show the same pattern of change in pCRH, person-centered approaches allow for more granular examination of heterogeneity in patterns of change in pCRH within a sample. While limited work to date has employed person-centered approaches to characterize profiles of prenatal stress physiology, one key exception recently reported that cortisol trajectories showed distinct links with maternal perinatal psychological distress (Peterson et al., 2020), providing initial evidence of the utility of such approaches to characterize links between stress physiology and maternal distress.

1.1. The present study

The current study examined whether pCRH levels at three times in pregnancy and trajectories over pregnancy were associated with postpartum depressive symptoms. First, we identified pCRH trajectories from early to late pregnancy using latent curve growth analysis (LCGA). Second, we tested whether pCRH levels in early, mid, and late pregnancy and pCRH trajectories were associated with postpartum depressive symptoms. Based on past research, we hypothesized that levels of pCRH during mid and late pregnancy, but not early pregnancy would predict postpartum depressive symptoms. Secondly, we expected that women with higher postpartum depressive symptoms would have accelerated pCRH trajectories over the course of pregnancy. Primary analyses focused on depressive symptoms early after birth, and exploratory analyses tested symptoms six and 12 months postpartum as outcomes. Primary study aims and hypotheses are pre-registered at https://osf.io/rg2ph/?view_only=b9412138d4474cfd9c4c5d795498175b.

2. Material and methods

2.1. Participants and procedure

A sample of 233 pregnant women was recruited by the Healthy Babies Before Birth study between 2013 and 2018. Participants were enrolled at clinic sites in Los Angeles, CA or Denver, CO and completed study visits in early pregnancy (8–16 weeks gestation), mid (20–26 weeks gestation), and late pregnancy (30–36 weeks gestation) followed by three postnatal visits that occurred 1.26 (SD=0.41), 6.10 (SD=0.45), and 12.35 (SD=0.55) months postpartum. Women who were 18 years of age or older with singleton intrauterine pregnancies and who were at least 12 weeks gestation at the time of recruitment were eligible for inclusion. Participants were excluded from the study if there was evidence of current substance abuse, HIV-positive status, smoking, or multiple gestations. The present sample includes 173 participants who provided at least one pCRH sample. Complete sample

characteristics are in Supplemental Table 1 as are differences between the current analytic sample and full sample.

Interviewers were trained extensively to administer structured interviews through in-person sessions, covering topics that included: ethical interviewing, interviewer roles and responsibilities, protecting patient confidentiality, scientific integrity, effective interviewing techniques, and REDCap training. Trainees demonstrated their interview skills through role playing and 1:1 practice interviews with the project coordinator and principal investigator (live and audiotaped) and were also provided with a training manual that detailed each module. Further detailed information pertaining to study recruitment and procedures is described elsewhere (Ramos et al., 2022). Each institution's Institutional Review Board approved all protocols and procedures prior to study inception.

2.2. Measures

2.2.1. Sociodemographic and Obstetric Information—Sociodemographic information (maternal age, per capita household income, education, marital status, race, and ethnicity) was collected via interview by research staff. Socioeconomic status was calculated as the sum of standardized measures of years of education completed and per capita household income. Per capita household income refers to total household income divided by number of persons living in the household and adjusted for cost of living by sites. Birth outcomes and maternal medical risk factors were obtained from medical charts abstracted by research staff.

2.2.2. Placental Corticotropin-Releasing Hormone—Blood samples were collected in aprotinin-coated vacutainer tubes by research staff through antecubital venipuncture (BD Biosciences, San Diego, California). For further detail on collection and assay, see Ramos et al., (2022). Blood samples were centrifuged, and 1 mL of serum was harvested and stored at −80°C. These samples were shipped to Dr. Smith's Endocrine Lab at the University of Newcastle for assay and pCRH was measured using a radioimmunoassay (limit of sensitivity=3 pg/mL). The intra- and inter-assay coefficients of variance were 10.2% and 8.2%, respectively.

2.2.3. Postpartum Depressive Symptoms—Participants reported on depressive symptoms in interviews at all postnatal assessments on the Edinburgh Postnatal Depression Scale (EPDS), a 10-item questionnaire that is validated for assessing perinatal depression (Cox et al., 1987). Participants rated symptoms of depression on a scale of 0–3 and ratings were summed, with cut-off scores equal to or greater than 10 indicating probable depression. Reliability was acceptable at one (α=0.85), six (α=0.81), and 12 months postpartum (α=0.78).

2.3. Data analysis

Data analysis was conducted in RStudio and M*plus*. Prior to analysis, primary study variables were examined for outliers (>3 SD from sample mean) and non-normality (skewness>2; kurtosis>7). Outliers were winsorized to 3 SD from the sample mean.[5] Distributions of pCRH were non-normal and were natural log-transformed for multiple

linear regression analyses, consistent with previous studies. Full information maximum likelihood was used to handle missing data. Rates of missing data ranged from 0% (early pregnancy pCRH) to 28% (late pregnancy pCRH) on primary study variables. The rates of missingness are primary due to missed study visits or timing of delivery.

2.3.1. Aim 1: LCGA of pCRH—We used unconditional LCGA with a robust multiple likelihood estimator to identify trajectories of pCRH, which included linear and nonlinear slope coefficients (Jung and Wickrama, 2008). LCGA identifies trajectories within a population such that individuals within a trajectory are more similar than individuals between trajectories. We compared models fitting one to five classes. Model fit was evaluated with the Bayesian Information Criteria, entropy, bootstrapped parametric likelihood ratio test, and posterior probabilities (Jung and Wickrama, 2008). We tested differences in pCRH trajectory by sociodemographic characteristics using Fisher's Exact Tests and one-way ANOVAs.

2.3.2. Aim 2: pCRH and postpartum depressive symptoms—A series of four multiple regression models were employed to test whether pCRH levels in early, mid, and late pregnancy and pCRH trajectories over the course of pregnancy were associated with depressive symptoms postpartum. Primary analyses adjusted for covariates based on significant associations with either pCRH or postpartum depressive symptoms in this sample. Ethnicity, marital status, education, per capita household income, mode of delivery, parity (defined as no previous live births vs. one or more), maternal age, smoking in pregnancy, preterm birth, and pre-pregnancy BMI were evaluated as potential confounding variables given their potential associations with postpartum depressive symptoms and/or pCRH. We retained the smallest set of variables that were significantly related to study variables in primary analyses in the interest of parsimony.

Marital status, per capita household income adjusted for cost of living, pre-pregnancy BMI, and parity were significantly associated with pCRH in this sample and were included as covariates in primary models. Mean prenatal depressive symptoms were also included as a covariate to test whether associations of pCRH levels with postpartum depressive symptoms was independent of depressive symptoms during pregnancy. Depressive symptoms were assessed at each prenatal study visit with the 9-item version of the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001).[6] Gestational age at each prenatal assessment was included as a covariate in models with pCRH levels as a predictor given that pCRH levels exponentially increase over the course of gestation and also given significant associations with pCRH in the present sample.

2.3.3. Exploratory analyses—Exploratory analyses examined postpartum depressive symptoms at six and 12 months as outcomes.

[5]Consistent with our pre-registered analysis plan, we conducted a robustness analysis with outliers not winsorized. Primary results did not change when outliers were vs. were not winsorized.

[6]Initial pre-registered analyses first tested regression models without controlling for prenatal depressive symptoms and controlled for prenatal depressive symptoms in robustness analyses. However, results did not significantly change when controlling for prenatal depressive symptoms as compared to not. In the interest of parsimony and clarity, we present results of analyses that control for prenatal depressive symptoms.

3. Results

Supplemental Table 2 presents descriptive statistics and bivariate correlations for study variables. As expected, sample mean pCRH levels increased over the course of pregnancy. However, there was variability in individual trajectories of pCRH from early to late pregnancy, particularly the nature of increases in pCRH levels (Supplemental Fig. 1). In the full sample, 13.9% of women reported depressive symptoms indicative of probable depression at one month postpartum. In bivariate correlations, pCRH levels in early, mid, and late pregnancy were not significantly associated with postpartum depressive symptoms.

3.1. Aim 1: LCGA of pCRH

The three-class model was the best fitting model (see Supplementary Table 3 for fit indices). The nonlinear slope term was significant, as is expected based on prior work demonstrating exponential increases in pCRH levels over the course of pregnancy (see Fig. 1). The *typical* trajectory included most of the sample and was characterized by moderate levels of pCRH that showed the expected exponential increases from mid to late pregnancy (50.9%). The *accelerated* trajectory was characterized by the highest levels of pCRH and steepest increases from mid to late pregnancy (25.4%). The *flat* trajectory included participants with low levels of pCRH and the flattest pattern of change (23.7%). Women in the accelerated pCRH trajectory had significantly higher income and had significantly lower pre-pregnancy BMI compared to women in the other pCRH trajectories. Women in the flat pCRH trajectory were significantly younger, less likely to identify as Asian, be married, and to have completed college compared to women in the other pCRH trajectories (Supplemental Table 1).

3.2. Aim 2: pCRH and postpartum depressive symptoms

Mean EPDS scores at one month postpartum were 4.41 (SD = 3.87, range = 0–15, 12.5% probable depression) in the typical pCRH trajectory, 4.92 (SD = 3.89, range = 0–13, 12.5% probable depression) in the flat pCRH trajectory, and 5.34 (SD = 3.56, range = 0–13, 17.1% probable depression) in the accelerated pCRH trajectory. In primary analyses testing associations between pCRH levels and postpartum depressive symptoms, early, mid, and late pregnancy pCRH levels were not significantly associated with depressive symptoms one month postpartum when adjusting for marital status, per capita income, pre-pregnancy BMI, parity, gestational age in weeks, and prenatal depressive symptoms (all p's >.30). However, when testing associations between pCRH trajectories and postpartum depressive symptoms, women with accelerated pCRH trajectories reported higher depressive symptoms one month postpartum compared to women with typical pCRH trajectories when statistically controlling for marital status, per capita income, pre-pregnancy BMI, parity, and prenatal depressive symptoms (p =.09). Complete regression coefficients, including for all covariates, are presented in Table 1.

3.3. Exploratory analyses

Neither pCRH levels in pregnancy nor trajectories were associated with depressive symptoms at six months or one year postpartum when controlling for marital status, per capita income, pre-pregnancy BMI, parity, and prenatal depressive symptoms (p's >.12).

4. Discussion

The current pre-registered longitudinal study addressed two primary aims. In Aim 1, we identified trajectories of pCRH from early to late pregnancy using a person-centered approach (LCGA). The person-centered approach we used identified three pCRH trajectories labeled *typical, flat, and accelerated*. Each trajectory was characterized by nonlinear increases in pCRH from early to late pregnancy, consistent with prior research showing exponential increases in pCRH levels over gestation (McLean et al., 1995), but differed in overall levels as well as rates of change. In Aim 2, we tested hypotheses concerning associations between pCRH levels during early, mid, and late pregnancy and the three pCRH trajectories with postpartum depressive symptoms. Results indicated that pCRH mean levels were not associated with postpartum depressive symptoms. However, there was some evidence that the *pattern of changes* in pCRH was associated with postpartum depressive symptoms. Specifically, pregnant women with accelerated pCRH trajectories reported marginally higher depressive symptoms at one month postpartum (p's =.09) compared to women with typical pCRH trajectories, which is consistent with three prior studies reporting accelerated increases in pCRH levels from mid to late pregnancy occurred among women with elevated depressive symptoms postpartum (Glynn and Sandman, 2014; Hahn-Holbrook et al., 2013; Yim et al., 2009). This association was independent of relevant covariates, specifically, parity, pre-pregnancy BMI, marital status, income, and prenatal depressive symptoms. Of note, this suggests that pCRH trajectories may influence postpartum depressive symptoms over and above prenatal symptoms. Collectively, these findings underscore the importance of examining dynamic HPA axis changes during pregnancy in addition to levels at specific timepoints.

Although a few studies have shown that accelerated pCRH changes predict postpartum depressive symptoms, this is the first study to use a person-centered approach to characterize distinct pCRH trajectories over the course of pregnancy. As compared to approaches that focus on pCRH levels at a single timepoint or mean levels over time or assume the same pattern of change across individuals, person-centered approaches parse heterogeneity by characterizing distinct subgroups of individuals based on HPA axis changes over time. In addition to differences in pCRH levels and patterns of change, women in each trajectory differed on several sociodemographic characteristics, such as age and race. Other recent work used a similar approach to study cortisol trajectories and found links between prenatal cortisol trajectories with maternal psychological distress over the course of gestation (Peterson et al., 2020). In the present findings, the pCRH trajectory patterns parallel the cortisol trajectories identified in the prior study (typical, flat, accelerated). Thus, this suggests three patterns of HPA axis changes over the course of pregnancy based on measures of cortisol and pCRH. Collectively, these findings suggest that person-centered approaches may meaningfully distinguish individuals based on patterns of HPA changes during pregnancy. Further investigation of how indicators of HPA axis changes relate to one another (e.g., cortisol; pCRH) and postpartum mental health is warranted.

Pregnancy is accompanied by substantial changes to neuroendocrine functioning that are necessary to maintain the pregnancy, support fetal development, and support the transition to parenthood (Duthie and Reynolds, 2013; Glynn et al., 2018). For example,

alterations to maternal cortisol levels during pregnancy have been implicated in differences in maternal behavior, attachment, and psychological functioning postpartum (see Glynn et al., 2018). Very little research has examined pCRH as compared to cortisol in the context of postpartum adjustment, and further investigation on how changes in pCRH relate to measures of maternal psychological and behavioral functioning is warranted given documented implications for birth outcomes and child development (Kassotaki et al., 2021; Ramos et al., 2022; Rinne et al., 2023).

A strength of this investigation is the repeated measurement of pCRH over pregnancy. Furthermore, we used the gold-standard assay techniques for determination of pCRH (radioimmunoassay), which are complex to perform and infrequently conducted in research studies as a result. In primary analyses, we examined depressive symptoms early in the postpartum period at 4–8 weeks when most symptoms first appear (O'Hara & McCabe, 2013). A limitation of this study is that mean postpartum depressive symptom levels were low in this sample, which could in part explain the marginal findings. Relatedly, this also precluded tests of cut-off scores for probable depression as an outcome due to small cell size, though descriptively there appeared to be differences in the rate of probable depression across pCRH trajectories. We also note that the current sample was well characterized biologically but women were medically mostly low risk and low in adverse outcomes, limiting our ability to test differences in clinical outcomes due to small cell size. Moreover, the subsample of the larger study included in the present analysis was older, more likely to be married, completed more years of education and reported higher income, which should be kept in mind with regard to generalizability of results. Nonetheless, the sample was diverse with respect to ethnicity, and had variation in demographics. In addition, it was outside of the scope of the present study to examine cortisol trajectories. Future work with larger samples of perinatal women should include a more comprehensive panel of endocrine and psychological markers using this person-centered approach.

This study informs an important body of work on the implications of changes in HPA axis regulation for postpartum depressive symptoms, focusing specifically on pCRH. These results contribute to our understanding of dynamic physiological changes during pregnancy and how such changes relate to postpartum mental health. Future work should attend to pCRH and its implications for postpartum adjustment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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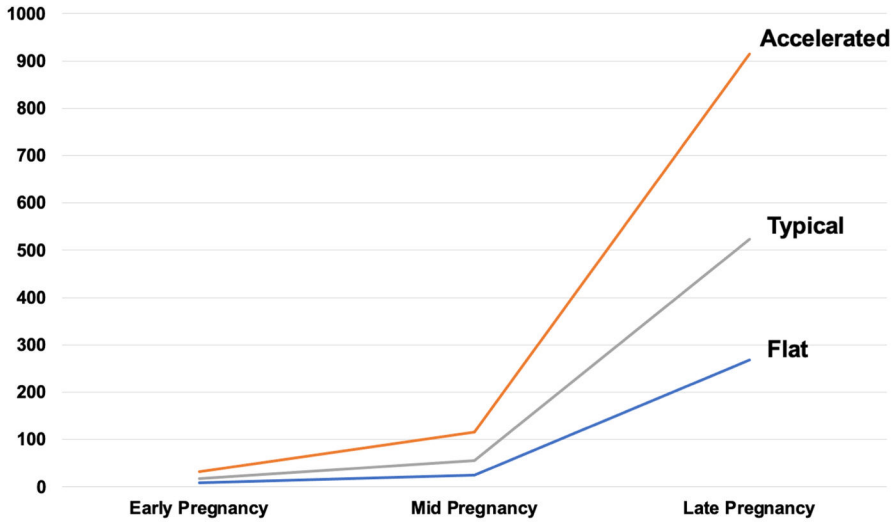

Mean Levels	Full Sample	Flat (23.7%)	Accelerated (25.4%)	Typical (50.9%)
Early Pregnancy pCRH	19.2	9.1	31.6	17.7
Mid Pregnancy pCRH	66.3	24.6	116.1	55.6
Late Pregnancy pCRH	582.9	267.6	915.1	522.6

Fig. 1.
Trajectories of pCRH from early to late pregnancy identified using LCGA.

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Table 1

Primary Analysis Results: pCRH levels and trajectories predicting depressive symptoms one month postpartum.

Model 1: pCRH trajectories						
	β	**B**	**SE**	**LLCI**	**ULCI**	***p*-value**
pCRH Trajectory: Typical	REF	REF	REF	REF	REF	REF
pCRH Trajectory: Flat	0.08	0.77	0.86	−0.94	2.45	.38
pCRH Trajectory: Accelerated	0.15	1.40	0.81	−0.20	2.99	.09^
Income	−0.06	−0.01	0.01	−0.04	0.02	.58
Parity	−0.001	−0.01	0.75	−1.48	1.46	.99
Pre-pregnancy BMI	0.01	0.004	0.065	−0.123	0.132	.95
Marital status	−0.07	−0.54	0.89	−2.28	1.20	.54
Prenatal depressive symptoms	0.46	0.56	0.16	0.26	0.87	<.001***
Model 2: Early pregnancy pCRH levels						
	β	**B**	**SE**	**LLCI**	**ULCI**	***p*-value**
Early pregnancy pCRH	0.08	0.53	0.68	−0.80	1.85	.44
Income	−0.03	−0.004	0.01	−0.03	0.02	.78
Parity	0.01	0.11	0.77	−1.40	1.63	.88
Pre-pregnancy BMI	0.02	0.01	0.07	−0.12	0.15	.84
Marital status	−0.03	−0.26	0.90	−2.04	1.51	.77
Early pregnancy GA	0.01	0.02	0.25	−0.47	0.51	.95
Prenatal depressive symptoms	0.46	0.56	0.16	0.26	0.87	<.001***
Model 3: Mid pregnancy pCRH levels						
	β	**B**	**SE**	**LLCI**	**ULCI**	***p*-value**
Mid pregnancy pCRH	0.02	0.16	0.60	−1.02	1.33	.79
Income	−0.05	−0.08	0.14	−0.35	0.22	.65
Parity	−0.06	−0.05	0.75	−1.53	1.43	.95
Pre-pregnancy BMI	−0.02	−0.01	0.07	−0.14	0.12	.86
Marital status	0.02	0.15	0.91	−1.64	1.94	.87
Mid pregnancy GA	−0.15	−0.35	0.21	−0.76	0.05	.09^
Prenatal depressive symptoms	0.48	0.59	0.16	0.29	0.90	<.001***

Model 4: Late pregnancy pCRH levels

	β	B	SE	LLCI	ULCI	*p*-value
Late pregnancy pCRH	0.10	0.58	0.56	−0.52	1.68	.30
Income	−0.05	−0.07	0.15	−0.36	0.22	.63
Parity	0.01	0.11	0.77	−1.39	1.61	.88
Pre-pregnancy BMI	−0.003	−0.002	0.06	−0.13	0.12	.98
Marital status	−0.03	−0.23	0.90	−2.01	1.54	.80
Late pregnancy GA	−0.01	−0.03	0.29	−0.60	0.55	.93
Prenatal depressive symptoms	0.45	0.55	0.16	0.25	0.86	<.001***

Note.

*** $p < .001$;

^ $p < .10$;

BMI = body mass index; GA = gestational age at prenatal assessment.