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## Ambulatory assessments of psychological and peripheral stress-markers predict birth outcomes in teen pregnancy

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### ABSTRACT

**Objective:** Pregnant adolescents have high rates of poor birth outcomes, but the causes are unclear. We present a prospective, longitudinal study of pregnant adolescents assessing associations between maternal psychobiological stress indices and offspring gestational age at birth and birthweight.

**Method:** Healthy nulliparous pregnant adolescents were recruited ( $n = 205$ ) and followed during pregnancy. Ambulatory assessments over 24 h of perceived psychological stress (collected every 30 min) and salivary cortisol (6 samples) and a summary questionnaire, the Perceived Stress Scale, were collected at three time points (13–16, 24–27, and 34–37 gestational weeks). Corticotropin-releasing hormone, C-reactive protein, and interleukin 6 were assayed from blood taken at the latter 2 sessions. A final sample of 119 participants was selected for analyses.

**Results:** The ambulatory assessment of perceived psychological stress was positively correlated with the Perceived Stress Scale ( $r = .20$ ,  $p = .03$ ) but neither was associated with any of the biological assays (all  $ps > .20$ ). Based on backward selection regression models that included all stress variables and relevant covariates, the ambulatory assessments of perceived psychological stress and cortisol – though not the Perceived Stress Scale – were negatively associated with gestational age at birth ( $F(4, 107) = 3.38$ ,  $p = .01$ ) while cortisol was negatively related to birthweight ( $F(5, 107) = 14.83$ ,  $p < .0001$ ).

**Conclusions:** Targeted interventions to reduce psychological and biological indicators of heightened stress during pregnancy may have positive public health benefits for the offspring given the associations of shortened gestation and lower birthweight with risk for poor mental and physical health outcomes.

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### Introduction

Despite recent declines, the U.S. adolescent pregnancy rate is among the highest in the developed world – about 367,678 births per year comprising about 9% of all U.S. births [1]. Adolescent pregnancies have high rates of poor birth outcomes that are known to set the stage for poor physical and mental health trajectories [2–12]. Specifically, compared to adult women (aged 20–34), adolescents (aged 15–19) have 20% higher rates of preterm birth (defined as  $\leq 37$  gestational weeks at birth) and low birthweight (below 2500 g): 13.6% versus 11.4% and 9.6% versus 7.8%, respectively [1]. Earlier born

and lower-birthweight babies are at risk for adverse health conditions such as epilepsy (see [10]), compromised cognitive development [2,5,6,8,11], lower school achievement [2], psychiatric syndromes including attention deficit hyperactivity disorder [5,7], anxiety and depression [9] and other social-emotional problems [5]. A recent neuroimaging study found that even normal variation in birthweight predicted differences across the lifespan in brain structure such that lower birthweight related to less cortical thickness, providing neural evidence that these basic characteristics of birth outcomes – timing and weight – are meaningful variables with functional significance for the future life course [12]. Independent of the tight coupling of adolescent pregnancy with poverty [3,4], it is unclear why adolescent pregnancies pose a risk to the offspring's future health.

Research indicates that maternal antenatal psychological stress – the appraisal that situational demands exceed one's personal resources (and the associated mood states, e.g., irritated, frustrated, angry)

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[13,14] – is negatively associated with birth outcomes [15–21], though some studies fail to show an association [22] and others have inconsistent findings (e.g., a positive association with birthweight yet a negative association with gestational age at birth [23]). Few studies have examined the role of antenatal psychological stress in adolescent pregnancy despite this population's increased risk for it as well as poor birth outcomes. Several factors point to the likelihood of high psychological stress in pregnant adolescents: they often live in poverty [3,4], are confronting significant social upheaval [24,25], and have histories of adverse childhoods [26], including as the victims of prior physical or sexual abuse [23,27–31], with the associated risk for current poor psychosocial adjustment. To date, there are only four published reports on psychological stress in adolescent pregnancy in relation to birth outcomes. Three found associations between higher stress or anxiety and adverse birth outcomes [32–34], and one did not [35]. However, two that showed significant results focused on the stressful sequelae of trauma [32,33] as opposed to current perceived psychological stress that is the focus of adult studies, and the one that showed null results [35] had a very small sample size ( $n = 38$ ). Moreover, recent research on perceived psychological stress and birth outcomes of adult pregnancies has begun to utilize a more ecologically-valid and reliable approach to its assessment [22,36] – diary reporting of mood states or emotional experiences on an electronic device multiple times during participants' daily lives [37–41] – but this approach has not yet been applied to pregnant adolescents.

Stress is a biopsychosocial process that involves multiple systems [42]; an emerging literature with adult pregnant women is examining the impact of psychological, endocrine and immune stress systems on birth outcomes. Of the few studies considering maternal antenatal stress as a factor in adolescents' poor birth outcomes, only one [35] included biological assays. Yet findings from the adult research that includes biological factors have been significant and informative. For example, recent studies have found a negative association between maternal antenatal cortisol awakening response (CAR)/diurnal salivary cortisol and gestational age at birth, birthweight and birth length [22,43].

There also is strong evidence for the role of immune system inflammatory pathways in pregnancy and parturition [44], and studies have linked maternal stress to elevated inflammatory markers during pregnancy [45–47]. One recent study demonstrated associations between elevated IL-6 and TNF- $\alpha$  and earlier gestational age at birth [45]. It is known that the endocrine and inflammatory systems interact and co-regulate [48]; however, as noted in a recent review [49], there are no studies examining the influence of psychological stress, HPA axis activation, and inflammation in the same model in relation to birth outcomes.

We conducted a prospective longitudinal observational study of pregnant adolescents to assess the effect of maternal antenatal stress on two key birth outcomes, gestational age at birth and birthweight. Participants were assessed at three time points (early, middle, and late pregnancy). We measured perceived psychological stress with the Perceived Stress Scale (PSS) [50] and also used the “ambulatory” approach, ecological momentary assessment (EMA), to collect momentary assessments of current mood states associated with perceived psychological stress such as “nervous”, “angry”, “strained”, “irritated”, “worried”, “stressed”, “frustrated” and “lonely” [14,50,51]. EMA offers an advantage in that momentary ratings of experiences are not dependent on recall as are traditional assessments such as the Perceived Stress Scale (PSS) [52]. Diurnal salivary cortisol was collected at the same time points. Corticotropin releasing hormone (CRH), interleukin-6 (IL-6) and C-reactive protein (CRP) were assayed from blood at the 2nd and 3rd study sessions. We hypothesized that (1) greater perceived psychological stress would predict poor birth outcomes; (2) higher cortisol would be associated with greater perceived psychological stress and poor birth outcomes; and (3) higher levels of CRH and inflammation would be associated with poor birth outcomes.

## Methods

### Participants

Nulliparous pregnant adolescents, ages 14–19,<sup>1</sup> were recruited through the Departments of Obstetrics and Gynecology at Columbia University Medical Center (CUMC) and Weill Cornell Medical College and flyers posted in the CUMC vicinity. To reduce unwanted between-subject variance, only nulliparous pregnant adolescents were enrolled. All had a healthy pregnancy at the time of recruitment. Participants were excluded if they acknowledged smoking or use of recreational drugs, lacked fluency in English, or were multiparous. Participants also were excluded on the basis of frequent use of the following: nitrates, steroids, beta blockers, triptans, and psychiatric medications.

We enrolled 205 participants (see Fig. 1 for the complete enrollment flow chart). Data analysis was performed on a final sample of  $n = 119$  adolescents and their infants.<sup>2</sup> All enrolled participants provided written-informed consent, and all procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute/CUMC.

### Study procedure

Mood and salivary cortisol assessment took place between 13–16, 24–27 and 34–37 gestational weeks (+/– 1 week). Blood measures were collected at the 2nd and 3rd study sessions. (Fig. 2 illustrates the study protocol.) Birth outcome information was culled from participants' medical charts. Participants also had one, randomly scheduled, urine toxicology screen to test for use of cannabinoids, amphetamines, benzodiazepines, opioids, and cotinine.<sup>3</sup>

### Perceived psychological stress

The PSS [52] is a 14-item instrument designed to measure the degree to which participants appraise their lives over the past month as “unpredictable, uncontrollable, and overloading” – i.e., high on perceived psychological stress [13]. On the PSS, respondents rate the frequency of specific experiences on a 5-point scale from “never” to “very often” (e.g., “In the last month how often have you found that you could not cope with all the things that you had to do?”). The PSS has been shown to have adequate reliability, reporting a coefficient alpha of .84 to .86 [50].

Following other research utilizing EMA assessments with adolescents [14,53], for 24-hour periods participants provided ratings on 18 mood states using a personal digital assistant (PDA). Mood states were scored on a 5-point Likert scale and included the following: cheerful, cooperative, responsible, caring, proud, friendly, relaxed, productive, hard-working, lonely, nervous, angry, frustrated, competitive, strained, worried, irritated, stressed (see below for the construction of the negative mood calculation). Participants were instructed to provide ratings every 30 min while awake at the time an automated ambulatory blood pressure unit inflated (data not included in this study). Participants were able to enter mood ratings at additional times. They were incentivized to provide ratings, earning \$0.50 per entry.

<sup>1</sup> To qualify for the study, participants needed to fall within this age range prior to 19 weeks of gestation.

<sup>2</sup> A benign tumor was found on the neck of a fetus in the 3rd trimester. The infant was born otherwise healthy, of normal weight and at term.

<sup>3</sup> One participant tested positive for cannabinoid use twice during pregnancy.

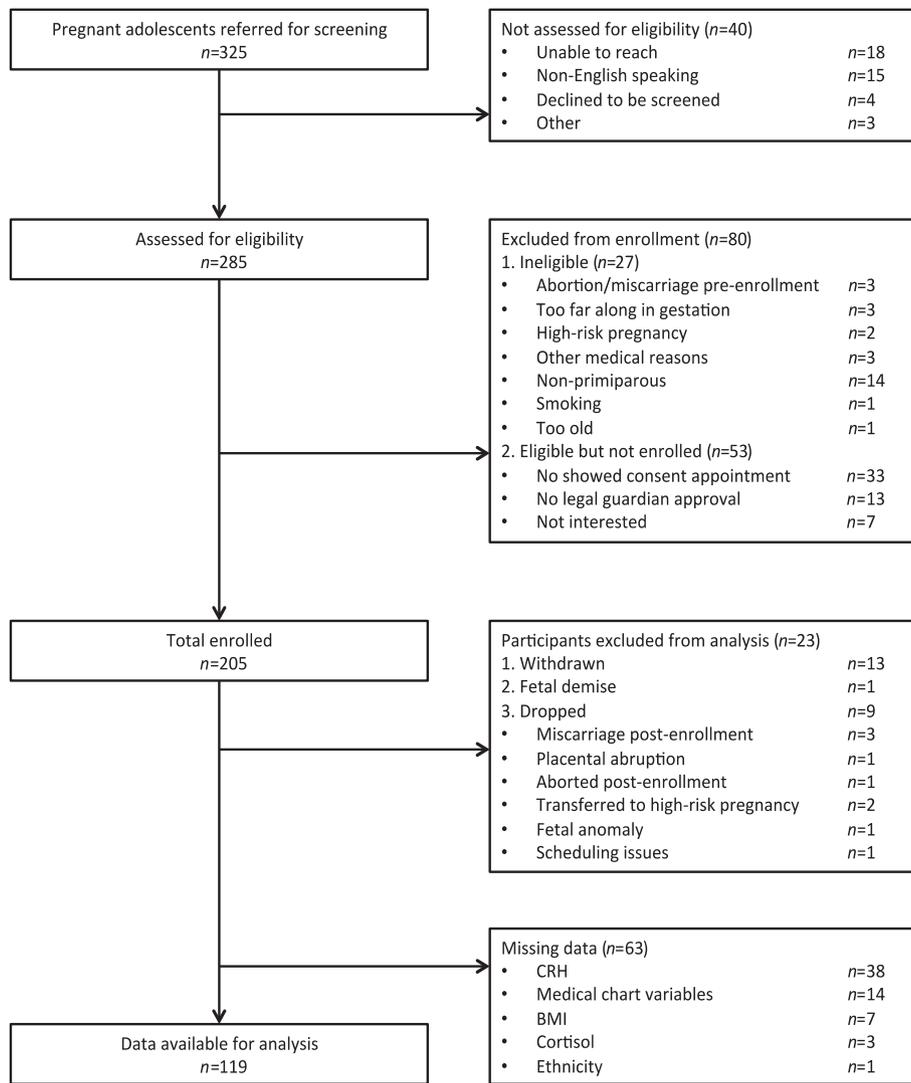


Fig. 1. Flow chart showing complete information on participant enrollment and final number for data analyses.

Salivary cortisol

Diurnal salivary cortisol was collected over 48 h beginning at the time of the study session visit. Subsequent samples were collected on the following schedule: at waking; 45 min, 2.5 h, 3.5 h, and 8 h after waking; and at 10 PM or before going to bed. (Participants continued the schedule of collection at the next collection point relative to their study visit.) Salivette tubes (Sarstedt, Newton, NC) were

used for cortisol collection. The cotton used for each sample was kept in a bottle with a Medication Event Monitoring System (MEMS) cap (Aardex, Union City, CA) to record the time of opening. Once used, the cotton was placed in a Salivette tube. After being returned to the lab, samples were kept frozen until assayed using a commercial ELISA kit (Salimetrics, State College, PA). Only samples from the second collection day, which included all time points and is equal to a total of 6 potential samples, were used in the analyses.

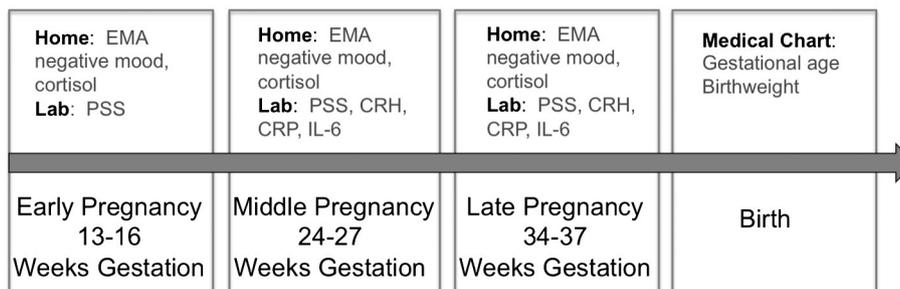


Fig. 2. Study procedure depicting measures collected at each time point. Measures were gathered in the laboratory, in the participant's home, or using the medical chart. The arrow represents time. Measures are listed above the arrow and time points of the study are listed below. CRH = corticotropin-releasing hormone; CRP = C-reactive protein; EMA = ecological momentary assessment; IL-6 = interleukin 6; PSS = Perceived Stress Scale.

### Cytokines and CRH

10 ml blood samples were collected in EDTA tubes. Samples were placed on ice, spun down and frozen at  $-80^{\circ}\text{C}$  within 60 min of collection. IL-6 and CRP were assayed using high sensitivity commercial ELISA kits (HS-IL-6: R+D Systems, Minneapolis, MN; Zymutest HS-CRP: Diapharma, West Chester, OH). Plasma CRH was measured by radioimmunoassay as previously described [54] with the following modifications: For the extraction procedure, 1 ml of each plasma sample was mixed with 4 ml ice-cold methanol in glass tubes, vortexed for 1 min and incubated on ice for 20 min. Tubes were spun at 3500 rpm for 15 min at  $4^{\circ}\text{C}$ . The top layer was transferred to a clean glass tube on ice. 0.5 ml of ice-cold methanol was added to the remainder fraction, vortexed and spun again at 3500 rpm for 15 min at  $4^{\circ}\text{C}$ . The top layer was added to the first removed aliquot and dried in a vacuum centrifuge. Samples were concentrated two-fold during reconstitution in an assay buffer and incubated at  $4^{\circ}\text{C}$  for 48 h. CRH antibody (Abcam, Cambridge, MA) was diluted 1:10<sup>6</sup>. CRH (Sigma, St. Louis, MO) was diluted for the standard curve of 0–2500 pg/ml and CRH I<sup>125</sup> tracer (PerkinElmer, Waltham, MA) to 4000 counts/tube. Extraction efficiency was 60%. The detection limit was 18 pg/ml and the intra-assay coefficient of variation was <10%.

### Birth outcomes

Gestational age at birth and birthweight were determined from the medical record as was information on the presence of pregnancy complications (defined as infection, preeclampsia/hypertension, vascular complications, diabetes mellitus, and other), C-section, and sex of the infant. Gestational age at birth was determined based on the medical record reporting of dating based on ultrasound examinations and last reported menstrual cycle.

### Data preparation

Body mass index (BMI) was calculated using pre-pregnancy weight from self-report and measured height, both ascertained at the first study session. To create an index of EMA perceived psychological stress, hereafter referenced as EMA negative mood, all items from the mood assessments were entered into an exploratory factor analysis using maximum likelihood estimation as the fitting method. Items with loadings below 0.5 were excluded from further analysis. The negative mood index at each time point was calculated based on the average of the following items: angry, frustrated, irritated, and stressed. All items included in the EMA negative mood index are associated with perceived stress [14,50,51]. Because of variability in the number of diary entries (see below), a weighted score was calculated as follows: For each person, for each diary entry, the mean of the four mood states (angry, frustrated, irritated and stressed) was calculated. Next, for each person, for each time point, the average of the four mood states was calculated. Then, the weight for each study session was applied to that average by multiplying the two terms, yielding the weighted score for that session. A weight was determined by dividing the number of diary entries at the session of interest by the total number of diary entries across all study sessions. The final weighted score was calculated by taking an average of the weighted scores across all sessions. (Average negative mood in session 1 \* # of entries in session 1 / total number of entries + average negative mood in session 2 \* # of entries in session 2 / total number of entries + average negative mood in session 3 \* # of entries in session 3 / total number of entries in session 3.) Area under the curve (AUC) cortisol [55] was calculated using units of  $\mu\text{g}/\text{dl}$  and requiring the presence of at least 4/6 cortisol samples within the 24-hour period. CRH was adjusted for gestational age at time of collection as follows: log transformed CRH values were regressed on estimated due date then residuals were used as the CRH predictor variable in the models [56]. To adjust birthweight

in relation to gestational age, we followed recent approaches that characterize the non-linear relationship and identify birthweight as rising with greater gestational age, with steeper slopes during the 3rd trimester, and leveling off beyond 40 weeks [57]. We added gestational age at birth, squared gestational age at birth, and cubed gestational age at birth to our model selection approaches (described below). The cubed gestational age at birth was removed during the model selection process to arrive at optimal model fitness (see details below). Log transformations were performed on CRH, CRP, IL-6, gestational age at birth and corrected birthweight variables as the raw values of these variables were not found to be normally distributed.

### Data analysis and criteria for missing data

To test the influence of psychological and biological stress variables on gestational age at birth and birthweight, backward selection regression models were designed including both a priori predictor variables (i.e., EMA negative mood, PSS, cortisol, CRH, CRP, IL-6) and covariates (i.e., birth complications, C-section, ethnicity, pre-pregnancy BMI, infant sex). Specifically, backward selection regression uses a backward elimination technique for model selection, starting from the full model including all possible independent effects, and then removes variables at each step to give the lowest value of the Akaike Information Corrected Criterion (AICC) and then deems the model most parsimonious at the point when deleting a variable would increase the AICC statistic. (Table 1 lists each of the variables entered into the models, excluding the outcome and 'other' variables.) These models included average values of predictor stress variables across pregnancy. Participants were excluded from analysis if average data were missing from

**Table 1**  
Descriptives

Variables	N	Mean	Std dev	Min	Max
<i>Outcome variables</i>					
Birthweight (grams)	118	3206.99	567.14	947.00	4525.00
Gestational age at birth (weeks)	119	39.03	2.28	26.57	41.57
<i>Predictor variables</i>					
Maternal pre-pregnancy BMI	119	25.97	6.32	16.57	47.6
EMA negative mood	119	0.61	0.30	0.33	1.93
Perceived Stress Scale	119	26.40	5.46	12.00	40.33
Cortisol ( $\mu\text{g}/\text{dl}$ ) <sup>a</sup>	119	3.02	0.92	1.00	6.21
Corticotropin releasing hormone (CRH) (pg/ml)	119	659.09	590.16	18.00	4664.00
C-reactive protein (CRP) (mg/ml)	119	8.33	7.86	0.01	43.23
Interleukin-6 (IL-6) (pg/ml)	119	1.97	1.19	0.50	7.54
Pregnancy complications					
No	59	-	-	-	-
Yes	60	-	-	-	-
C-section					
No	89	-	-	-	-
Yes	29	-	-	-	-
Ethnicity					
Hispanic	107	-	-	-	-
Non-Hispanic	12	-	-	-	-
Infant sex					
Male	73	-	-	-	-
Female	46	-	-	-	-
<i>Other</i>					
Maternal age (years)	119	17.88	1.15	14.00	20.00
EMA – total # of entries	119	50.25	23.44	4.00	118.00
EMA <sup>b</sup> – # of entries each day	119	19.61	8.07	3.00	59.00
Cortisol – total # samples submitted	119	13.59	3.72	4.00	19.00
Cortisol – # of samples each day	119	5.78	0.56	4.00	7.00

Std dev = standard deviation; BMI = body mass index; EMA = ecological momentary assessment; Min = minimum; Max = maximum.

<sup>a</sup> Area under the curve with respect to ground.

<sup>b</sup> As previously described, EMA negative mood data were weighted to account for variability in the number of responses.

any variable in the model. SAS 9.3 was used for all statistical analyses. All tests were two-tailed with the alpha set at 0.05. The White test was used to evaluate the variance of residuals as homogeneous ( $p > .05$ ) for both the birthweight and gestational age models. Kolmogorov–Smirnov tests were used to test for normal distribution. Due to significant missing data, the fully conditional specification (FCS) method was used to impute missing values for additional analyses. The missing values of each predictor/control variable were imputed by regression on all the others. Outcome variables were not imputed. The final models of log transformed birthweight and log transformed gestational age at birth were rerun with multiple imputations.

## Results

### Missing data

As noted, 63 participants had missing data for at least one variable, which excluded them from the analyses (see Fig. 1).

### Descriptives

Descriptive statistics are provided in Table 1. In all, 89.9% of the pregnant adolescents were Hispanic, 50.4% experienced birth complications, 61.3% of the babies were male, 8.4% were born preterm, and 10.1% were born with low birthweight. National rates for pregnant Hispanic adolescents are as follows: 12.7% were born preterm and 7.9% were born with low birthweight [1]. Compared to the enrolled sample ( $n = 205$ ), Wilcoxon–Mann–Whitney tests showed that the participants who were included in the analyses ( $n = 119$ ) did not differ on any of the demographic variables, e.g., BMI, ethnicity (all  $ps > .05$ ).

### EMA negative mood, cortisol collection, and PSS

Participants submitted on average 50.25 ( $sd = 23.44$ ) total EMA negative mood entries and on average, 19.61 ( $sd = 8.07$ ) entries a day; they provided 13.59 ( $sd = 3.72$ ) total salivary cortisol samples and on average 5.78 ( $sd = 0.56$ ) a day, indicating reasonable compliance with the study protocol (Table 1). Specifically, with respect to the EMA diary reporting, the average of nearly 20 entries over a 24-hour period suggests almost one entry every 30 min (as requested) for a 12-hour period. However, as previously indicated, given the range of number of responses (see Table 1), the EMA negative mood data were weighted to control for variability in response compliance. For cortisol, the average total of nearly 14 (out of a possible 18 samples) and of almost 6 daily samples shows overall good conformity with the study protocol. More specifically, across each study period, the following proportion of participants supplied  $>5$  cortisol samples (and the others included in models supplied 4): 86.5%, 91.3%, and 91.1%, at the 1st, 2nd and 3rd sessions, respectively. The average PSS score was 26.4 ( $sd = 5.46$ ). This score is comparable to those obtained by DiPietro et al. [58] and Evans et al. [59], though notably closer to that of the depression, anxiety and comorbid groups of Evans et al. [59].

### Correlations

Correlations between the predictor and outcome variables were assessed (Table 2). A modest positive correlation between EMA negative mood and PSS score ( $r = .20$ ,  $p = .03$ ) was detected, but there were no correlations between psychological and biological markers of stress (all  $ps > .20$ ).

### Maternal stress and birth outcomes

Tables 3 and 4 show results from backward selection regression models that provide some support for hypotheses 1 and 2; they indicate that across all participants included in analyses, EMA negative mood and cortisol were each negatively associated with gestational age at birth; there are only trend associations predicting birthweight. However, despite log transforming the gestational age at birth and birthweight variables, these models did not reach criteria testing for normality: Normality test of residuals: Kolmogorov–Smirnov test,  $D = 0.16$ ,  $p < .01$ , and  $D = 0.14$ ,  $p < .01$ , respectively.

Based on data inspection of boxplots, we identified 7 infants with gestational ages at birth that qualified as outliers (each was below 36 weeks) and 5 with birthweights that qualified as outliers (4 below 2200 g and one above 4000 g). Tables 5 and 6 show results from backward selection regression models excluding outliers; they indicate that EMA negative mood and cortisol were each negatively associated with gestational age at birth and that cortisol was negatively associated with birthweight. The results of normality test of residuals were as follows:  $D = 0.08$ ,  $p < .06$ , and  $D = 0.08$ ,  $p < .09$ , respectively.

Finally, because our sample size was significantly reduced due to missing data (see Fig. 1), we applied imputation methods to our data (see above). Tables 7 and 8 indicate that for these analyses, the results for gestational age at birth are similar to those from

the complete data set; for birthweight, while cortisol remains in the model, it no longer is a significant variable.

To visually represent the associations between the significant maternal stress variables and infant birth outcomes, Fig. 3 shows average gestational age at birth and birthweight in relation to adolescents with the lowest quartile values for cortisol and EMA negative mood versus those with the highest quartile across all participants.

### Removal of other outliers and other confounds

Because the number of EMA mood assessments and cortisol samples varied, boxplots for these variables were assessed to identify possible outliers. Two outliers were identified for EMA mood and one outlier was identified for cortisol. To determine whether these participants unduly influenced the results, the primary models were rerun with these participants excluded. The results were unchanged. Because 34 participants (28.57%) had urinary tract infections (UTIs) at some point during pregnancy, we re-ran the two birth outcome models excluding these participants. The results were unchanged.

## Discussion

Using a psychobiological approach to adolescent risk for poor birth outcomes, we assessed the influence of maternal antenatal perceived psychological (EMA PSS), endocrine (cortisol, CRH) and inflammatory (CRP, IL-6) stress markers averaged over the course of pregnancy on gestational age at birth and birthweight. Several notable results were found. First, averaged over the course of pregnancy, EMA negative mood and cortisol were found to relate negatively to gestational age at birth while cortisol was associated with earlier birthweight; no effects of the inflammatory markers were found. Second, we found that it was EMA negative mood, but not the PSS, that was associated with birth outcomes. Importantly, these results were found with a sample of pregnant adolescents recruited through routine prenatal care appointments, drug-free according to random urine screens, and with rates of preterm birth and low birthweight below the national averages; thus maternal antenatal stress effects were found in a sample possibly shifted towards health compared to the norms of this population.

### Birth outcomes – average stress effects

Gestational age at birth is a robust predictor of cognitive and health outcomes, and it is becoming increasingly recognized that the effects extend from early preterm through full term [2,7,60]. For example, a recent study showed that gestational age at birth – treated continuously among term babies alone – related positively to academic ability at 8 years of age [2]. Negative associations between the maternal psychological [15,16,18,19,21,23] and endocrine [22,43] stress systems and infant gestational age at birth have been well documented. Here, treating gestational age at birth as a continuous measure, we found that both maternal EMA negative mood and AUC cortisol were negatively associated with earlier birth age. These results were stable with and without outliers included (7 children born prior to 36 weeks), and in our imputation model. Specifically, even when we removed the 7 outlier infants – possibly those most affected by maternal stress as suggested by the change in the model estimates – we found that for every unit increase in AUC ( $\mu\text{g/dl}$ ) cortisol, gestational age at birth dropped by 0.79%; when the weighted EMA negative mood score increased from the median (0.51) to the 90th quantile (0.92), gestational age at birth dropped by 0.88%.<sup>4</sup> We did not observe effects of the immune markers.

Though the pathways to gestational age at birth and birthweight may differ, as with gestational age at birth, birthweight has been shown to be a robust predictor of cognitive and health outcomes [5–7,9–11], and the effects hold up within the healthy range of birthweight [6,8,61]. Similar to gestational age at birth, negative associations between birthweight and the maternal psychological [15,18,20]

<sup>4</sup> Due to the nature of log-transformed variables, these outcomes can only be reported in terms of percent, not raw units.

**Table 2**  
Correlations between predictor and outcome variables in backward selection regression models

	Pre-pregnancy Body Mass Index	Perceived Stress Scale	EMA Negative Mood	C-reactive Protein (CRP) <sup>a</sup>	Interleukin-6 (IL-6) <sup>a</sup>	Corticotropin- releasing Hormone (CRH) <sup>a</sup>	Cortisol <sup>b</sup>	Maternal Age	Gestational Age at Birth <sup>a</sup>	Birthweight <sup>a,c</sup>
Pre-pregnancy Body Mass Index										
Perceived Stress Scale	-0.04 0.64									
EMA Negative Mood	-0.05 0.61	0.20 0.03								
C-reactive Protein (CRP) <sup>a</sup>	0.43 0.00	-0.06 0.50	-0.02 0.87							
Interleukin-6 (IL-6) <sup>a</sup>	0.31 0.00	-0.12 0.20	-0.08 0.41	0.31 0.00						
Corticotropin- releasing Hormone (CRH) <sup>a</sup>	-0.17 0.06	-0.04 0.70	-0.07 0.47	-0.01 0.91	0.06 0.52					
Cortisol <sup>b</sup>	-0.17 0.07	0.06 0.50	-0.02 0.79	-0.07 0.42	0.12 0.20	0.20 0.03				
Maternal Age	0.12 0.18	-0.12 0.20	0.07 0.46	0.19 0.04	0.15 0.1	0.09 0.34	0.03 0.71			
Gestational Age at Birth <sup>a</sup>	0.10 0.26	0.04 0.64	-0.40 0.00	-0.07 0.47	-0.1 0.25	-0.16 0.08	-0.28 0.00	-0.03 0.71		
Birthweight <sup>a,c</sup>	0.12 0.20	-0.12 0.20	0.1 0.25	0.03 0.78	0.09 0.32	-0.1 0.25	-0.10 0.28	0.04 0.66	0 1.00	

Pearson correlation coefficients (*r*-values) appear at the top of each cell. *p*-Values (two-tailed test) appear at the bottom of each cell.

All *n*'s and units of measurement are listed in Table 1.

<sup>a</sup> Log-transformed variable.

<sup>b</sup> Area under the curve with respect to ground.

<sup>c</sup> Quadratic correction for gestational age at birth.

and endocrine [62] stress systems have been demonstrated, though there is at least one report of psychological stress indicating effects in the opposite direction [23]. In the present study, treating birthweight as a continuous measure and correcting for gestational age at birth, in support of our hypotheses, we found a negative association between maternal AUC cortisol and birthweight, though this association only emerged once birthweight outliers were removed from analyses, and

was not maintained in the imputation model (cortisol was kept in the model but did not reach significance). Specifically, the results showed that for every unit increase in AUC ( $\mu\text{g}/\text{dl}$ ) cortisol, birthweight dropped by 2.43%.

The impact of elevations in maternal cortisol and perceived psychological stress (as reported via EMA assessment of negative mood) was comparable to that found in relation to smoking during

**Table 3**  
Backward selection regression model: gestational age at birth<sup>a</sup> (*n* = 119)  $F(4,114) = 11.29$ ,  $p < .0001$ 

Variables	Estimate ( $\beta$ )	Standard error	<i>p</i> -Value
Perceived Stress Scale	0	0	.080
EMA negative mood	-0.10	0.02	<.001
Corticotropin-releasing hormone (pg/ml) <sup>a</sup>	-0.01	0.01	.113
Cortisol ( $\mu\text{g}/\text{dl}$ ) <sup>b</sup>	-0.02	0.01	.001

Bold indicates significant effects.

<sup>a</sup> Log-transformed variable.

<sup>b</sup> Area under the curve with respect to ground.

**Table 4**  
Backward selection regression model: birthweight<sup>a</sup> (*n* = 118)  $F(5,112) = 51.01$ ,  $p < .0001$ 

Variables	Estimate ( $\beta$ )	Standard error	<i>p</i> -Value
Gestational age at birth (weeks)	19.94	9.68	.042
Gestational age at birth * gestational age at birth (weeks)	-2.39	1.36	.083
Infant sex (male = 0, female = 1)	-0.04	0.02	.099
Perceived Stress Scale	-0	0	.087
EMA negative mood	0.08	0.04	.087

Bold indicates significant effects.

<sup>a</sup> Log-transformed variable.

**Table 5**Backward selection regression model: gestational age at birth<sup>a</sup> (n = 112) F(4,107) = 3.38, p < .0120

Variables	Estimate (β)	Standard error	p-Value
Perceived Stress Scale	0	0	.098
EMA negative mood	−0.02	0.01	<b>.043</b>
Corticotropin-releasing hormone (pg/ml) <sup>a</sup>	−0	0	.280
Cortisol (μg/dl) <sup>b</sup>	−0.01	0	<b>.013</b>

Bold indicates significant effects.

<sup>a</sup> Log-transformed variable.<sup>b</sup> Area under the curve with respect to ground.

pregnancy. Specifically, across all babies, those exposed to the highest compared to the lowest quartile of maternal cortisol had birthweights of 3008.69 versus 3321.83 g and gestational ages at birth of 38.17 versus 39.41 weeks; for EMA negative mood the results were 38.09 versus 39.41 gestational weeks at birth (see Fig. 3). In two reports of pregnant women smokers versus non-smokers, the results were 38.3 versus 38.6 weeks [63] or 3139 versus 3409 g (unadjusted) and 38.6 versus 39.5 weeks [64].

#### EMA vs. PSS

As noted, EMA negative mood was associated negatively with gestational age at birth. Though it has been found to relate to a variety of interesting and important outcomes [50,65], and though it related positively to EMA negative mood in the current study, the PSS was not found to have predictive value on birth outcomes relative to the other variables included in the models. It is of interest to note that the PSS is a one-time measurement depending on participant recall of the past month whereas the EMA method gathers ratings in the present. Thus, EMA may be a more sensitive method of assessing perceived psychological stress (and associated emotional states) [22] in relation to biological or health variables, with the current study adding to a growing body of work demonstrating such results [53,66,67]. One prior study of adult pregnancy, which did not find an effect of EMA on birth outcomes, had a much smaller sample size and range of gestational ages at birth [22].

#### A psychobiological approach

The present study offers the advantage that the influence of psychological stress was assessed along with the influence of endocrine and immune stress markers on birth outcomes. The results based on average indices of psychological and biological stress revealed an influence of both EMA and endocrine stress measures, but none were found for the inflammatory markers. This is consistent with a

**Table 6**Backward selection regression model: birthweight<sup>a</sup> (n = 113) F(5,107) = 14.83, p < .0001

Variables	Estimate (β)	Standard error	p-Value
Gestational age at birth (weeks)	−34.79	16.24	<b>.034</b>
Gestational age at birth * gestational age at birth (weeks)	5.01	2.24	<b>.028</b>
Infant sex (male = 0, female = 1)	−0.06	0.02	<b>.011</b>
Ethnicity (non-Hispanic = 0, Hispanic = 1)	−0.08	0.03	<b>.030</b>
Cortisol (μg/dl) <sup>b</sup>	−0.02	0.01	<b>.034</b>

Bold indicates significant effects.

<sup>a</sup> Log-transformed variable.<sup>b</sup> Area under the curve with respect to ground.**Table 7**Backward selection regression model: gestational age at birth<sup>a</sup> (n = 173)

Variables	Estimate (β)	Standard error	95% confidence limits		p-Value
Perceived Stress Scale	0	0	−0	0	.320
EMA negative mood	−0.04	0.01	−0.06	−0.02	<b>&lt;.001</b>
Corticotropin-releasing hormone (pg/ml) <sup>a</sup>	−0.01	0.01	−0.03	0.01	.312
Cortisol (μg/dl) <sup>b</sup>	−0.02	0.01	−0.03	−0.01	<b>.004</b>

Bold indicates significant effects.

<sup>a</sup> Log-transformed variable.<sup>b</sup> Area under the curve with respect to ground.

recent study that also failed to find a relationship between circulating levels of immune system markers, IL-6 and TNF-α, and birth outcomes [68]. Associations between inflammatory markers and preterm birth are more commonly found in local tissues such as amniotic fluid and vaginocervical fluid [69,70], though a recent study has demonstrated associations between elevated systemic IL-6 and TNF-α (but not CRP) and reduced gestational age at birth [45]. We also did not find any associations between maternal psychological reports of stress using PSS or EMA and assays of the biological effectors of stress, e.g., cortisol, CRH or inflammatory systems, suggesting that psychological stress and cortisol have independent effects on birth outcomes. Our failure to demonstrate an association between maternal perceived stress and cortisol is consistent with other reports in the literature [71,72]. Our findings contrast with a report by Entringer et al. [22] showing a positive correlation between EMA negative mood and cortisol in adults. On the other hand, the few existing studies on pregnant adolescents have identified aspects of cortisol regulation that differ from adults, and thus may indicate a unique psychobiological regulation that contributes to our null results predicted based on some findings with adults. For example, pregnant adolescents who scored lower on self-reports of anxiety and depression had greater cortisol reactivity to a novel situation [73]. In other research, pregnant adolescents who scored lower on a measure of state anxiety had higher resting cortisol – the opposite of what would be predicted [14,74].

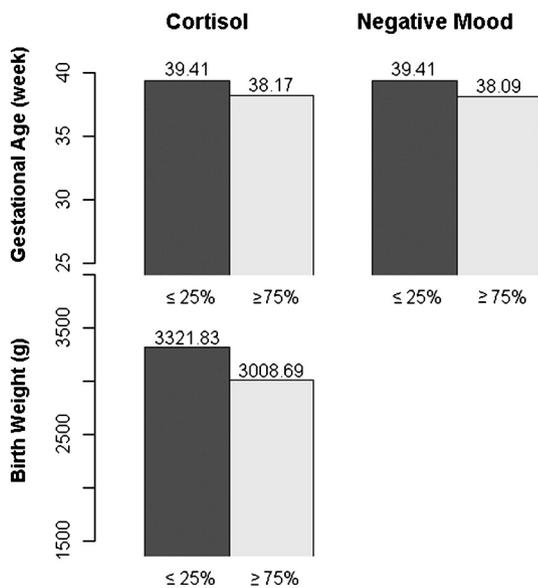
While use of an EMA approach to stress measurement for the characterization of maternal antenatal stress appears to be more sensitive than retrospective self reports (even those spanning just a few weeks, as is typical) for predicting birth outcomes, we were unable to demonstrate an association between the EMA measure and any of our hypothesized endocrine or immune mediators. Other studies have also failed to demonstrate a physiological mediator of the effects of stress on birth outcomes (see [75]). It is possible that the effects of maternal psychological stress on birth outcomes are mediated through other physiological mechanisms that were not included here, such as glucocorticoid feedback sensitivity, the autonomic nervous system, or endocrine and immune changes in specific tissues.

**Table 8**Backward selection regression model: birthweight<sup>a</sup> (n = 176)

Variables	Estimate (β)	Standard error	95% confidence limits		p-Value
Gestational age at birth (weeks)	33.80	7.90	18.29	49.31	<b>&lt;.001</b>
Gestational age at birth * gestational age at birth (weeks)	−4.39	1.12	−6.58	−2.20	<b>&lt;.001</b>
Infant sex (male = 0, female = 1)	−0.04	0.02	−0.08	−0	<b>.037</b>
Ethnicity (non-Hispanic = 0, Hispanic = 1)	−0.05	0.03	−0.11	0.01	.134
Cortisol (μg/dl) <sup>b</sup>	−0.02	0.01	−0.04	0.01	.185

Bold indicates significant effects.

<sup>a</sup> Log-transformed variable.<sup>b</sup> Area under the curve with respect to ground.



**Fig. 3.** The left bars (dark) represent participants with average cortisol or average EMA negative mood  $\leq 25\%$ ; the right bars (light) are for those with values  $\geq 75\%$ . Bar height: mean of outcomes (gestational age or birthweight).

#### Limitations and future directions

Our study has several limitations that should be noted. Our results may not generalize to other pregnant adolescent populations. There may have been self-selection bias among our participants as ours was a longitudinal study that involved several time points of data collection and a large amount of interaction between the researchers and participants. It is possible that our participants were ones who found the study to be a source of social support during pregnancy and were able to remain engaged. In addition, exclusion criteria such as drinking or smoking may limit the generalizability of our results. The sample also was largely Hispanic so the results may not generalize to other ethnic/racial groups. In addition, though our sample was relatively compliant with the extensive protocol demands, there were significant missing data; the failure of the imputation model of birthweight to be consistent with the findings based on the smaller, albeit complete, data set underscores the need to replicate our findings. An important consideration for research of stress during pregnancy is the population that is being studied. Several studies have focused on low-income women due to their increased risk for life stress [42,76]; we chose the adolescent period, one that is also characterized by increased risk for stress, as well as poor birth outcomes. Whether these results generalize to adult pregnant women is an empirical question.

#### Summary and conclusions

The present study is the first in pregnant adolescents to examine perceived psychological stress and stress biomarkers in relation to birth outcomes. Strengths of the study include: (1) dimensional approach to birth outcomes, (2) EMA mood assessment and (3) endocrine stress biomarkers, including ambulatory cortisol collection. Overall, it was found that even in a sample of pregnant adolescents with better birth outcomes than the national averages, higher average EMA negative mood and cortisol during pregnancy related to lower gestational age at birth and that higher cortisol predicted lower birthweight. Of note, only these measures that had repeated ambulatory assessments were associated with birth outcomes. Targeted interventions to reduce psychological and biological indicators of heightened stress during pregnancy may have positive public health benefits for the offspring

given the associations of shortened gestation and lower birthweight with risk for poor mental and physical health outcomes.

#### Competing interest statement

All authors have completed the Unified Competing Interest form at [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf). The authors have no competing interests to report.

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