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Psychological Stress And Cortisol During Pregnancy: An Ecological Momentary Assessment (EMA)-Based Within- And Between-Person Analysis.

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Abstract

Background.—Although the linkage between psychological stress and cortisol is believed to mediate the association of stress with health outcomes, several studies have been unable to demonstrate this association. We suggest this inability may be a consequence of limitations in the measurement approach and/or reliance on analytic strategies that focus on associations across, rather than within individuals. The link between psychological stress and cortisol is of particular interest in the context of pregnancy and fetal development. Using an ecological momentary assessment (EMA) design, we examined the association between psychological stress and cortisol at the between- and the within-person level.

Methods.—152 participants completed a 4-day long EMA protocol serially in early, mid and late pregnancy to provide momentary stress appraisals (average of 150 measures/subject) and saliva samples (average of 55 samples/subject) for quantification of cortisol. The association between stress and cortisol was estimated using linear mixed models.

Results.—After accounting for the effects of key determinants of variation in cortisol, momentary stress was significantly and positively associated with cortisol at the within-person

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level (B = .030, p = .031), but not at the between-person level. No association was evident for traditional retrospective measures of stress with cortisol at either the between- or the within-person level.

Conclusions.—Our study highlights the value of the EMA and linear mixed-modeling approaches in linking maternal psychological and physiological states across pregnancy. These findings may have important implications for the development of personalized risk identification and "just-in-time" intervention strategies to optimize maternal and child health.

Keywords

Ecological-Momentary-Assessment; Stress; Cortisol; Pregnancy; Linear Mixed Modelling; Psychoendocrine Covariance

1 Introduction

The association between psychological stress and disease risk is believed to be mediated, in large part, by stress-responsive physiological systems, notably the hypothalamus-pituitary-adrenal (HPA)-axis and its end product, cortisol (McEwen, 2012). It, therefore, seems reasonable to expect a high degree of correspondence between an individual's psychological and physiological state (referred to as "response coherence"; Mauss et al., 2005, p. 175). However, and somewhat surprisingly, several studies have been unsuccessful in documenting this link (reviewed in: Mikkelsen et al., 2017). The absence of this association, which has been referred to as "lack of psychoendocrine covariance" (Campbell and Ehlert, 2012; Schlotz et al., 2008), may reflect one of two possibilities: *a*) there is no covariance, or, *b*) there are methodological limitations in measurement or analytic approaches that obscure the association. The first possibility seems unlikely given the ample evidence from experimental studies in animals and humans that demonstrate the induction of psychological stress consistently and reliably produces activation of the HPA axis and cortisol (Kirschbaum et al., 1993; Kudielka et al., 2007; McCormick et al., 2010). In terms of the second and more likely possibility, we suggest that three sets of potential issues may be particularly salient: *1)* the failure to account for the idiographic (or subjective) nature of the appraisal of psychological stress; *2)* the lack of temporal coupling in the assessment of psychological and physiological states; and *3)* the reliance on retrospective recall measures to assess psychological stress appraisals.

Studies that examine psychoendocrine covariance have moved away from single (one-time) assessments and now typically employ repeated measurement designs to assess psychological and biological measures. However, even in this second generation of studies, the analytic focus has usually remained on the *average* association *across* a group of individuals, i.e., the *between-person* effect. This between-person approach assumes uniformity across individuals in the magnitude of the association between the appraisal of psychological stress and the physiological state, thereby potentially discounting the idiosyncratic (subjective) nature of such psychological appraisals. Individuals may vary widely in their subjective interpretation of stress level indicators that are commonly used in self-report measures (*i.e.*, the interpretation of descriptors of stress such as "1 = a little," "2 = a moderate amount" and "3 = a lot"). This subjectivity, or non-differential measurement

error, may add “noise” to the ascertainment of stress and thereby attenuate effects. Consequently, the absence of between-person effects in quantifying psychoendocrine covariance may not necessarily be indicative of the absence of within-person effects (Molenaar, 2004, 2013; Molenaar and Campbell, 2009). We note that this limitation can be addressed by conducting a series of repeated measurements and adopting a *within-person* perspective, wherein the quantification of psychological state (stress) for a given individual at any given measurement moment is expressed relative to her or his own average state across measurements (*i.e.*, mean centering an individual’s stress appraisals; reviewed in: Curran and Bauer, 2011; Molenaar, 2004, 2013; Molenaar and Campbell, 2009; Voelkle et al., 2014; Voelkle et al., 2018). Thus, upon doing so, effects that quantify the statistical association between psychological and endocrine measures are a reflection of both between-person and within-person effects, that then can be further deconstructed (reviewed in: Voelkle et al., 2018).

The second issue potentially contributing to the lack of psychoendocrine covariance may arise from the fact that psychological and endocrine states are often measured along different time scales. In many studies, ratings of prior stress levels (*e.g.*, measures that instruct the respondent to provide a summary measure of her or his stress appraisals over a certain time frame such as during the previous four weeks) are linked to the indicators of endocrine state (*e.g.*, individual’s cortisol concentrations assessed in saliva or blood) that do not reflect or correspond to the same time frame (*e.g.*, cortisol concentrations in saliva reflect adrenal cortisol production over only the previous 20–30 minutes of time; Kirschbaum et al., 1993). And even in the case of studies that do collect multiple biological samples and then collapse them across a day or multiple days into measures that represent the average cortisol output (area under the curve (AUC) of cortisol measurements across a day or multiple days; Hellhammer et al., 2009), the time windows of collection of psychological and cortisol measures are often misaligned in terms of the temporal occurrence of stress and its biological indicator (Weckesser et al., 2019).

Third, the use of retrospective recall measures of stress may represent another potential limitation. Respondents are typically asked to rate how stressed they have felt over a prior period such as the past week, month, or longer. For example, one of the most commonly-used instruments to assess stress appraisals is the Perceived Stress Scale (PSS), a measure that instructs respondents to provide an average (summary) evaluation of the extent to which their life has been unpredictable, uncontrollable, and overwhelming over the past four weeks (Cohen et al., 1983). Such self-report retrospective recall measures are prone to numerous systematic biases that undermine their reliability and validity (Podsakoff et al., 2012), including recall bias (Loaiza et al., 2018), the use of heuristics (Availablility heursitic, Affect heuristic; Bradburn et al., 1987), personal significance, social desirability, and current affective state (Thomas and Diener, 1990). Moreover, such assessments are typically not conducted in the environment in which the stress-related affective states were experienced, limiting their external validity. It is, therefore, not surprising that several previous studies using measures such as the PSS have been unable to provide empirical evidence for a linkage between psychological and physiological states (Engert et al., 2018; reviewed in: Mikkelsen et al., 2017; Weckesser et al., 2019).

Based on these conceptual and methodological challenges, we suggest that study designs that incorporate repeated and concurrent measures of psychological and endocrine states over time may be better equipped to address the question of psychoendocrine covariance and to parse within- and between-person effects. The ecological momentary assessment (EMA) approach is an example of one such design (Conner and Barrett, 2012; Shiffman et al., 2008). In contrast to retrospective recall summary assessments, EMA incorporates real-time, repeated measurements of respondents' momentary conditions, states, behaviors and physiology in real time and in the everyday life (ecologically-relevant) context (Mehl and Conner, 2012; Stone et al., 1998). In addition to minimizing the potential limitations discussed above, the availability of serial (repeated) EMA measures within individuals enables the computation and use of measures of deviations of an individual's momentary psychological state from her/his average psychological state, thereby re-scaling each measure to her or his average stress level and facilitating disaggregation of between-person effects and within-person effects. We note that only a relatively small number of studies have used EMA in the context of assessing psychoendocrine covariance. These studies have more consistently uncovered significant associations between psychological stress and cortisol concentrations, notably at the within-person level (Adam et al., 2006; Jacobs et al., 2007; Smyth et al., 1998; Stawski et al., 2013), but even these investigations have not simultaneously examined both between- and within-person associations.

The relationship between psychological stress and cortisol concentrations is of particular interest in the context of pregnancy and fetal development because maternal stress during pregnancy has been linked to many critical pregnancy-, birth- and offspring-related outcomes (Buss et al., 2017; Entringer et al., 2018; Heim et al., 2019; Van den Bergh et al., 2017; Wadhwa et al., 2011). The stress hormone cortisol is postulated as a key potential mediator of these observed associations. Moreover, it may be important to examine this association across different stages of pregnancy because the responsiveness of the maternal HPA axis to psychological stress may vary as a function of pregnancy stage (the state of pregnancy produces a progressive two- to three-fold increase in maternal cortisol production over the course of gestation (Mastorakos and Ilias, 2003; Wadhwa et al., 2011) that we and others have suggested may attenuate the responsiveness of the system (Entringer et al., 2010; Wadhwa, 2005; Wadhwa et al., 2009; Wadhwa et al., 2011).

In light of these considerations, the aim of the current study was to examine the association between maternal psychological stress and cortisol during pregnancy. We conducted a longitudinal investigation in a population of healthy pregnant women and employed a repeated measures EMA design to examine within- and between-person effects at the momentary, day, and stage-of-pregnancy (early, mid, late) level. Our EMA protocol incorporated the collection of real-time psychological, behavioral and biological data over a consecutive four-day period, and it was serially administered at three windows in early, mid and late pregnancy. We used linear mixed models to account for the nested data structure and to evaluate between-person and within-person associations at the three time scales (moments, days, and stages of pregnancy; Snijders and Bosker, 2012). Analyses were adjusted for the effects of previously-established covariates of cortisol, including time of day, exact gestational age at assessment (GA), weekend/weekday, meal intake, and pre-

pregnancy body-mass-index (BMI; Bleker et al., 2017; Gibson et al., 1999; Kudielka et al., 2012; Kunz-Ebrecht et al., 2004; Schlotz, 2018).

2 Materials and Methods

2.1 Participants

Women with a singleton, intrauterine pregnancy were recruited in early pregnancy for a prospective, longitudinal EMA-based study at the University of California, Irvine's Development, Health and Disease Research Program. The study population (N = 152) was relatively healthy and consisted predominately of non-Hispanic white and Hispanic women. The study protocol included three study visits during early, mid, and late pregnancy (for sample characteristics, see Table 1). The attrition rate for the three serial pregnancy assessments from early to late gestation was 8%. Exclusion criteria included twin pregnancies, uterine, placental/cord anomalies, fetal congenital malformations, and systemic corticosteroid intake. The UCI Institutional Review Board approved the study, and all participants provided written consent.

2.2 Measures

2.2.1 Maternal characteristics.—A structured sociodemographic interview was conducted by trained study personnel to obtain information about maternal age, education, household income, race/ethnicity, pre-pregnancy weight, height, and parity. Estimated date of conception and GA was computed using standard obstetric criteria (combination of LMP and fetal biometry ultrasound). Obstetric data were abstracted from the medical record.

2.2.2 Perceived stress.—At each visit, we assessed maternal perceived stress along three different time scales (momentary, daily, and "last four weeks"/monthly level). We assessed *momentary* perceived stress using an EMA protocol for ambulatory, real-time measurement (see Figures 1). The 4-day EMA-protocol spanned two consecutive weekdays and a weekend (i.e., Thursday - Sunday, or Saturday - Tuesday). Participants were provided a smart phone containing electronic diary measures, an actigraphy device, and a saliva collection kit. Throughout the EMA period, participants were prompted an average of one time per hour (i.e., every 60 ± 10 mins) during waking hours to evaluate their momentary perceived stress level using a short validated version of the perceived stress scale (PSS-EMA; Cohen et al., 1983; Cohen and Williamson, 1988). At each prompt subjects answered additional questions about contextual factors such as previous meal intake. Following the 4-day EMA protocol, subjects returned to the research office, where they were then administered the PSS-10 questionnaire regarding their perceived stress during the *last four days* (EMA period, PSS-past-4-days). In addition, perceived stress over the *last four weeks* was assessed using the validated PSS-10 (retrospective self-report instrument; (PSS-past-4-weeks; Cohen et al., 1983; Cohen and Williamson, 1988).

2.2.3 Cortisol assessments.—During each EMA-period participants provided five daily saliva samples in salivettes immediately upon, and 30 mins after awakening, and at 12pm, 4pm, and 8pm. The electronic diary prompted the participants to provide samples. Participants stored the salivettes in a refrigerator until the post-EMA visit. Electronic

monitors (MEMS®, Aardex group, Union City, CA, USA) were used to date-time-stamp the sampling. Participants were fitted with an Actiheart monitoring device to continuously record their EKG and physical activity. To verify compliance with the immediately-upon-awakening saliva sampling each participant's EKG and actigraphy was examined by two independent raters to establish time of awakening indicated by a substantial change in heart rate and physical activity (Steinberg et al., 2017). Salivary cortisol concentrations were analyzed using ELISA (Salimetrics, Carlsbad, CA). 10% of the samples were run in duplicates. The assay had a lower limit of sensitivity of 0.007 μg/dl, standard curve range from 0.012 μg/dl to 3.0 μg/dl, an average intra-assay coefficient of variation (CV) of 5.42%, and an average inter-assay CV < 10%. At the day and stage-at-pregnancy level, momentary cortisol concentrations were aggregated across the day and across the entire 4-day EMA-periods, respectively, using the area-under-the-curve with respect to ground (AUC.g; Khoury et al., 2015).

2.3 Statistical Analysis

We performed all statistical analyses in R version 3.5.1 (R Development Core Team, 2018). The R-package nlme version 3.1–137 was used for linear mixed model analyses (Pinheiro et al., 2018) .

2.3.1 Variance decomposition of momentary measures.—We used linear mixed(-effect) models (LMMs; cf. multilevel models) to identify the sources of variance in momentary PSS-EMA and cortisol across the different levels of the data (Snijders and Bosker, 2012). Momentary cortisol was log-transformed due to its skewed distribution (Table S1, Supplement). This paper focuses on the association between perceived stress and cortisol during the everyday life of individuals. In contrast to controlled experimental settings with discrete time points for stressor onset and end of stress exposure, in which cortisol peaks within 20–30 mins after the beginning of the stressor (Hellhammer and Schubert, 2012; Kirschbaum et al., 1993; Kudielka et al., 2007), perceived stress in everyday life might extend across longer periods. We therefore decided *a priori* to use the closest perceived stress ratings to the cortisol sample within a window of ± 60 min around cortisol sampling. In case of more than one response, the perceived stress rating closest to the cortisol sampling was chosen. In two separate 4-level LMMs, random intercepts for momentary measurements (level 1), days (level 2), stages of pregnancy (level 3), and participants (level 4) were estimated and used to calculate the percentage of total variance in PSS-EMA, and cortisol. To account for the unequal spacing of auto-correlated measurements across a day a continuous autoregressive covariance structure was specified. Restricted maximum likelihood was used for parameter estimation.

2.3.2 Linear mixed models.—(a) To examine the relationship between PSS-EMA and cortisol at the momentary level, a 4-level LMM was fitted to the hierarchical data. We used a continuous autoregressive covariance structure of order 1. To account for the diurnal shape of cortisol (Adam and Kumari, 2009), time since awakening on each day was modeled using B-spline functions (Eilers and Marx, 1996). The derived estimates (t1- t5) were used as predictors in the LMM, interpolating the time course on to the momentary cortisol measures. The complete model specification is provided in the Supplement A1. (b) To examine the

coupling at the day level, aggregated PSS-EMA on a day and the AUC.g on that day were associated in a similar 4-level LMM (for model specifications, see Supplement A2). (c) To compare traditional recall questionnaires and EMA-based stress with respect to their association with cortisol, PSS-EMA was aggregated across each EMA-period (PSS-EMA.4days). At each stage-of-pregnancy level, the aggregated PSS-EMA-4-days (Supplement A3), the PSS-past-4-days (Supplement A4), and the PSS-past-4-weekss (Supplement A5) were used to predict the AUC.g aggregated across each EMA-period in three separate 3-level LMMs.

2.3.3 Centering.—To differentiate the within-person and between-person effects of stress, all PSS scores were centered (Enders and Tofighi, 2007). The individual PSS-EMA scores were centered at the individual's mean PSS-EMA across all EMA responses (PSS-EMA.cwc, cwc = "centered within cluster"). Therefore, the PSS-EMA.cwc represents the extent to which an individual deviates at each given momentary assessment from their average stress level (i.e., the within-person effect). Both, PSS-EMA.cwc and the individual's mean PSS-EMA (PSS-EMA.pm, i.e., between-person effect) were included as predictors in the LMMs. At the day level, PSS-EMA was aggregated across each day and centered at the person mean as described (PSS-EMA.day.cwc). The PSS-EMA.day.cwc represents the deviation of a person's average PSS-EMA on a given day from their average stress level. At the stage-of-pregnancy level, PSS-EMA was aggregated across each EMA-period within the stages of pregnancy and centered as described (PSS_EMA.4day.cwc). The same was done for PSS-past-4-weeks (PSS-past4weeks.cwc) and PSS-past-4-days (PSS-past4days.cwc).

2.3.4 Covariates.—The following covariates were included as fixed effects in the LMMs (for formal model specifications, see Supplement A1–A5): at the momentary level (A1), time since awakening (t1-t5), meal intake (yes = 1, no = 0), GA, weekend/weekday (weekend = 1, weekday = 0), and pre-pregnancy BMI; at the day level (A2), GA, weekend/weekday, and pre-pregnancy BMI; at the stage-of-pregnancy level (A3-A5), GA, and pre-pregnancy BMI.

3 Results

3.1 Descriptive statistics of cortisol and perceived stress

3.1.1 Salivary cortisol.—As expected, momentary cortisol concentrations exhibited a diurnal pattern, with a steep morning increase and a progressive decrease across the rest of the day. Also as expected, maternal cortisol increased with advancing gestation, and were positively skewed (see Supplement Table S1). Compliance for saliva collection was high (M = 93.8 % ± 10.4 % (SD) of samples were collected). Participants collected on average 56 out of 60 possible samples on average across gestation. Reasons for missing data included attrition over the course of the study, and non-compliant EMA or saliva collection.

3.1.2 Perceived Stress Scale (PSS).—The sample had a relatively low prevalence of highly stressed individuals (see Supplement Table S1). Compliance with the EMA-protocol was very high (M = 90.3 % ± 9.0 % (SD) of prompts were answered). Participants answered on average 143 prompts out of the 157 possible prompts within the stipulated 5-min time

window over the 4-day period (three times across gestation).The different PSS measures were significantly correlated (for bivariate correlations, see Supplement Table S2 and S3). PSS-EMA increased slightly across gestation, whereas the PSS-4-weeks and PSS-4-days measures were not associated with GA (detailed results displayed in the Supplement, Table S4).

3.2 Decomposition of variance of momentary cortisol and momentary perceived stress

3.2.1 Salivary cortisol.—The variance decomposition indicates how much of the total variation in cortisol is derived from different data levels (i.e., variation between individuals, within an individual, across the stages of pregnancy, across a day, and across moments; de Haan-Rietdijk et al., 2016; Schmiedek et al., 2013). Based on the LMM, cortisol varied primarily at the momentary level (79.6%), and there was a relatively small degree of variance between individuals (7.0%) and across the stages of pregnancy (12.9%; for detailed results, see Supplement, Table S5).

3.2.2 PSS-EMA.—The decomposition of variance of PSS-EMA based on the LMM suggested that momentary stress varied considerably from moment-to-moment (39.5%) and between individuals (44.5%). The variations due to stage of pregnancy and day-to-day changes accounted for only small proportions of variance (stage-of-pregnancy: 10.8%; day-to-day: 8.1%; Supplement, Table S6).

Taken together, these findings suggest that psychoendocrine covariance is more likely to be observed within an individual, rather than across individuals, and that this covariation potentially occurs at the momentary level.

3.3 Momentary-level associations between PSS-EMA and cortisol

At the within-person level, momentary stress was positively associated with momentary cortisol, indicating that in moments when a participant reported higher momentary stress (PSS-EMA.cwc) relative to her average stress level (PSS-EMA.pm), her momentary cortisol was higher than in those moments when she reported momentary stress that was lower than her average stress level (log-transformed cortisol, $B = 0.030$, $p = .031$, Table 2). At the between-person level, the average stress level across participants based on momentary EMA assessment (PSS-EMA.pm) was not associated with momentary cortisol ($B = 0.023$, $p = .583$). In addition, significant effects on cortisol were evident for GA (increase in cortisol across the course of pregnancy ($B = 0.116$, $p<.001$), the diurnal course of cortisol (t1-t5, Table 2), weekend/weekday ($B = -0.058$, $p = <.001$), and preceding meal intake ($B = 0.104$, $p = <.001$). Momentary cortisol increased as pregnancy progressed, was higher after a meal, and was lower on weekends compared to weekdays. Pre-pregnancy BMI was negatively associated with cortisol ($B = -0.008$, $p = .022$).

3.4 Day-level associations between PSS-EMA and cortisol

At the within-person day level, cortisol output (log-transformed AUC.g of cortisol) was greater on days when the subject reported higher EMA-based day-level stress (PSS-EMA.day.cwc) than her average stress level (PSS-EMA.pm) ($B = 0.038$, $p = .035$; Table 3). At the between-person level there was no significant association between average stress level

(PSS-EMA.pm) and overall cortisol output. Similar to the momentary level, GA ($B = 0.104$, $p < .001$), weekend/weekday ($B = -0.088$, $p = <.001$), and pre-pregnancy BMI (B = −0.009, $p = .018$, Table 3) were significantly associated with day-level cortisol output.

3.5 Stage-of-pregnancy (early-, mid and late-pregnancy averages) associations between PSS and cortisol

As shown in Table 4 Model A, there was no association between average EMA-stress and the average cortisol output across the corresponding 4-day EMA-period (AUC.g.4days) at either the between-person (PSS-EMA.4days.pm) or the within-person level (PSS-EMA.4days.cwc). With regard to retrospective recall questionnaires, neither of the PSS measures (based on the recall over the last four days or the traditional PSS recalling the past four weeks) were associated with cortisol output across four days at either the within-person level (PSS.4weeks.cwc, PSS.4days.cwc) or the between-person level (PSS.4weeks.pm, PSS.4days.pm, Table 4, Model B and C). At the stage-of-pregnancy level, the effects of GA and pre-pregnancy BMI were similar in direction, magnitude, and significance level to the day level and momentary level results. In summary, the results of these analyses do not provide evidence for psychoendocrine covariance at the stage-of-pregnancy level when stress was assessed retrospectively, and when momentary stress was aggregated across multiple days.

4 Discussion and Conclusions

Our study addressed the issue of the association across pregnancy between maternal psychological (stress) and endocrine (cortisol) states using EMA-based and traditional retrospective recall-based questionnaires. To the best of our knowledge, this is the first study to examine the question of whether this psychoendocrine covariance is evident at the between- or within-person level during pregnancy. To summarize, our key findings suggested, firstly, that variation in stress as well as in cortisol occurred primarily within individuals from moment to moment; and secondly, that after accounting for the effects of key covariates maternal stress was significantly and independently associated with cortisol, and this association was evident only within (but not across) individuals, and only when stress and cortisol were assessed concurrently and analyzed at the momentary or at the day level. This association was not evident using measures aggregated across individuals or psychological measures based on retrospective recall approaches.

Although the overall (average) level of perceived stress in our study population was relatively low (which is consistent with expectations for a normative, low risk population), there was considerable variation within individuals across time, and also across individuals. Thus, these findings support the importance of accounting for subjectivity across individuals in psychological stress appraisals, temporal alignment in the assessment of psychological and physiological states, and the reliance on momentary (EMA) as opposed to retrospective recall measures to assess psychological stress appraisals. With respect to the nature and magnitude of the maternal stress and cortisol relationship, our findings suggest that after accounting for the effect on cortisol of time of day, prior meal intake, GA, weekday/weekend, and pre-pregnancy BMI, each 1 SD difference in an individual's stress at a given

moment from her own average stress level was associated with a 3% difference in her cortisol concentration. And at the day level, a difference of 1 SD stress relative to the average stress level was associated with an approximately 4% difference in cortisol output (AUC.g) over the course of the day. To place the magnitude of this effect in context, we suggest it may be important to appreciate that the major determinants of variation in cortisol production are time of day (cortisol production was approximately double in the mornings compared to evenings), meal intake (10% higher cortisol following a meal), and stage of pregnancy (11% higher cortisol with each 1 SD advance in gestation). Against the backdrop of these major drivers of cortisol production (i.e., over and above these influences), we suggest that an effect of 3% change in cortisol of each SD unit relative (within subject) change in psychological stress is meaningful in magnitude.

Our study has several notable strengths. First, as previously mentioned, this investigation represents the first study to examine the within-person and between-person association of psychological stress and stress physiology (cortisol) during pregnancy at different time scales. Second, in the context of EMA-based studies, the size of our study population is considerable, and subject compliance with the data collection protocol was very high compared to that reported in other studies (Jones et al., 2019; Wen et al., 2017). Previous studies in this context have used smaller sample sizes and were based on fewer assessment days and fewer assessment windows during gestation (Giesbrecht et al., 2012). Third, we employed a state-of-the-art approach to model cortisol over the course of each day using non-linear spline functions to capture different aspects of cortisol's diurnal variation. Moreover, we validated the exact time of awakening using EKG and actigraphy data, thereby ensuring greater reliability in the assessment of the awakening and post-awakening cortisol measures. By using a continuous autoregressive covariance structure, our models also accounted for the unequal spacing of time between cortisol measurements - a limitation that has often been noted in previous studies.

There are some limitations of our study. Because our study participants represented a normative, low risk population of pregnant women in terms of sociodemographic or obstetric risk, the range of variation in stress appraisals was relatively constricted, thereby potentially limiting the generalizability of our findings to other high risk populations (Lasikiewicz et al., 2008; Simpson et al., 2008). We note, however, that for this very reason the magnitude of our observed effects is likely to be a conservative estimate of that which would be expected in more heterogeneous high-risk populations. Second, the psychological stress measures in our study captured only the stress appraisal component, but not other components such as exposure and responses to discrete stressful events (Linz et al., 2018; Smyth et al., 2018) .

As discussed previously, many prior studies of stress and stress physiology make the implicit assumption that the effect of stress on physiology is uniform across individuals. Based, however, on our findings, it appears that the magnitude of the within-person coupling (assessed necessarily at the momentary level) between stress and cortisol may represent a better psychobiological indicator of the pathway from psychological stress to disease risk. We suggest this observation may have important implications for the development and subsequent evaluation of risk identification and intervention strategies. Here, we discuss

these implications in the specific context of our interest in the process of fetal/developmental programming of health and disease risk. Briefly, the fetal/developmental programming paradigm refers to the process wherein conditions during critical developmental periods exert a major influence on structural and functional characteristics of cells, tissues and organ systems, with important implications for the individual's subsequent state of health and susceptibility for a range of common disorders. In this context, maternal exposure to stress has been identified as an important condition of interest, and cortisol has been identified as a key mediator of the programming effects of stress. Higher cortisol concentrations during pregnancy are linked to increased risk for adverse pregnancy and birth outcomes such as spontaneous abortion and preterm birth (Buss et al., 2009; Nepomnaschy et al., 2006), thereby constituting a risk factor for such outcomes. Under physiological conditions, the fetus is protected from higher concentrations of cortisol by 11β-HSD, a placental enzyme transforming cortisol in to its inactive form cortisone (Siebe et al., 1993; Wadhwa et al., 1996; Wadhwa et al., 2011; Wadhwa et al., 2004; Wadhwa et al., 1998; Welberg et al., 2000). However, higher concentrations of maternal cortisol reduce the activity of the enzyme (reviewed in: Chapman et al., 2013; Clarke et al., 2002; Kerzner, 2002) potentially exposing the fetus to higher concentrations of cortisol. In the fetal compartment, cortisol binds to glucocorticoid responsive elements (GREs) in DNA to induce or repress gene expression (Binder, 2009; Reddy et al., 2012), potentially resulting in long lasting changes in the biological characteristics of fetal tissues and organ systems, with important implications for long-term developmental and health outcomes over the life span of the individual (Entringer et al., 2012, 2015; Entringer et al., 2018; Entringer et al., 2011; Segar et al., 1995). Based on the consideration that the effects of stress on various maternal and child health outcomes of interest are expected to vary as a function of individual differences in the responsivity of stress-responsive physiological systems (cortisol), we and others have highlighted the need for the development of measures to better identify vulnerable/susceptible individuals and to develop and test the efficacy of targeted, personalized intervention strategies. Based on our findings, we suggest, firstly, that subject-specific indicators of the strength of the association between stress and cortisol could be computed and used as an individual difference measure in predicting the index individual's risk of developing stress-related disorders. This concept is akin to that which relies on the use of markers of individual differences in stress reactivity that typically are obtained by characterizing individual differences in evoked physiological changes after experimental (in-laboratory) induction of stress, but with the advantage of inferring this analogous measure in the context of the individual's day-to-day natural (ecologically-relevant) setting. And secondly, we suggest that this approach could be used to develop and test the efficacy of individualized (personalized) "just-in-time" interventions, i.e., those that are tailored to the identification and delivery in real time and natural environment of any given index individual's need based on their stress appraisal and/or psychophysiological coupling (e.g.: Nahum-Shani et al., 2018; Spruijt-Metz and Nilsen, 2014).

In conclusion, our study highlights the value of the ecological momentary assessment and multilevel modeling approach in addressing prior limitations and establishing the nature and magnitude of the linkage between maternal psychological (stress) and physiological (cortisol) states across human pregnancy. These findings may, in turn, have important

implications for the development and subsequent evaluation of personalized risk identification and “just-in-time” intervention strategies to optimize maternal and child health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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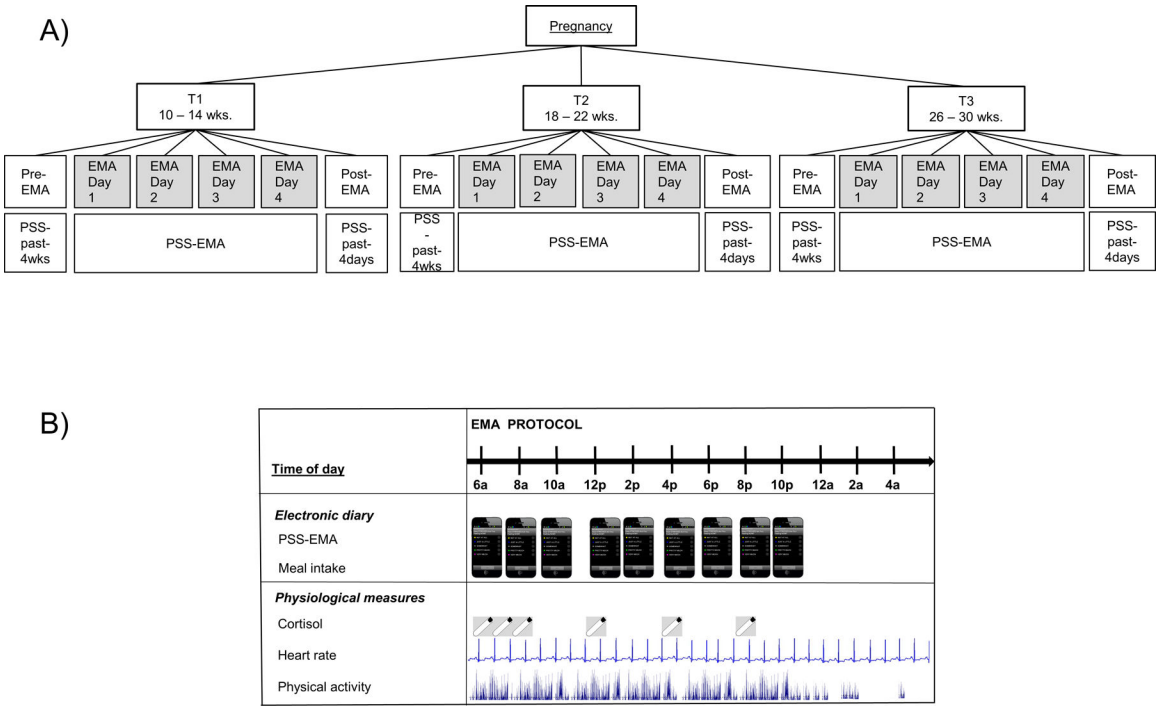

Figure 1.

Study design; **A)** Ecological-Momentary-Assessment (EMA) sampling scheme across pregnancy: The pre-EMA visit included assessment of stress during the past 4 weeks (PSS-past-4-weeks), followed by the 4-day EMA-period assessing momentary stress via PSS-EMA, and followed by a post-EMA visit assessing stress over the past 4 days (PSS-past-4-days); **B)** Ecological-Momentary-Assessment (EMA) protocol within a 4-day EMA-period.

Table 1.

Maternal sociodemographic and obstetric characteristics.

Maternal characteristics	***N* = 152**
Gestational age (GA) at assessment (weeks gestation, *M ± SD*)	
T0 – early gestation	12.3 ± 1.7
T1 – mid gestation	19.3 ± 1.3
T2 – late gestation	28.7 ± 1.3
Maternal age (years, *M ± SD*)	27.8 ± 5.5
Education (*n*, %)	
Some high school or less	31 (21.7%)
Technical or vocational school or certificate	16 (11.2%)
Some college or associate degree	54 (37.8%)
Bachelor's degree or higher	42 (29.4%)
Income (USD, *n*, %)	
<15k	14 (10.4%)
15–50k	54 (40.3%)
50–100k	49 (36.6%)
>100k	17 (12.7%)
Race/ethnicity (*n*, %)	
Non-Hispanic white	54 (38.8%)
Hispanic	53 (38.1%)
Others	32 (23.1%)
Pre-pregnancy BMI (*M ± SD*)	27.2 ± 6.4
Normal weight (< 25)	70 (47.3%)
Overweight (25 – 30)	40 (27.0%)
Obese (> 35)	38 (25.7%)
Obstetric characteristics	
Obstetric risk factors (*n*, %)	16 (6.7%)
Severe infection	4 (2.7%)
Preeclampsia	3 (2.0%)
Diabetes	9 (2.0%)
Parity (*n*, %)	
0	57 (40.1%)
1	38 (26.8%)
2	31 (21.8%)
>2	16 (11.3%)

Note. Due to rounding, some totals may not correspond with the sum of the separate figures.

Table 2.

Momentary-level associations between PSS-EMA (Perceived Stress Scale – Ecological-Momentary-Assessment) and cortisol: Results from linear mixed models predicting momentary log-transformed cortisol by PSS-EMA (within-/between-person effect), adjusted for time of day, meal intake, gestational age (GA), weekend/-day, pre-pregnancy body-mass-index (BMI).

Fixed effects				
	***B* (*SE*)**	**beta**	**95% CI for *B***	***p***
Intercept	−2.290 (0.164)		−2.613 – −1.968	<.001***
Level 1				
PSS-EMA.cwc	0.030 (0.014)	.021	0.003 – 0.058	.031*
t1	1.625 (0.159)	.496	1.312 – 1.938	<.001***
t2	0.801 (0.108)	.226	0.588 – 1.013	<.001***
t3	0.367 (0.124)	.135	0.124 – 0.610	.003**
t4	−0.143 (0.119)	−.042	−0.376 – 0.090	.230
t5	−0.846 (0.131)	−.187	−1.103 – −0.589	<.001***
Meal intake	0.104 (0.019)	.052	0.067 – 0.141	<.001***
GA	0.116 (0.007)	.250	0.102 – 0.129	<.001***
Level 2				
Weekend	−0.058 (0.016)	−.037	−0.091 – −0.026	<.001***
Level 3				
Level 4				
PSS-EMA.pm	0.023 (0.046)	.017	−0.066 – 0.117	.583
Pre-pregnancy BMI	−0.008 (0.003)	−.007	−0.014 – −0.001	.022*

Random effects		
	Variance	***SD***
ID	0.067	0.258
Stage of pregnancy	0.027	0.164
Day	0.015	0.123
Residual	0.185	0.430

Note. Significance codes:

$p > .01$ ‘ ‘

$p < .10$ ‘.’

$p < .05$ ‘*’

$p < 0.01$ ‘**’

$p < .001$ ‘***’.

Results displayed for log-transformed cortisol. Transformation did not change magnitude, direction nor significance level of the reported effects. For fit indices, see Supplement Table S7.

Table 3.

Day-level associations between PSS-EMA (Perceived Stress Scale – Ecological-Momentary-Assessment) and cortisol: Results from linear mixed model predicting log-transformed AUC.g (area under curve) of cortisol by PSS-EMA aggregated across a day (within-/between-person effect) adjusted for gestational age (GA), weekend/weekday, pre-pregnancy body-mass-index (BMI).

Fixed effects				
	***B* (*SE*)**	**beta**	**95% CI for *B***	***p***
Intercept	0.841 (0.116)		0.619 – 1.070	<.001***
Level 1				
PSS-EMA.day.cwc	0.038 (0.016)	. 037	0.006 – 0.069	.035*
GA	0.104 (0.005)	.431	0.093 – 0.114	<.001***
Level 2				
Weekend	−0.088 (0.012)	−.107	−0.111 – −0.065	<.001***
Level 3				
Level 4				
PSS-EMA.pm	0.019 (0.043)	.024	−0.066 – 0.104	.320
Pre-pregnancy BMI	−0.009 (0.004)	−.132	−0.016 – −0.001	.018*

Random effects		
	Variance	***SD***
ID	0.065	0.256
Stage of pregnancy	0.020	0.143
Day	0.046	0.215
Residual	0.009	0.094

Note. Significance codes:

$p > .01$ ‘ ‘

$p < .10$ ‘.’

$p < .05$ ‘*’

$p < 0.01$ ‘**’

$p < .001$ ‘***’.

Results displayed for log-transformed AUC.g. Transformation did not change magnitude, direction nor significance level of the reported effects. Default covariance structure corresponding to no within-group correlations was chosen based on non-significant likelihood ratio test comparing different covariance structures. For fit indices, see Supplement Table S7.

Table 4.

Stage-of-pregnancy associations between PSS (Perceived Stress Scale) and cortisol: Results from linear mixed models predicting log-transformed AUC.g (area under the curve) averaged across four days by averaged PSS-EMA (Model A), PSS-past-4-days (Model B), and PSS-past-4-weeks (Model C) adjusted for gestation age (GA) and pre-pregnancy body-mass-index (BMI).

MODEL A				
Fixed effects				
	B (*SE*)	**beta**	**95% CI for B**	***p***
Intercept	0.834 (0.120)		0.598 –1.071	<.001***
Level 1				
PSS-EMA-4-day.cwc	0.040 (0.041)	.026	−0.041 – 0.122	.330
GA	0.102 (0.006)	.459	0.090 – 0.114	<.001***
Level 2				
Level 3				
PSS-EMA.pm	0.014 (0.044)	.019	−0.073 – 0.101	.758
Pre-pregnancy BMI	−0.009 (0.004)	−.144	−0.016 – −0.001	.021*
Random effects				
	Variance		***SD***	
ID	0.067		0.259	
Stage of pregnancy	0.035		0.187	
Residual	0.007		0.088	
MODEL B				
Fixed effects				
	B (*SE*)	**beta**	**95% CI for B**	***p***
Intercept	0.887 (0.122)		0.647 – 1.127	<.001***
Level 1				
PSS-past-4-days.cwc	0.032 (0.032)	.028	−0.031 – 0.095	.316
GA	0.104 (0.006)	.469	0.091 – 0.117	<.001***
Level 2				
Level 3				
PSS-past-4-days.pm	−0.034 (0.044)	−.049	−0.122 – 0.053	.439
Pre-pregnancy BMI	−0.009 (0.004)	−.148	−0.016 – −0.002	.018*
Random effects				
	Variance		***SD***	
ID	0.066		0.257	
Stage of pregnancy	0.037		0.191	
Residual	0.008		0.089	
MODEL C				
Fixed effects				
	B (*SE*)	**beta**	**95% CI for B**	***p***

MODEL A

Fixed effects

	B (*SE*)	beta	95% CI for B	*p*
Intercept	0.943 (0.127)		0.694 – 1.192	<.001***
Level 1				
PSS-past-4-weeks.cwc	0.013 (0.034)	.011	−0.053 – 0.080	.693
GA	0.103 (0.006)	.465	0.091 – 0.115	<.001***
Level 2				
Level 3				
PSS-past-4-weeks.pm	−0.060 (0.045)	−.083	−0.149 – 0.028	.180
Pre-pregnancy BMI	−0.009 (0.004)	−.149	−0.016 – −0.002	.016*

Random effects

	Variance	*SD*
ID	0.066	0.256
Stage of pregnancy	0.036	0.190
Residual	0.007	0.088

Note. Significance codes:

$p > .01$ ‘ ‘

$p < .10$ ‘.’

$p < .05$ ‘*’

$p < 0.01$ ‘**’

$p < .001$ ‘***’.

Results displayed for log-transformed AUC.g averaged across four days. Transformation did not change magnitude, direction nor significance level of the reported effects. Default covariance structure was chosen based on non-significant likelihood ratio test comparing different covariance structures. For fit indices, see Supplement Table S7.