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TITLE

Limited association between markers of stress during pregnancy and fetal growth in "Born into Life", a new prospective birth cohort

RUNNING TITLE

Maternal stress and fetal growth

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FINANCE

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ABSTRACT

Aims*:* We aimed to investigate the associations between perceived maternal stress or salivary cortisol levels during pregnancy and birth weight.

Methods*:* In 2010–2012 we recruited 92 women living in Stockholm, Sweden, and followed them from before conception and through pregnancy and childbirth. Their Perceived Stress Scale (PSS) scores and salivary cortisol levels were collected at 26-28 gestational weeks. Birth weight was collected from medical records. Linear regression analyses and Pearson correlations were performed between the PSS scores or cortisol levels and birth weight respectively, adjusted for gestational age.

Results*:* No significant associations were found between PSS scores or cortisol levels and birth weight. There was a trend towards higher salivary cortisol levels among infants with lower birth weights and this effect was attenuated after adjusting for gestational age. Morning cortisol levels (r=-0.31, p=0.01), the decline in cortisol levels (r=-0.26, p=0.03) and evening cortisol levels (r=-0.21, p=0.09) were negatively correlated with PSS scores.

Conclusion*:* Maternal stress during pregnancy was not associated to birth weight. The inverse correlation between PSS scores and cortisol levels may indicate other mechanisms for maternal stress on child outcomes than the previous explanation of hypothalamic-pituitary-adrenal axis activity.

Keywords*:* Birth weight, cortisol, fetal development, stress, pregnancy

KEY NOTES

- We studied the relationship between maternal salivary cortisol levels, Perceived Stress Scale scores and child birth weight in a birth cohort that comprised 92 mother-infant dyads in Stockholm, Sweden.
- Maternal stress during pregnancy was not associated to birth weight, but the two measurements of stress were negatively inter-correlated.
- These findings indicate that increased hypothalamic-pituitary-adrenal activity may not be the mechanism behind the effects of stress during pregnancy on offspring.

INTRODUCTION

There is growing evidence for the model of fetal programming, which indicates that the in utero environment influences the development of the fetus, and pathophysiology in the child (1). Research shows that maternal stress during pregnancy predisposes the infant to both premature birth and a low birth weight (2–5). Evidence suggests that the impact of maternal stress on birth weight depends on the type of stressor and that perceived stress has been reported to have less of an impact than objectively assessed major life events or chronic stress. In particular, pregnancy-specific anxiety has been identified as a risk factor for preterm delivery (5). In pregnant women, measures of self-reported stress, such as the established Perceived Stress Scale (PSS), have not been related to lower child birth weight (6,7).

The major proposed mechanism linking maternal stress during pregnancy to child outcomes is steroid hormones secreted by the hypothalamic-pituitary-adrenal (HPA) axis (8). During pregnancy, the maternal HPA axis undergoes significant changes, with progressive increases in plasma concentrations of corticotropin-releasing hormones, adrenocorticotropic hormones and cortisol (9). Even though the majority of studies suggest that cortisol is a mediator in the relationship between maternal stress during pregnancy and child outcomes (3,8,10,11), the effect of self-reported stress on maternal cortisol levels during pregnancy is still unclear (12). Most studies have only found weak, or non-significant associations between self-reported stress during pregnancy, defined using various standardised measurements, and maternal cortisol levels (13). Specifically, studies have also failed to find significant associations between self-reported perceived stress measured using the PSS (7,12) or other psychological self-reported measurements of stress (14,15) and maternal salivary cortisol levels during pregnancy.

Despite the lack of evidence for the mediating role of cortisol in the relationship between maternal stress during pregnancy and child outcomes, it is becoming increasingly clear that cortisol plays an important role in fetal development. In a systematic review, Zijlmans *et al* showed that multiple studies had examined the connections between maternal cortisol levels during pregnancy, using various methods to measure maternal cortisol in plasma, saliva or urine, and the physical, cognitive, psychological and cortisol outcomes in the child (16). With respect to birth weight, negative

associations have been reported between maternal cortisol levels and child birth weight (17), suggesting that even though cortisol is important for fetal growth, overly augmented levels during pregnancy may be harmful to fetal development. However, only a few studies have used salivary cortisol as a measurement of cortisol physiology (7,12,18).

In this study we aimed to investigate the associations between maternal stress during pregnancy and fetal growth in the Swedish Born into Life birth cohort study, using data collected before, during and after pregnancy. Our aims were three-fold: to investigate the effect of perceived maternal stress on child birth weight, the relationship between perceived maternal stress and salivary cortisol levels and the link between maternal salivary cortisol levels and birth weight.

METHODS

Study design

This study was part of the prospective longitudinal birth cohort study Born into Life, which was originally created from the larger LifeGene study (19). It followed a cohort of women before, during and after pregnancy and followed their children in the perinatal and postnatal period (Figure 1). Between the years 2010 and 2012, women who already were participating in the LifeGene study and living in the Stockholm County Council area were recruited to Born into Life. The goal of combining prenatal, pregnancy and postnatal data was to address questions concerning fetal growth and health outcomes during childhood in relation to early exposure to maternal lifestyle and environment.

Pregnant women who agreed to take part in the Born into Life study answered questionnaires regarding pregnancy, lifestyle and health at 10-14 and 26-28 gestational weeks. During pregnancy, they also provided biological material including blood at 10-14 gestational weeks, blood, saliva and faeces at 26-28 gestational weeks and blood upon admission to antenatal care. Cord blood and placenta samples were obtained from delivery. Blood and faeces were collected in conjunction with the newborn screening test of their child 2-4 days after delivery and faeces samples at six months after delivery. The birth records regarding both mother and child at delivery were collected from Danderyd Hospital, Stockholm. Children were followed at six, 12 and 24 months of age with self-reported parental questionnaires and biological material, including blood, saliva and faeces from the child.

The inclusion criteria for the mothers in Born into Life were that they had responded to baseline questionnaires from the wider LifeGene study, were pregnant, and gave informed consent. They were recruited both before and after 10-14 gestational weeks, but no later than 26-28 weeks. For children, the existing inclusion of their mothers in the maternal cohort and informed consent from both parents were the only inclusion criteria.

Ethical approval was granted by the Regional Ethics Review Board in Stockholm, Sweden. Informed consent from both parents was obtained for all study participants.

Study participants

Originally 107 pregnant women were included in Born into Life. The women were asked to complete questionnaires and provide saliva samples during 26-28 gestational weeks of pregnancy and their child's birth weight at delivery was recorded. We only included the 92 women who completed the questionnaires and saliva tests in this study.

Measures

Data regarding smoking during pregnancy were obtained from the Born into Life questionnaires administered at 26-28 gestational weeks. Data regarding pre-pregnancy body mass index (BMI), in kg/m^2, and highest attained educational level, ranging from mandatory secondary school to high school, university or other, were retrieved from the baseline LifeGene questionnaires. Maternal age at delivery, in years, was calculated from mothers' date of birth.

In order to measure maternal psychosocial stress, a 10-item version of the PSS (PSS-10) was administered in the questionnaires to the mothers at 26-28 gestational weeks. These questions assessed the frequency of situations being perceived as subjectively uncontrollable or stressful on a five-point Likert scale ranging from never to often. We reversed the scores of the positive questions and added together the scores for all ten questions to provide a total score that ranged from 0 to 40, with higher scores indicating a higher degree of perceived stress (20).

In order to determine cortisol concentrations, as a measurement of maternal stress, saliva samples were collected from pregnant women during 26-28 gestational weeks. Women were

instructed to produce one saliva sample the evening before their visit to the test centre and one sample from the same morning as their visit. Participants were asked to chew a swab for one minute to saturate it with saliva and then to store it in a plastic tube, marked with the date and time, at standard refrigerator temperature. Once the samples had been handed in they were centrifuged for two minutes, transported at standard refrigerator temperature and then stored at –20°C. The cortisol levels in the saliva samples from both the mother and the child were analysed at the Centre for Child Research, Stockholm South General Hospital, Stockholm, Sweden, using the standardised CORT-CT2 radioimmunoassay kit (Cisbio Bioassays, Codolet, France) according to the manufacturer's instructions. The detection interval ranged from concentrations of 1 to 100 nmol/L. Inter-assay and intra-assay variations were below 5%. All samples were duplicated and averaged.

The infants' birth weights in grams were recorded by the midwives on delivery and later collected from the mothers' and children's joint medical birth records, together with their head circumference and their body length, both in centimetres. Data regarding the infants' sex, gestational age in weeks and mode of delivery, defined as vaginal delivery or Caesarean section, were also collected from the records.

Data analysis

The data on all 92 women and children were initially analysed for extreme values and outliers by calculating residuals and Cook's distance. The characteristics of our two study samples were described using frequencies, means, medians and standard deviations for continuous values and numbers of observations and percentages for categorical values. Both the exposure and outcome variables were analysed for normality of distribution. Outliers were excluded, including one child with a very low birth weight of less than 1,500 g and the two highest evening cortisol values (117.1 and 117.6 nmol/L). These were not included in any of the descriptive or inferential statistical analyses. Due to skewed distribution, the values of the morning and evening cortisol levels and the cortisol decline were logarithmically transformed using natural logarithms with base e. Cortisol decline was calculated by subtracting the evening values from the morning values (12). All subsequent analyses using cortisol values were performed with logarithmic values, and, for better interpretation, the results

were transformed back into the original units by exponentiation. The mean values of the morning and evening cortisol levels were compared using a paired t-test.

The associations between maternal stress, measured as both PSS scores and separate cortisol levels - for morning, evening and decline - and child birth weight were examined using linear regression analysis, adjusting for gestational age. A Pearson product-moment correlation was applied to determine the associations between measurements of maternal stress. Results with a p value of <0.05 were considered statistically significant. All data analysis was conducted using STATA/IC 14.0 for Windows (StataCorp LLC, Texas, USA).

RESULTS

Study sample characteristics

The participants' mean age was 32.5 (±3.7) years. The sample represented a highly-educated population with most women (88.5%) having received a university-level education. The mean pre-pregnancy BMI was 19.8 (±2), 28 women were classified as underweight and one woman was overweight. During pregnancy, four women reported that they had smoked one or more times. The total PSS scores ranged from 12-38, with higher values indicating more perceived stress. The mean value was 25.4 (±5.9) and the median value was 26 (Table 1). In total, 87 saliva samples from the morning and 85 saliva samples from the evening were analysed for cortisol levels. The two highest evening cortisol values (117.1 and 117.6 nmol/L) were identified as outliers. These were not included in any of the descriptive or inferential statistical analyses. The mean cortisol levels for our sample (Table 1) were 41.3 nmol/L (±13) in the morning, 10.4 nmol/L (±3.4) in the evening and 30.2 nmol/L (±12.2) for the decline from morning to evening. There was a statistically significant mean difference between morning and evening values.

The majority of children (82%) were delivered by normal vaginal delivery and all children were born alive. The mean gestational age was 40 weeks (±1.4) with four preterm and three post-term deliveries. All children were born with a normal birth weight (2,500-4,500g), apart from one child who had a high birth weight above 4,500 g. The mean birth weight was 3,547g (±432.9) (Table 2).

Maternal stress during pregnancy does not predict child birth weight

The results of the linear regression analyses (Table 3) showed that the maternal total PSS scores (β=-5.9, 95% CI -23.4–11.5) and the salivary cortisol levels (morning β=-22.0, 95% CI -50.6–6.6; evening β=-24.4, 95% CI -50.2–1.5; decline β=-15.6, 95% CI -41.1–9.9) were not significantly associated to child birth weight. The direction of the association between cortisol levels and birth weight indicated a trend where higher salivary cortisol levels yielded a lower child birth weight. This effect was, however, attenuated after adjustment for gestational age.

Negative relationship between psychosocial stress and cortisol levels

There was a statistically significant negative association between total PSS scores and morning cortisol levels (r=-0.31, p=0.01) and cortisol decline (r=-0.26, p=0.03), showing that women with higher PSS scores generally exhibited lower morning cortisol levels and a smaller cortisol decline (Figure 2). A similar tendency was observed for evening cortisol levels (r=-0.21, p=0.09).

DISCUSSION

In this new birth cohort using data before, during and after pregnancy, we found that total PSS scores, as a measurement of self-reported maternal stress during pregnancy, as well as maternal cortisol levels were unrelated to child birth weight. Morning salivary cortisol levels and cortisol decline, but not evening levels, were significantly negatively correlated to PSS scores.

Our findings of no significant associations between total PSS scores from 26-28 gestational weeks and child birth weight are in line with the findings of similar studies that have previously examined the specific relationship between PSS as a measurement of self-reported maternal stress and child birth weight (6,7). In contrast to this, a number of reviews have presented evidence for the existence of a link between self-reported maternal stress during pregnancy and child birth weight (2–5). The studies we have included used other measurements of maternal stress during pregnancy than PSS, such as maternal trait anxiety, general health questionnaires, major life events or chronic stress. There has been a lack of evidence for a specific association between total PSS scores and child birth weight, compared to significant reports of the effect of other measurements of self-reported stress on

fetal growth. Therefore, it is reasonable to assume that perceived stress is less of a predictor of adverse child outcomes, such as low birth weight, than other markers of distress (5).

The inverse relationship we found between total PSS scores and morning cortisol levels and cortisol decline is similar to the findings of Pluess *et al* who showed that high anxiety levels in early pregnancy, defined as 10-20 gestational weeks, predicted low cortisol levels, measured as a diminished cortisol awakening response (21). In parallel, Obel *et al* showed that women with high levels of pregnancy-specific stress, due to their fear of pregnancy complications, had lower morning cortisol levels in early pregnancy, at 14 gestational weeks, and higher levels in late pregnancy, at 30 gestational weeks. The authors argued that the response to stress may have been dependent on the stage of pregnancy (22). A theory that could explain this negative relationship between self-reported stress and cortisol levels is the suggested gradual dampening of HPA axis responsiveness throughout pregnancy. Mediated via physiologically high levels of corticotropin-releasing hormone and cortisol in pregnant women (23,24), receptors in the maternal HPA axis system are down-regulated towards later gestation, causing stress to be less effective in triggering an endocrine response (25). However, the current evidence supporting this theory is weak, the timing of the unresponsiveness of the HPA axis during pregnancy has not yet been established and the inter-individual variability of the phenomenon has not been examined (26). These conflicting results, presented in our study and previous research, emphasise the importance of not assuming that cortisol is the sole, or even main, mediator in the relationship between maternal stress during pregnancy and child outcomes and that there could be multiple alternative mechanisms behind this association (4,14,26,27).

We did not find that salivary cortisol levels were related to child birth weight. This was in contrast to the positive findings of most of the similar studies that found associations between cortisol levels and lower birth weight (7,12,16–18). However, we were limited when it came to comparing these studies to ours due to differences in the measurements of salivary cortisol levels, sampling methods, large inter-individual variability in biological material and the fact that not all studies reported raw values of cortisol levels. An observation from our results was that the strength of the trend of the negative association between cortisol levels and child birth weight diminished after adjusting for gestational age. Logically, this implies that gestational age was shorter for children

exposed to higher cortisol levels, thus leading to lower birth weight. This finding was in line with studies that showed an association between maternal stress hormone levels and preterm delivery and shorter gestational periods (28).

Strengths and limitations

A major strength of this new cohort study was its longitudinal design, which allowed us to collect maternal data before and during pregnancy and link it to data on the mothers and children from the delivery and perinatal periods. In addition, the measures of exposure used in this study had previously been validated and used in other studies. For example, salivary cortisol levels reflect the free, unbound and biologically active fraction of cortisol in the blood (29) and the diurnal rhythm of salivary cortisol has been determined throughout pregnancy (30). Other studies have demonstrated the validity of the PSS (20). Furthermore, the quality of data was high, originating from reliable sources such as medical birth records. The fact that the study participants had Swedish personal identification numbers facilitated the data collection and linkage of data between sources.

There were also limitations to this study. Firstly, the sample size was small, resulting in limited statistical power. This is highlighted by the wide confidence intervals of the β-coefficients in the regression analyses, covering both positive and negative associations. Furthermore, the sample represented a healthy, homogenous population of highly-educated women, which may have decreased the generalisability of our study. However, despite their overall health, the women in our sample exhibited higher levels of both PSS scores and salivary cortisol levels than previous studies (20,30), indicating that they were, in fact, more stressed than the general population, both subjectively, as measured by the PSS, and objectively, as measured by their cortisol levels. This increased our incentive to study the presented associations in this sample. Secondly, the collection of saliva samples relied on the mothers' adhering to the instructions they were given, including accurate self-reporting of when the samples were taken, and participants only provided one sample of saliva from the morning and evening respectively. Nevertheless, obtaining two saliva samples during the same 24-hour period from each mother allowed us to compare morning and evening cortisol levels, as well as the decline over the day, and to separately examine their associations with both the PSS scores and

birth weight. Thirdly, birth weight is an equivocal measurement for fetal growth, considering that a child can be born with low birth weight either because it is born too early or because it is small for its gestational age. However, in our study, the associations in the results were further weakened after adjusting for gestational age, implicating that children who weighed less at birth were simply born earlier and not small for gestational age.

Future studies

There are a number of possible recommendations for future studies. Research should focus on ascertaining the role of the HPA axis and gestational timing effects of cortisol levels in the link between maternal stress during pregnancy and fetal development, as well as trying to develop a better understanding of the other mechanisms that could explain this link. Concerning the measurement of stress, future studies should try to use multiple measurements of the circadian rhythm of cortisol, such as the cortisol awakening response or diurnal decline, measured at several time points throughout the entire pregnancy. Whereas salivary cortisol levels collected during basal conditions are good at measuring disturbances in the circadian pattern of cortisol secretion, it would be appropriate to add the method of measuring cortisol reactivity in response to stressful events to future studies. Regarding the measurement of fetal growth, future studies should, apart from birth weight, also use other measurements of fetal development, such as intrauterine growth retardation and small for gestational age.

Future studies carried out as part of the Born into Life study will be able to take advantage of the unique study design that enables researchers to study mothers and children born into a cohort, with both pre-pregnancy and prenatal maternal data. This will often be supplemented with paternal data and perinatal and postnatal data from the mothers and children. Our continued work in this cohort will aim to further investigate the associations between maternal risk factors and health determinants, and trajectories of fetal and child growth, as well as maternal immunity and metabolism, prior to conception, throughout pregnancy and in early infancy.

CONCLUSION

This study found that maternal stress during pregnancy was not associated with child birth weight, but that the different measures of stress, namely maternal perceived stress and cortisol levels, were negatively inter-correlated. This inverse correlation suggests that other mechanisms than the HPA axis activity may lie behind the effects of maternal stress on child outcomes.

LIST OF ABBREVATIONS

BMI body mass index

HPA hypothalamic-pituitary-adrenal

PSS Perceived Stress Scale

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Table 1. Descriptive statistics of the mothers in the study sample.

Characteristic (n=92)	n (%)	Mean (±SD), median, (min–max)
Demographics		
Age (*years*)	92	32.4 (±3.5), (23–42)
Highest attained level of education	86	
Mandatory secondary school	0	
High-school	7 (8%)	
University	76 (89%)	
Other	3 (4%)	
Pre-pregnancy weight (*kg*)	86	65.2 (±10.2), (48–100)
Pre-pregnancy height (*m*)	87	168.8 (±5.8), (153.5–184)
Pre-pregnancy BMI (kg/m^2)	86	19.7 (±2), (16.4–27.9)
Underweight (<18.5)	28 (29%)	
Normal	60 (70%)	
Overweight (>25)	1 (1%)	
Smoking during pregnancy	76	
Yes	4 (5%)	
No	72 (95%)	
Alcohol during pregnancy	76	
Yes	6 (8%)	
Only before awareness of being pregnant	36 (47%)	
No	34 (45%)	
Illicit drugs during pregnancy	76	
Yes	0	
No	76 (100%)	
Maternal stress		
Morning cortisol levels	87	41.3 (±13), (16.8–86.7)
Evening cortisol levels	83	10.4 (±3.4), (4–23.4)
Cortisol decline	83	30.2 (±12.2), (-3.2–72)
Total PSS scores	74	25.4 (±5.9), 26, (12–38)

Abbreviations: BMI, body mass index, n=number, SD, standard deviation.

Table 2. Descriptive statistics of the study sample of children.

Characteristic (n=91*)	n (%)	Mean (±SD), (Min–Max)
Mode of delivery		
Vaginal delivery	75 (82%)	
Caesarean section	16 (18%)	
Gestational age (*weeks*)		39.8 (±1.4), (35.6–42.4)
Preterm (<37)	4 (4.5%)	
Term	84 (92.5%)	
Post-term (>42)	3 (3%)	
Sex		
Male	55 (60%)	
Female	36 (40%)	
Birth weight (*g*)		3,547.1 (±419.6), (2,720–4,625)
Body length (*cm*)		50.6 (±1.9), (45–55)
Head circumference (*cm*)		34.9 (±1.4), (32–38.5)

* From the 92 mother-infant dyads, one child was identified as an outlier and therefore excluded from all analyses.

Abbreviations: n=number, SD, standard deviation.

Table 3. Maternal stress and child birth weight.

	Birth weight			
	Univariate		*Adjusted for gestational age*	
	β	95% CI	*β*	95% CI
Total PSS score	-5.9	-23.4–11.5	-10.8	-25.7–4.1
Morning cortisol *	-22.0	-50.6–6.6	-15.3	-40.0–9.5
Evening cortisol *	-24.4	-50.2–1.5	-17.5	-40.0–5.0
Cortisol decline *	-15.6	-41.1–9.9	-8.8	-31.4–13.8

Regression analyses between maternal salivary cortisol levels and PSS scores during gestational week 26–28 and child birth weight. The regression analyses were performed with and without adjustment for gestational age.

* In order to interpret the *β*-coefficient using log-transformed independent variables, the coefficient is displayed as *β* x 0.1 (= *β* x log (1.10)), ie the mean difference in expected birth weight associated with a 10% increase in (non log-transformed) cortisol levels. The confidence intervals correspond to this *β*.

Abbreviations: CI, confidence interval, PSS, Perceived Stress Scale

FIGURES

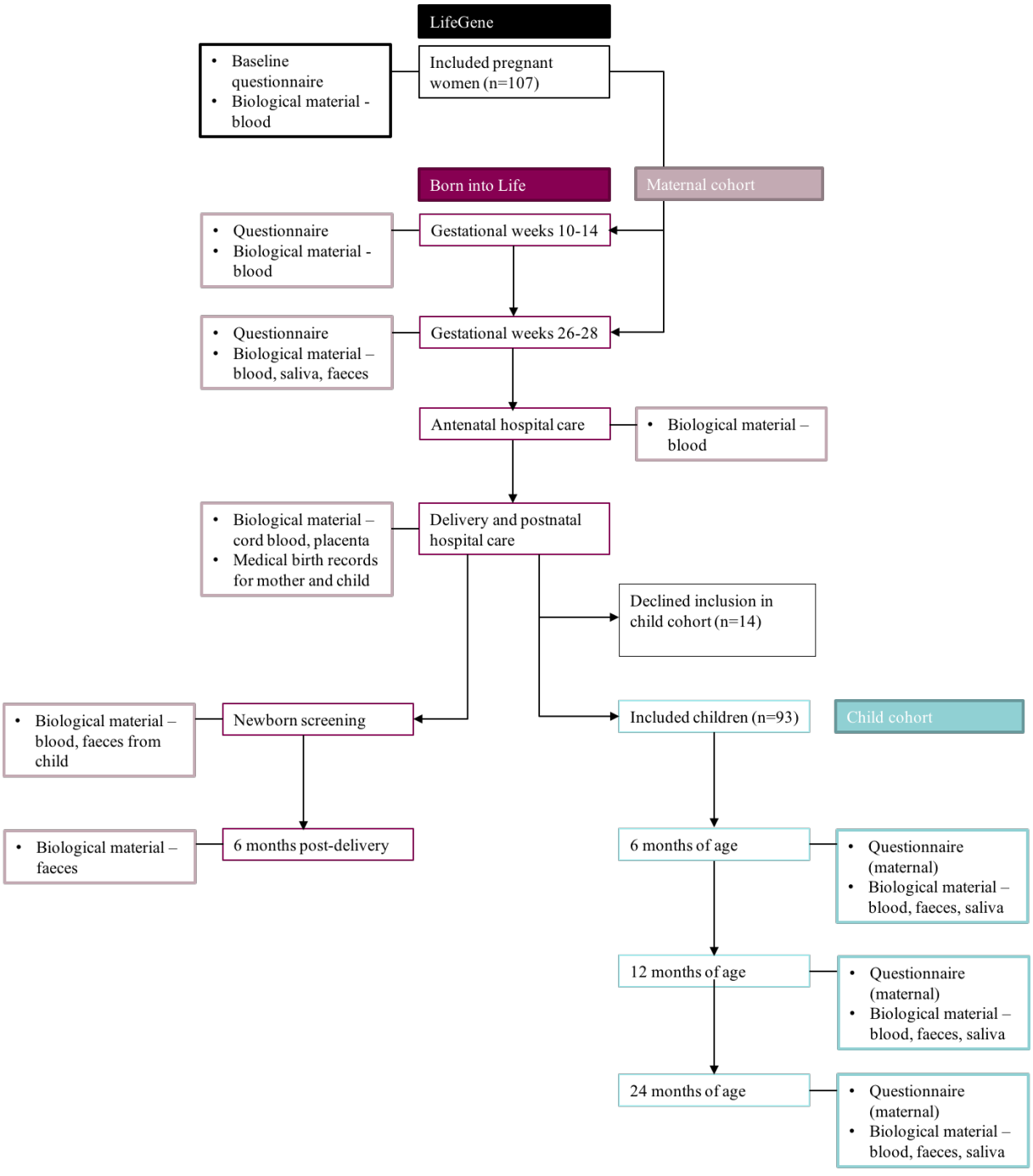

Figure 1. Flowchart of the Born into Life study.

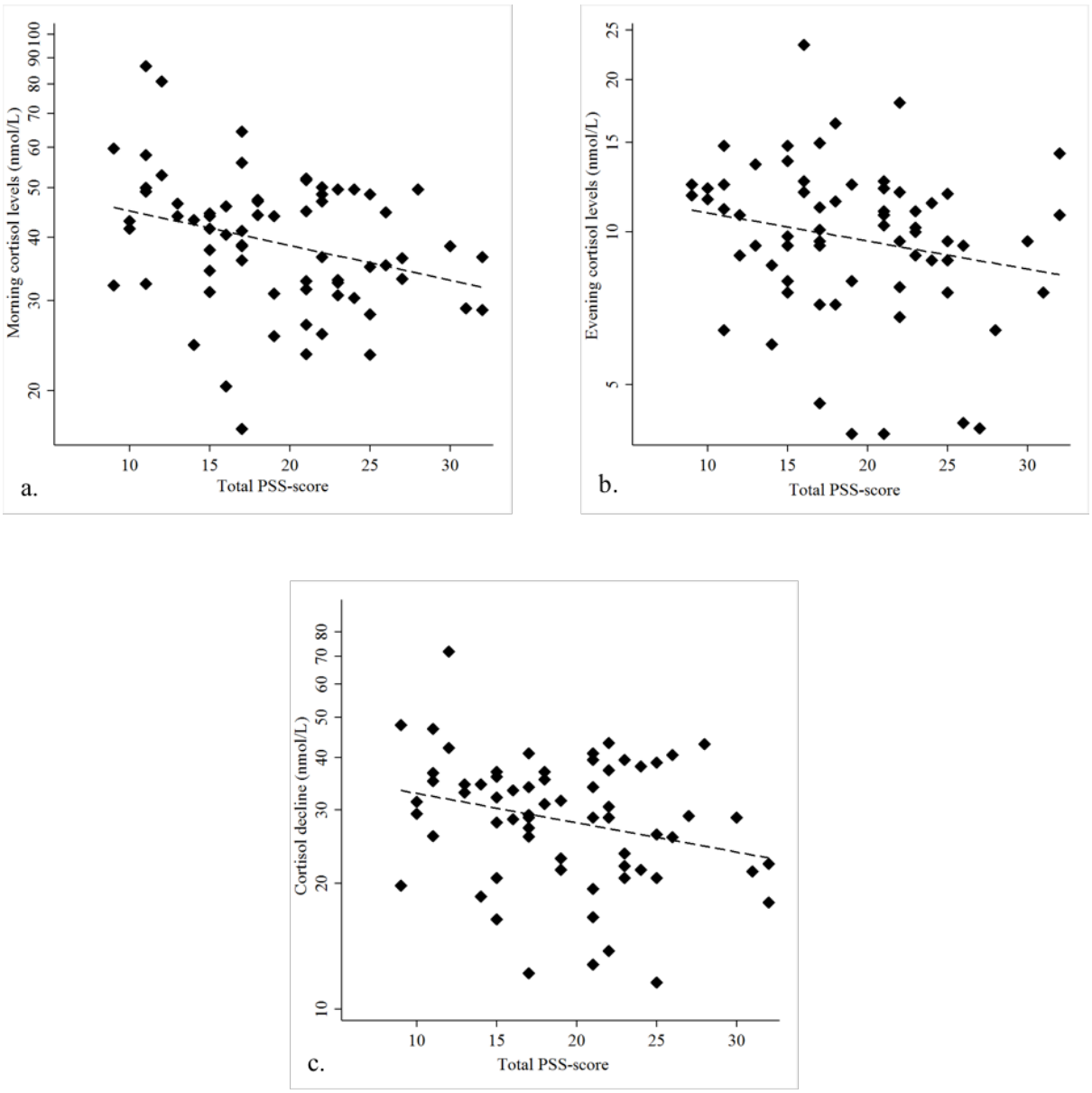

Figure 2. Self-reported maternal stress and salivary cortisol levels during pregnancy.
Scatterplots with regression lines showing the relationships between total PSS scores and morning (a) (p=0.01) and evening (b) salivary cortisol levels (p=0.09) and cortisol decline (c) (p=0.03). PSS scores, as a measurement of self-reported stress, and salivary cortisol levels were measured in pregnant women at 26-28 gestational weeks. The logarithmic scale of cortisol levels on the y-axis has been labelled in original units.

Abbreviations: PSS, Perceived Stress Scale.