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Maternal Depressive Symptoms, Perceived Stress, and Fetal Growth

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Objectives—To determine whether longitudinal fetal growth is altered among pregnant women reporting greater perceived stress or more symptoms of depression.

Methods—This analysis was based on a multicenter longitudinal study of fetal growth. Women were screened at gestational ages of 8 weeks to 13 weeks 6 days for low-risk status and underwent serial sonographic examinations. At each study visit during pregnancy, women were asked to complete the Cohen Perceived Stress Scale (PSS) and Edinburgh Postpartum Depression Survey (EPDS). Growth curves for estimated fetal weight and individual biometric parameters were created by using linear mixed models with cubic splines and compared on the basis of whether women scored 15 or higher on the PSS or 10 or higher on the EPDS either at the start of or at any time during pregnancy.

Results—Of the 2334 women enrolled in the study, 2088 (89%) and 2108 (90%) completed the PSS and EPDS, respectively, at least once in all trimesters. The longitudinal growth curves of estimated fetal weight as well as all individual biometric parameters were similar ($P > .05$) regardless of whether the participants reported PSS of 15 or higher or EPDS of 10 or higher in the first trimester or whether these scores persisted throughout the pregnancy. Similarly, effect modification by race/ethnicity was not statistically significant for the biometric parameters under study ($P > .05$ for all race/ethnicity interactions).

Conclusions—More depressive symptoms and greater perceived stress, as quantified by the EPDS and the PSS, respectively, are not associated with alterations in fetal growth throughout gestation.

Key Words—depression; fetal growth; obstetric ultrasound; psychosocial; stress

Fetal growth restriction, often defined as weight below the 10th percentile, has been associated with increased perinatal morbidity and mortality.[1] The pathologic etiologies for fetal growth restriction are manifold and include aneuploidy, anatomic anomalies, and infectious agents, although the most common cause is insufficient placental function.

In some cases, the cause of placental insufficiency can be traced to a preexisting maternal illness, such as hypertension, diabetes mellitus, or rheumatologic disease. In other cases, however, the underlying cause of placental dysfunction remains uncertain. One postulated etiology for placental dysfunction and altered fetal growth is excessive maternal stress.[2] For example, Borders et al[3] reported that multiple psychosocial factors, including food insecurity and poor coping skills, were significantly associated with low birth weight at delivery. Other

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Abbreviations
EPDS, Edinburgh Postpartum Depression Survey; PSS, Perceived Stress Scale

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investigators have found a relationship between maternal depression and poor fetal growth as well.[4,5]

However, several aspects of the relationship of fetal growth with maternal stress and depression remain uncertain. Studies that have investigated these relationships largely have used birth weight as an outcome and, as such, have been unable to determine at what point in gestation growth deviation related to stressful exposures manifests or which biometric parameters are most affected by these exposures. Additionally, because of many confounding factors that prior studies have not been able to take into account, the independent relationship between stressful exposures and fetal growth alterations remains uncertain.

The National Institute of Child Health and Human Development Fetal Growth Study of singletons provides a unique opportunity to assess the relationship of maternal stress and depression with longitudinal fetal growth. We hypothesized that women with greater perceived stress or depressive symptoms, either at the start of or during pregnancy, would have fetuses whose growth was less than that of women without these psychosocial burdens.

Materials and Methods

The National Institute of Child Health and Human Development Fetal Growth Study was a prospective cohort study in which pregnant women were recruited from 12 participating clinical sites from July 2009 through January 2013. Full details of the protocol and study methods have been published previously.[6] In summary, women were eligible for the study if they were at low risk of obstetric or medical complications. Exclusion criteria were a history of a preterm, low– birth weight (<2500 g), or macrosomic (>4000 g) neonate; history of stillbirth or neonatal death; medically assisted conception; cigarette smoking or illicit drug use in the past 6 or 12 months, respectively; 1 or more daily alcoholic drinks; previous fetal congenital malformation; a history of noncommunicable diseases (asthma requiring weekly medication, autoimmune disorders, cancer, diabetes mellitus, epilepsy or seizures requiring medication, hematologic disorders, hypertension, psychiatric disorders, renal disease, and thyroid disease); or a history of gravid diseases (gestational diabetes, severe preeclampsia, eclampsia, hemolysis, elevated liver enzymes, and low–platelet count syndrome). After undergoing a screening sonographic examination between gestational ages of 8 weeks and 13 weeks 6 days to ensure sonographic dating consistent with last–menstrual period dating, consenting women were randomized to 1 of 4 study visit schedules for the remainder of their pregnancy.

At each study visit, participants underwent a sonographic fetal assessment as well as in-person interviews. Women were administered the Cohen Perceived Stress Scale (PSS) and the Edinburgh Postpartum Depression Survey (EPDS) as part of the interview.[7,8] The former is a 10-item survey in which items are coded 0 to 4 and are summed to compute a total score ranging from 0 to 40. Higher scores indicate greater perceived stress. The latter is a 10-item survey in which items are coded 0 to 3 and are summed to compute a total score ranging from 0 to 30. Higher scores indicate more symptoms of depression, with scores of at least 10 indicating possible depression and at least 13 indicating a high likelihood of a depressive disorder.[7]

Based on their scores, women were dichotomized into groups to indicate those who had evidence of greater perceived stress and depressive symptoms. Given that the PSS has no validated discriminatory point, women in the upper quartile of scores (ie, those with scores $\geq$15 in the first trimester of pregnancy) were defined as those with high perceived stress. For the EPDS, women were defined as manifesting evidence of greater depressive symptoms at a score of 10 or higher. In a sensitivity analysis, women were instead dichotomized on the basis of a score of 13 or higher.

Serial sonographic data were used to estimate fetal growth, with individual biometric parameters (biparietal diameter, head circumference, abdominal circumference, and femur length) and estimated fetal weight[9] log transformed to stabilize variances across gestational ages and to improve normal approximations for the error structures. All participating sonographers underwent ante hoc training and credentialing for quality control, and their measurement techniques were subject to rigorous post hoc quality assurance.[10] Biometric measurements were performed according to standard operating procedures with identical equipment (Voluson E8; GE Healthcare, Milwaukee, WI) using a transabdominal curved multifrequency volume transducer (real-time abdominal, 4–8 MHz) and a transvaginal multifrequency volume transducer (real-time intracavity, 6–12 MHz).

The primary analysis was performed by using linear mixed models with cubic splines. Three knot points

(25th, 50th, and 75th percentiles) were chosen at gestational ages that evenly split the distributions. Percentiles were estimated on the basis of the assumed normal distribution of the random effects and error structure. Estimated curves for the mean of each parameter were determined across gestational ages between 15 and 40 weeks. Curves were then compared in 2 different types of analysis.

In an analysis of cross-sectional data, women were compared according to the perceived stress and depression scores (ie, high versus low perceived stress and high versus low depression scores) that they had in their first trimester of pregnancy. The second analysis used longitudinal exposure data as the basis for group comparisons. In this analysis, women who had high perceived stress scores in all trimesters (ie, ≤ 14 weeks, 14 weeks–27 weeks 6 days, and 27 weeks–41 weeks 3 days) were compared with those who exceeded a cut point in only 1 or 2 trimesters as well as with those who did not exceed a cut point in any trimester. A similar analysis was done on the basis of the depression scores.

For estimated fetal weight and each individual anthropometric parameter, we tested for overall differences in growth curves by using a likelihood ratio test. If a global test was significant ($P < .05$ level), we tested for week-specific differences by using Wald tests at each week of gestation. These tests were conducted on the estimated curves with and without adjustment for the following maternal characteristics: age, prepregnancy body mass index, and parity.

Last, we evaluated whether there was an interaction between race/ethnicity and high perceived stress or depression scores with respect to fetal growth. Women's race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, and Asian or Pacific Islander. These categorizations were based on self-identified race/ethnicity provided by participants on their study questionnaire.

All analyses were performed with SAS version 9.4 software (SAS Institute Inc, Cary, NC) or R version 3.1.2 software (http://www.R-project.org). Institutional Review Board approval was obtained from all participating sites before initiation of the study, and all women gave informed consent before enrollment and data collection.

Results

Among the 2334 enrolled women, 2088 (89%) completed the PSS, and 2108 (90%) completed the EPDS at least once in each trimester. Characteristics of the study population are presented in Table 1. As illustrated, the women in the study population were racially and ethnically diverse, and represented a wide range of socioeconomic strata. The 25th, 50th, and 75th percentiles for the PSS and EPDS scores in each trimester are presented in Table 2. Also presented in Table 2 are the proportions of women in each trimester whose EPDS score was 10 or higher or 13 or higher.

Figures 1 and 2, respectively, illustrate fetal growth trajectories for estimated fetal weight, as well as for the individual biometric parameters of biparietal diameter, head circumference, abdominal circumference, and femur length, stratified by PSS and EPDS scores in the first trimester. The unadjusted P associated with the comparisons of these curves are presented in Table 3. As demonstrated in the graphs and by the P values, estimated fetal weight was similar regardless of whether the participants reported high scores on the PSS or EPDS. In the unadjusted analyses, the trajectories of most

Table 1. Characteristics of the Study Population

Characteristic	Value
Age, y	28.2 ± 5.5
Body mass index, kg/m^2	23.6 ± 3.0
Gestational age at enrollment, wk	12.7 ± 1.0
Nulliparity	1149 (49.2)
Race/ethnicity	
Non-Hispanic white	614 (26.3)
Non-Hispanic black	611 (26.2)
Hispanic	649 (27.8)
Asian	460 (19.7)
Marital status	
Never	500 (21.5)
Living as married/married	1769 (75.9)
Divorced/separated	62 (2.7)
Education	
No college	658 (28.2)
Some college	683 (29.3)
College graduate	565 (24.2)
Postgraduate degree	428 (18.3)
Annual family income	
<$30,000	562 (28.2)
$30,000–$49,999	340 (17.1)
$50,000–$74,999	245 (12.3)
$75,000–$99,999	265 (13.3)
≥$100,000	580 (29.1)
Health insurance	
Commercial	1239 (57.6)
Government/self-pay	913 (42.4)

All data are presented as mean ± SD and number (percent) where applicable.

individual biometric parameters also were similar, although the trajectories for biparietal diameter and abdominal circumference were statistically significantly higher (albeit minimally different in absolute value) for those women with higher stress scores. In adjusted analyses, results were largely unchanged, although the difference in abdominal circumference trajectories became nonsignificant. The findings were unchanged when a cutoff for the EPDS of 13 or higher was used (data not shown).

Figures 3 and 4, respectively, illustrate fetal growth trajectories for estimated fetal weight and the individual biometric parameters after stratification of PSS and EPDS scores based on scores throughout the pregnancy (ie, exceeding the cut point in all trimesters, intermittently exceeding the cut point, or never exceeding the cut point in any trimester). Results presented in Table 3 were similar to those obtained from the cross-sectional analysis: there were no differences among groups for any growth parameter trajectory in either univariable analysis other than that women who consistently scored above the cut point on the PSS had a statistically significantly greater abdominal circumference trajectory. This difference did not persist in the multivariable analysis, and findings were similar regardless of whether an EPDS score of 13 or higher was used instead of 10 or higher.

Last, we evaluated whether there was any effect modification between survey scores and race/ethnicity with regard to the curves for fetal growth parameters. Tests evaluating for effect modification were not statistically significant for the biometric parameters under study, suggesting that the lack of a relationship between PSS and EPDS scores and fetal growth was similar across race/ethnic groups (Table 4).

Discussion

In this analysis, we investigated whether higher scores on the PSS or EPDS during pregnancy were associated with alterations in fetal growth. There was no evidence that a greater burden of either stress or depressive symptoms translated into alterations in overall fetal weight or individual biometric parameters. The similarity in fetal growth existed whether women had the exposure of interest relatively early in pregnancy or persistently throughout pregnancy. Moreover, this lack of an association of perceived stress and depression with fetal growth was extant to a similar degree for women of varying races and ethnicities.

An association between a psychosocial burden and fetal growth has been found by some but not by others. For example, Borders et al[3] investigated a cohort of low-income women and found that multiple factors suggesting a stressful environment, including food insecurity (odds ratio, 3.2; 95% confidence interval, 1.4–7.2) and poor coping skills (odds ratio, 3.8; 95% confidence interval, 1.7–8.7), were associated with low birth weight at delivery. A South African study documented that women with more depressive symptoms had a greater risk of decreased infant weight for age and head circumference for age at birth.[11] Zhu et al,[12] who studied 1800 women who delivered after 32 weeks, found that each unit increase of perceived life event stress during the first trimester was associated with a 99-g decrease in infant birth weight. However, other studies that have examined both stressful events and perceived stress have not found these associations.[2,13]

There are several reasons to believe that the results of this study, which are aligned with the results of the studies that have not found an association, are valid. As

Table 2. Distribution of Scores From the PSS and EPDS

	PSS[a]			EPDS[a]			
Trimester	**Median (IQR)**	**n**	**n ≥ 15 (%)**	**Median (IQR)**	**n**	**n ≥ 10 (%)**	**n ≥ 13 (%)**
1st	11 (7–15)	2307	669 (29.0)	4 (2–7)	2329	327 (14.0)	118 (5.1)
2nd	9 (5–13)	2175	514 (23.6)	4 (1–7)	2180	263 (12.1)	98 (4.5)
3rd	9 (5–13)	2143	651 (28.7)	3 (1–6)	2144	376 (17.5)	114 (5.3)

IQR indicates interquartile range.
[a]The proportions of women who reached a PSS score of 15 or higher in every trimester, who reached it only intermittently, and who never reached it in any trimester were 11.45%, 34.72%, and 53.83%, respectively. The proportions of women who reached an EPDS score of 10 or higher in every trimester, who reached it only intermittently, and who never reached it in any trimester were 3.32%, 25.76%, and 70.92%.

Figure 1. Fetal growth trajectories for estimated fetal weight (EFW), biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) based a PSS score of 15 or higher.

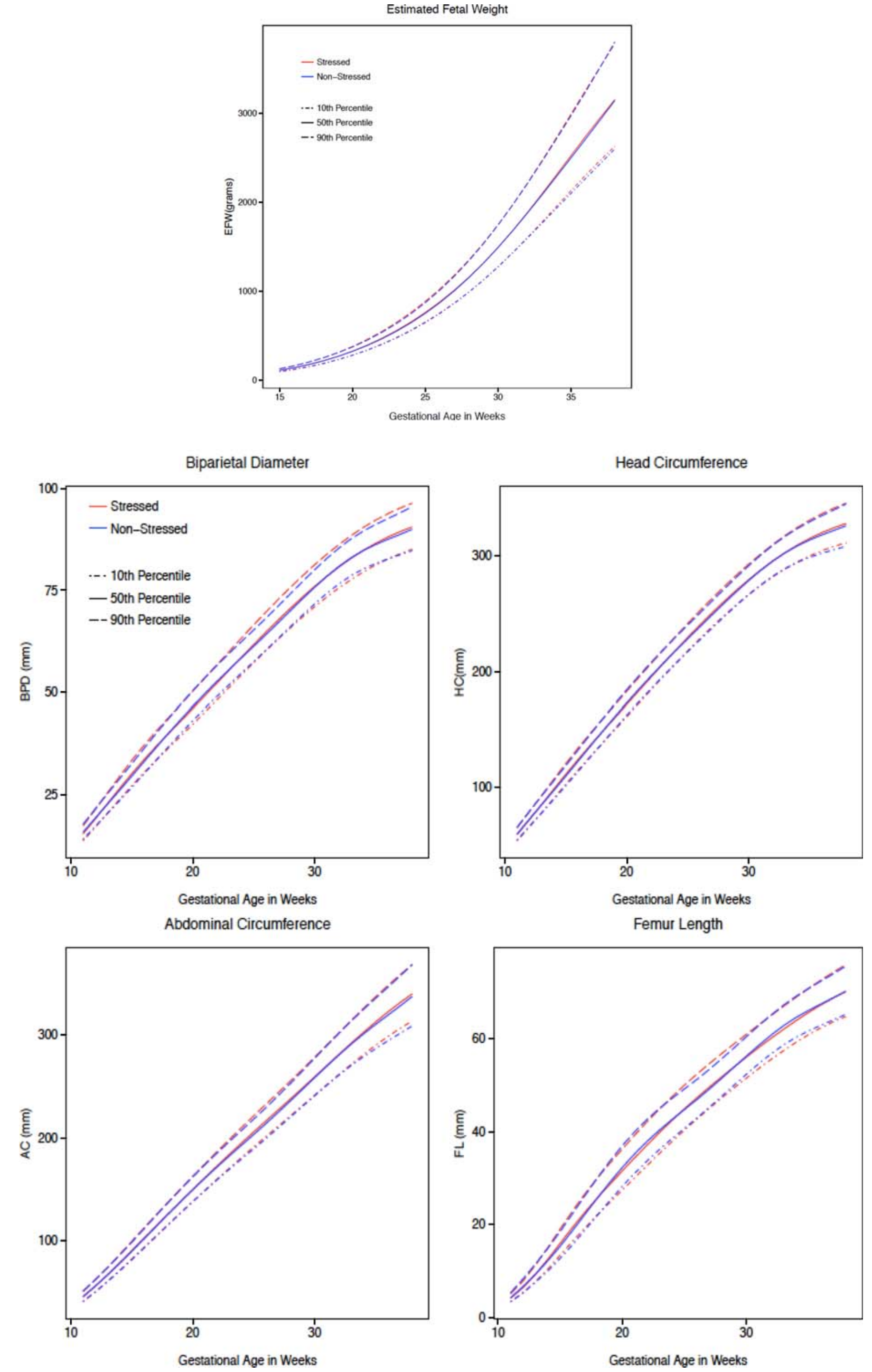
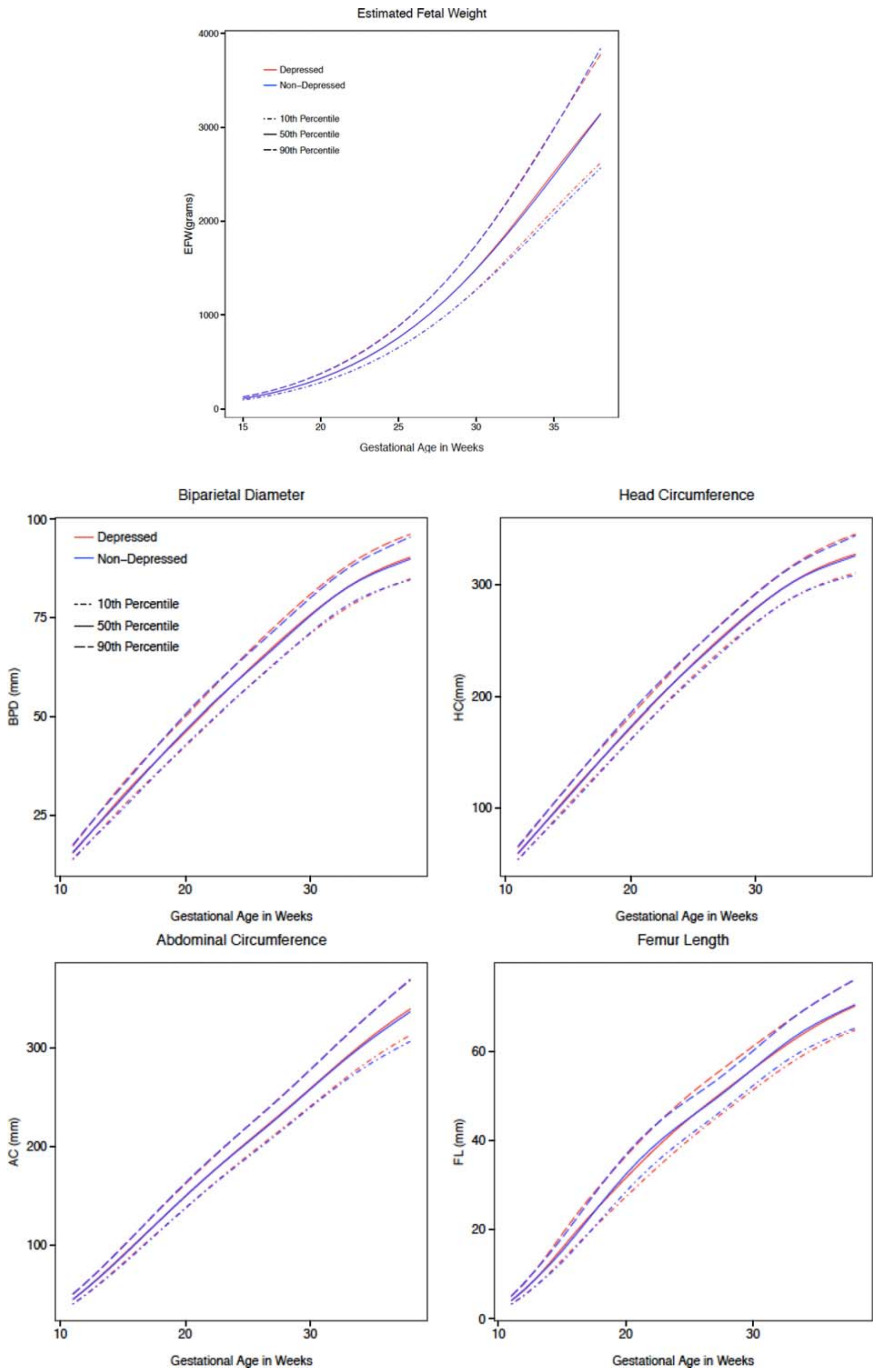


Figure 2. Fetal growth trajectories for estimated fetal weight (EFW), biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) based on an EPDS score of 10 or higher.



opposed to studies that assessed weight and biometric parameters at only a single point in time, this study analyzed fetal growth and multiple biometric parameters longitudinally and was able to compare growth curves throughout gestation. Exposure data were obtained prospectively and serially from participants, and outcome data (ie, growth curves) were determined only after all exposure data and potential confounding factors were collected. The inclusion criteria for the study, moreover, were designed to result in a study population that did not have other factors, such as extreme poverty and preexisting comorbidities, that have been present in other studies and may be the actual culprits for the observed associations of perinatal growth with psychosocial assessments. Such factors may be difficult to adjust for adequately in multivariable analyses because of collinearity or because they serve as proxies for related confounding factors that are difficult to quantify.

Nevertheless, even if greater perceived stress and depressive symptoms during pregnancy have no association with reduced fetal growth, the possibility that the psychosocial environment affects pregnancy outcomes remains possible. We assessed perceived stress and depressive symptoms because the relationship with fetal growth was biologically plausible and has been suggested by other observational studies.[3–5,9,11,12] However, other unmeasured psychosocial constructs may have stronger associations with pregnancy outcomes. Similarly, we measured depressive symptoms and not the actual clinical diagnosis of depression. The surveys used assessed events and feelings that were relatively acute and proximate to the pregnancy. However, some work has suggested that chronic stress and affective symptoms, which were not measured in this study, are the etiologic factors in the psychosocial domain that are most likely responsible for adverse pregnancy outcomes.[14] Last, the exclusion of women with the most extreme poverty and with medical comorbidities may have removed a population that is particularly vulnerable to additional psychosocial hardship and in which an association would have been observed.

Ultimately, however, there was no evidence in this longitudinal cohort study that greater perceived stress or depressive symptoms, as measured by the PSS and EPDS, were associated with alterations in fetal growth. This work suggests that these factors alone are not sufficient to result in altered fetal biometric parameters, and further work will be necessary to delineate whether a

Table 3. Unadjusted *P* Values for Comparisons of Fetal Growth Trajectories Based on PSS and EPDS Scores

	1st Trimester		Throughout Pregnancy[a]	
Measurement	**PSS ≥ 15 (n = 2307)**	**EPDS ≥ 10 (n = 2329)**	**PSS ≥ 15 (n = 2088)**	**EPDS ≥ 10 (n = 2108)**
Estimated fetal weight	.55	.54	.62	.73
Biparietal diameter	.012	.61	.66	.13
Head circumference	.058	.89	.097	.75
Abdominal circumference	.017	.30	.024	.16
Femur length	.47	.07	.0001	.43

[a]Three-group comparison: women always exceeding the given score, women intermittently exceeding the given score, and women never exceeding the given score in each trimester.

Table 4. *P* Values for the Interaction of Women's Race/Ethnicity With the PSS and EPDS Scores for Fetal Growth Trajectories

	1st Trimester		Throughout Pregnancy[a]	
Measurement	**PSS ≥ 15**	**EPDS ≥ 10**	**PSS ≥ 15**	**EPDS ≥ 10**
Estimated fetal weight	.68	.28	.84	.83
Biparietal diameter	.93	.71	.07	.34
Head circumference	.77	.57	.31	.12
Abdominal circumference	.51	.80	.39	.46
Femur length	.072	.06	.55	.73

[a]Three-group comparison: women always exceeding the given score, women intermittently exceeding the given score, and women never exceeding the given score in each trimester.

Figure 3. Fetal growth trajectories for estimated fetal weight (EFW), biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) based on a PSS score of 15 or higher always versus intermittently versus never during pregnancy.

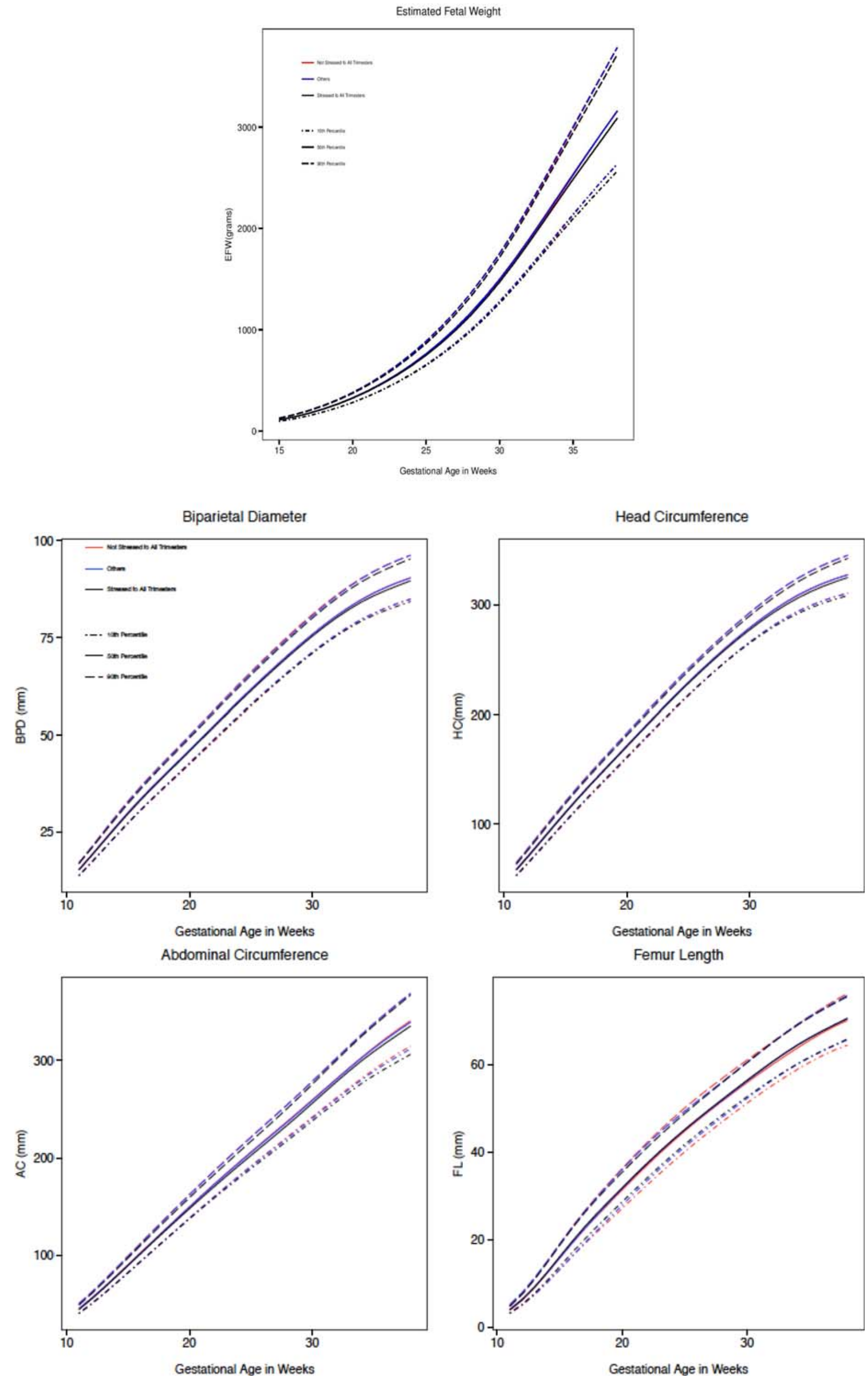
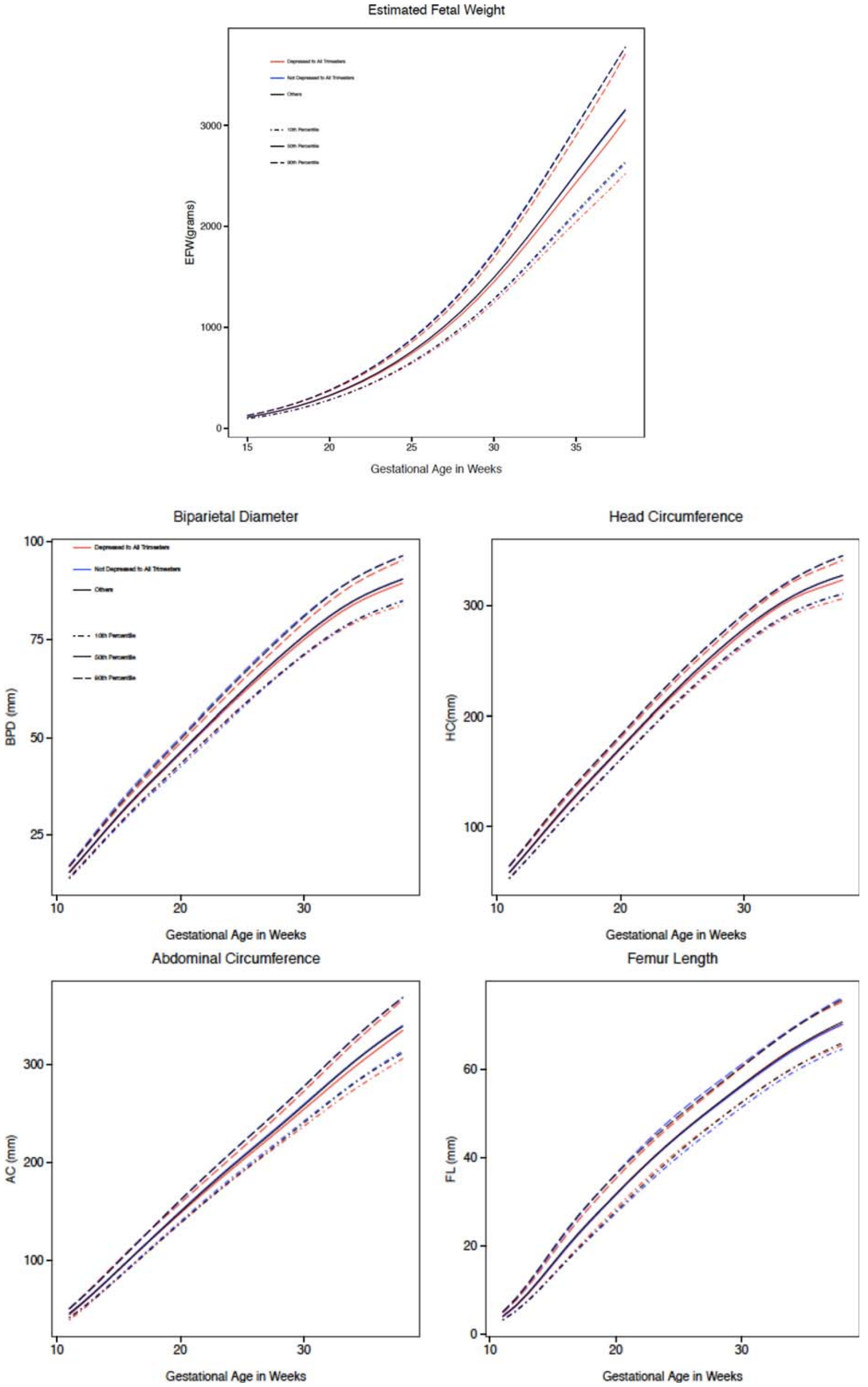


Figure 4. Fetal growth trajectories for estimated fetal weight (EFW), biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL) based on an EPDS score of 10 or higher always versus intermittently versus never during pregnancy.



greater psychosocial burden, either alone or in confluence with other environmental factors, contributes to impaired fetal growth.

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