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Serum brain-derived neurotrophic factor (BDNF) across pregnancy and postpartum: Associations with race, depressive symptoms, and low birth weight

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ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) is implicated as a causal factor in major depression and is critical to placental development during pregnancy. Longitudinal data on BDNF across the perinatal period are lacking. These data are of interest given the potential implications for maternal mood and fetal growth, particularly among Black women who show ~2-fold greater risk for delivering low birth weight infants.

Methods: Serum BDNF, serum cortisol, and depressive symptoms (per CES-D) were assessed during each trimester and 4–11 weeks postpartum among 139 women (77 Black, 62 White). Low birth weight (<2500 g) was determined via medical record.

Results: Serum BDNF declined considerably from 1st through 3rd trimesters (ps $\leq$ 0.008) and subsequently increased at postpartum ($p < 0.001$). Black women exhibited significantly higher serum BDNF during the 1st trimester, 2nd trimester, and postpartum (ps $\leq$ 0.032) as well as lower serum cortisol during the 2nd and 3rd trimester (ps $\leq$ 0.01). Higher serum cortisol was concurrently associated with lower serum BDNF in the 2nd trimester only ($p < 0.05$). Controlling for race, serum BDNF at both the 2nd and 3rd trimester was negatively associated with 3rd trimester depressive symptoms (ps $\leq$ 0.02). In addition, women delivering low versus healthy weight infants showed significantly lower serum BDNF in the 3rd trimester ($p = 0.004$). Women delivering low versus healthy weight infants did not differ in depressive symptoms at any time point during pregnancy (ps $\geq$ 0.34).

Conclusions: Serum BDNF declines considerably across pregnancy in Black and White women, with overall higher levels in Blacks. Lower serum BDNF in late pregnancy corresponds with higher depressive symptoms and risk for low birth weight in Black and White women. However, the predictive value of serum BDNF in pregnancy is specific to within-race comparisons. Potential links between racial differences in serum BDNF and differential pregnancy-related cortisol adaptation require further investigation.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in the modulation of synaptic plasticity and long-term potentiation in the brain (Nagahara and Tuszynski, 2011). In addition, BDNF serves unique functions during pregnancy, as it is important for follicular development, implantation, and placentation within reproductive tissues (Kawamura et al., 2007; Kawamura et al., 2009; Mayeur et al., 2010). Two cross-sectional studies with sample sizes ≤80 reported median serum BDNF levels to be 30–50% lower among pregnant versus non-pregnant women in late pregnancy (≥28 weeks gestation) (Kim et al., 2012; Lommatzsch et al., 2006). Data demonstrating the trajectory of change in serum

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BDNF across pregnancy and postpartum are lacking. These data would inform understanding of typical versus atypical adaptation in serum BDNF and implications for perinatal mental health and pregnancy outcomes.

A sizable literature supports a relationship between BDNF and depression in non-pregnant adults (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2008; Molendijk et al., 2014; Sen et al., 2008). The neurotrophin hypothesis posits that stress-induced reductions in BDNF result in aberrant neurogenesis and subsequent major depression (Duman et al., 1997; Duman and Monteggia, 2006) and concentrations of BDNF in serum/plasma are related to BDNF activity in the brain (Klein et al., 2011; Sartorius et al., 2009). A meta-analysis of 55 studies concluded that there is a consistent relationship between low serum BDNF and depression as well as increases in serum BDNF following antidepressant treatment, with stronger effects among those showing greater improvement in depressive symptoms (Molendijk et al., 2014). Though limited, some data indicate that relationships between low serum BDNF and depressive symptoms are also observed during pregnancy and postpartum (Fung et al., 2015; Gazal et al., 2012). However, available data are cross-sectional, preventing examination of temporal associations or stability of relationships in the midst of significant pregnancy-associated physiological adaptation.

In addition to potential implications for perinatal mood, low BDNF bioavailability has been implicated in placental pathology; lower placental BDNF gene expression has been observed in women with preeclampsia which may have implications for impaired placental development observed in this context (D'Souza et al., 2014). BDNF plays an important role in healthy placental development through promotion of trophoblast invasion (Kawamura et al., 2007; Kawamura et al., 2009; Mayeur et al., 2010). The syncytiotrophoblast – the specialized transporting multinucleate epithelium of the placenta – is critical in nutrient transfer and removal of waste products to promote fetal growth (Sibley et al., 2010). Thus, it has been posited that lower maternal BDNF may result in impaired fetal growth (Kawamura et al., 2007; Kawamura et al., 2009; Mayeur et al., 2011; Mayeur et al., 2010). Of clinical importance, consistent and marked racial disparities in low birth weight (<2,500 g or 5.5 lbs) are evidenced in the US; approximately 13% of non-Hispanic Black infants are born at low birth weight compared to 7% of non-Hispanic White infants (March of Dimes Peristats). Thus, the potential role of BDNF in this racial disparity merits examination.

Addressing gaps in the current literature, this study examined serum BDNF longitudinally with assessment during each trimester of pregnancy and at 4–11 weeks postpartum in a racially diverse sample of 139 women (77 Black, 62 White). The trajectory of change in serum BDNF across time was examined. It was hypothesized that lower serum BDNF would be associated with higher depressive symptoms as well as increased risk for low birth weight. In addition, given data linking cortisol with suppressed BDNF production, and the robust increases in maternal cortisol observed in pregnancy, the association between serum BDNF and serum cortisol were examined. Throughout analyses, potential differential effects among Black versus White women were examined.

2. Methods and materials

2.1. Study design and participants

This study enrolled 144 pregnant women who were recruited from The Ohio State University Wexner Medical Center (OSUWMC) Prenatal Clinic and the community of Columbus, Ohio. Data collection occurred from 2009 to 2014. Study visits were conducted at 1st, 2nd, and 3rd trimesters, as well as 4–11 weeks postpartum. At each visit, participants provided a blood sample and completed demographic and psychosocial measures.

Women were ineligible if they had any known fetal anomaly, used illicit drugs, consumed more than two alcoholic drinks per week during pregnancy (per self-report or medical record), or had a major immunological or endocrine condition (e.g., rheumatoid arthritis, hypothyroidism). Women were excluded from the current analyses if they missed more than two study visits ($n = 5$); thus, analyses were conducted with 139 women. Informed consent was obtained at the first study visit, and participants received modest financial compensation at the completion of each visit. The study was approved by The Ohio State University Biomedical Institutional Review Board.

2.2. Demographics

Race/ethnicity, age, marital status, education, annual household income, and parity were collected by self-report at first study visit. Pre-pregnancy body mass index (BMI; kg/m2) was calculated utilizing self-reported pre-pregnancy weight and height measured at the first study visit.

2.3. Depressive symptoms

The Center for Epidemiologic Studies Depression Scale (CES-D) is a widely used and well-validated measure consisting of 20 items assessing cognitive, emotional, and somatic depressive symptoms (Radloff, 1977). The CES-D has shown predictive validity for physiological processes (e.g., serum proinflammatory cytokines) as well as health outcomes (e.g., preterm birth) in pregnancy in prior studies (Christian et al., 2009; Christian et al., 2010; Li et al., 2009; Orr et al., 2002; Phillips et al., 2010).

2.4. Health behaviors

Smoking, exercise, prenatal vitamin use, and antidepressant use were assessed via self-report at the first study visit. Smoking was defined as current or not current, including those who had never smoked. Exercise was operationalized as the frequency with which the participant engaged in a vigorous activity long enough to build up a sweat. Prenatal vitamin use was categorized as never, 1–3 days per week, 4–6 days per week, or 7 days per week. Antidepressant use within the last year was dichotomized as yes or no.

2.5. Blood parameters

Blood was primarily drawn between the hours of 0700 h and 1300 h (93% of draws), allowed to clot at room temperature, centrifuged, and serum aliquoted and stored at −80° C until assayed. Samples were all run at the same time with kits from the same lot. All samples from the same participant were batched together (i.e., run on the same plate). Serum BDNF was measured by solid phase enzyme-linked immunosorbent assay according to manufacturer instructions (R&D Systems, Inc. 614 McKinley Place NE, Minneapolis, MN) and using a spectrophotometric plate reader (Molecular Devices Corporation Spectra Max 190, 1311 Orleans Drive, Sunnyvale, California USA). The lower limit of detection was 20 pg/ml. Intra- and inter-assay coefficients of variation are 5% and 9%, respectively.

Serum cortisol was measured by solid-phase competitive chemiluminescent immunoassay and the Immulite 1000 per manufacturer instructions (Siemens Healthcare Diagnostics, Inc., 1717 Deerfield Rd., Deerfield, IL.). Analytical sensitivity was 0.2 ug/dL. Intra-assay and inter-assay coefficients of variation were 7.1% and 7.9%, respectively.

2.6. Birth outcomes

Birth weight and gestational age at delivery were obtained by medical record review. Infants weighing <2500 g were categorized as low birth weight.

2.7. Statistical analyses

Serum BDNF levels were log-transformed (base 10) to fit the normality assumption. Descriptive statistics were calculated for all participants. Data at all four study visits were available for 72.7% (n = 101), while 21.6% (n = 30) and 5.8% (n = 8) of participants had missing data at one or two study visits, respectively. Thus, data were missing from 46 of 556 study assessments (7.7%). In addition, two women were excluded from birth weight analyses because medical records following delivery were unavailable. To account for missing data, prior to analyses, missing values for CES-D scores, BDNF levels, and serum cortisol levels were imputed using multiple imputation procedures in SPSS 22. Five imputations were generated and results across the five imputed datasets were averaged to arrive at the final statistical values (Rubin, 2004). To examine differences between Black and White women on the demographic variables and health behaviors, t-tests and chi-square tests were conducted. Partial correlations were employed to assess the relationship between depressive symptoms and serum BDNF at each time point. Repeated measures ANOVAs were used to examine serum BDNF and cortisol levels across pregnancy and postpartum, including their associations with race, depressive symptoms, and low birth weight, as appropriate. Bivariate correlations were used to examine the relationship between serum BDNF and serum cortisol at each study visit. Logistic regressions were conducted to examine whether serum BDNF at any study visit during pregnancy subsequently predicted low birth weight.

3. Results

3.1. Sample characteristics

Study visits occurred in the 1st trimester (12.0 ± 1.89 weeks), 2nd trimester (21.7 ± 2.2 weeks), 3rd trimester (30.3 ± 2.0 weeks), and postpartum (7.6 ± 1.82 weeks). In this sample, 55% (n = 77) were Black and 45% (n = 62) were White, including 5 White women endorsing Hispanic ethnicity. Black and White women did not differ on their age, education, or pre-pregnancy BMI; however, Black women were more likely to be unmarried, to report a household income ≤$15,000, and to be multiparous (Table 1). In terms of health behaviors, no racial differences in smoking status or exercise frequency were observed. However, Black women reported less use of prenatal vitamins (Table 2). Antidepressant use within the year prior to pregnancy was reported by 11 women, with only 2 women reporting continued use after pregnancy was known. Overall, 13 women delivered low birth weight infants (8 Black, 5 White). Of these 13 infants, 7 (54%) were also born preterm (<37 weeks gestation).

3.2. Serum BDNF across pregnancy and postpartum

Repeated measures ANOVA demonstrated a significant quadratic pattern of change in serum BDNF over the course of pregnancy and postpartum ($F(1137) = 122.58$, $p < 0.001$) as well as a main effect of race ($F(1137) = 7.78$, $p = 0.006$). Post-hoc comparisons showed that serum BDNF significantly declined from the 1st to 2nd trimester ($p = 0.008$), declined further from 2nd to 3rd trimester ($p = 0.002$), and subsequently increased at postpartum ($p < 0.001$). In addition, Black women exhibited significantly higher serum BDNF levels than White women during the 1st trimester ($p = 0.021$), 2nd trimester ($p = 0.032$), and at postpartum ($p = 0.021$).

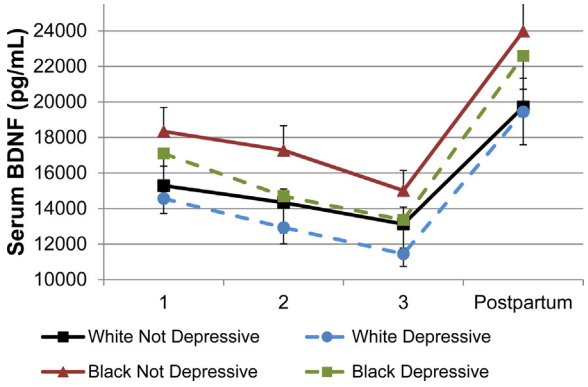

Fig. 1. Serum BDNF across time by race in women with high versus low depressive symptoms in late pregnancy.
A differential quadratic trajectory of change across time was observed in women with higher versus lower depressive symptoms in late pregnancy ($F(1126) = 4.15$, $p = 0.044$). Controlling for race, higher depressive symptoms in the 3rd trimester were predicted by lower serum BDNF in both the 2nd and 3rd trimester ($ps < 0.05$). *To view this figure in color, the reader is referred to the web version of the article.*

3.3. Depressive symptoms and serum BDNF across pregnancy and postpartum

Black and White women did not differ in depressive symptoms at any study visit ($ps > 0.31$). Given the observed racial differences in serum BDNF, the relationship between depressive symptoms and serum BDNF was examined utilizing partial correlations controlling for race. During the 3rd trimester assessment, depressive symptoms and serum BDNF were inversely associated ($r = -0.17$, $p = 0.045$). Analyses of CES-D subscales demonstrated that this effect was driven by depressed mood ($r = -0.21$, $p = 0.02$) and somatic symptoms ($r = -0.17$, $p = 0.06$), rather than positive symptoms ($r = -0.11$, $p = 0.23$) or interpersonal symptoms ($r = -0.09$, $p = 0.30$). No concurrent associations were observed between depressive symptoms and serum BDNF at other time points ($ps \geq 0.60$).

Next, non-concurrent associations were examined to determine whether lower serum BDNF was predictive of subsequent depressive symptoms. Controlling for race, serum BDNF during the 1st trimester was not associated with depressive symptoms at later time points ($ps \geq 0.25$). However, also controlling for race, lower serum BDNF at the 2nd trimester predicted higher depressive symptoms at the 3rd trimester ($r = -0.25$, $p = 0.005$). This effect remained after controlling for depressive symptoms during the 2nd trimester ($r = -0.31$, $p = 0.001$), indicating that lower serum BDNF at mid-pregnancy preceded the onset of depressive symptoms in late pregnancy. No associations were observed between serum BNDF at the 2nd or 3rd trimester for depressive symptoms at postpartum ($ps \geq 0.11$)

Given the relationship between depressive symptoms and serum BDNF at 3rd trimester, the trajectory of serum BDNF across pregnancy and postpartum was examined by dichotomizing groups using a median split on depressive symptoms at this time point. Repeated measures ANOVA demonstrated a differential quadratic trajectory of change among women with higher versus lower depressive symptoms in late pregnancy ($F(1126) = 4.15$, $p = 0.044$) (Fig. 1). In follow-up sensitivity analyses, effects were unchanged when women who reported antidepressant use within the year prior to study initiation ($n = 11$) were excluded.

Table 1
Demographic characteristics.

	Total (n = 139)	Black (n = 77)	White (n = 62)	Black vs. White Comparisons
Age [Mean (SD)]	24.8 (4.16)	24.7 (4.4)	24.9 (3.9)	p = 0.54
Marital Status [n (%)]				p < 0.01[a]
Married	41 (29.5)	14 (18.2)	27 (43.5)	
In a relationship	73 (52.5)	45 (58.4)	28 (45.2)	
Single	25 (18.0)	18 (23.4)	7 (11.3)	
Education [n (%)]				p = 0.35
Less than high school	23 (16.5)	14 (18.2)	9 (14.5)	
High school graduate	33 (23.7)	17 (22.1)	16 (25.8)	
Some college	53 (38.1)	33 (42.9)	20 (32.3)	
College degree	30 (21.6)	13 (16.9)	17 (27.4)	
Income [n (%)]				p = 0.04[a]
<$15,000	64 (46.0)	43 (55.8)	21 (33.9)	
$15,000–29,999	37 (26.6)	17 (22.1)	20 (32.3)	
$ > 30,000	38 (27.3)	17 (22.1)	21 (33.9)	
Parity (# of prev. births) [n (%)]				p = 0.03[a]
0	33 (23.7)	12 (15.6)	21 (33.9)	
1	51 (36.7)	29 (37.7)	22 (35.5)	
2 or more	55 (39.6)	36 (46.8)	19 (30.6)	
Pre-pregnancy BMI [Mean (SD)]	28.14 (7.1)	28.5 (7.3)	27.7 (7.0)	p = 0.63
Low birth weight [n (%)]	13 (9.5)	8 (10.5)	5 (8.2)	p = 0.77

[a] Black women were more likely to be unmarried, lower income, and multiparous than White women.

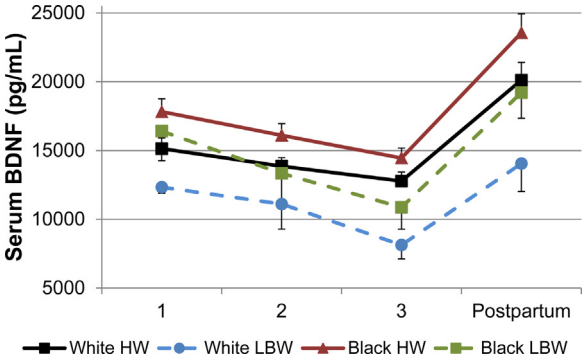

Fig. 2. Serum BDNF across time by race in women delivering healthy versus low birth weight infants.
A main effect for low birth weight in predicting serum BDNF was observed (F(1133) = 4.97, p = 0.027). Controlling for race, women delivering low birth weight infants exhibited significantly lower serum BDNF during the 3rd trimester (F(1134) = 8.4, p = 0.004). [HW = Healthy Weight; LBW = Low Birth Weight (<2500 g)]. *To view this figure in color, the reader is referred to the web version of the article.*

3.4. Serum BDNF and low birth weight

In this sample, 9.49% (n = 13) of women delivered infants of low birth weight (< 2500 g). Rates of low birth weight did not differ significantly by race, with occurrence in 5/61 (8.2%) of Whites and 8/76 (10.5%) of Blacks (p = 0.77). Repeated measures ANOVA showed main effects for low birth weight (F(1133) = 4.97, p = 0.027) as well as the previously described main effect for race (F(1133) = 3.63, p = 0.06) in predicting serum BDNF levels. In post-hoc test one-way ANOVAs, controlling for race, women delivering low birth weight infants did not differ from those delivering healthy weight infants in serum BDNF at the 1st (F (1134) = 0.63, p = 0.43) or 2nd (F(1134) = 2.28, p = 0.13) trimesters but exhibited markedly lower serum BDNF during the 3rd trimester (F(1134) = 8.4, p = 0.004; Fig. 2). Further, logistic regression showed that, controlling for race, each 100 pg/ml lower serum BNDF in the 3rd trimester predicted 3.5 times greater odds of delivering a low birth weight infant (p = 0.009). This finding remained significant after controlling for gestational age at delivery (p = 0.017).

3.5. Low birth weight and depressive symptoms

Finally, we examined the relationship between birth weight and depressive symptoms to determine the extent to which these parameters shared common pathways. In this sample, women who delivered low birth weight infants did not differ from those delivering healthy weight infants in depressive symptoms at any time point during pregnancy (ps ≥ 0.23). However, they did exhibit higher depressive symptoms at postpartum (Mean = 17.0 vs 11.1; p = 0.04).

3.6. Serum cortisol, race, and serum BDNF

Analyses were conducted to examine a potential role of differential cortisol adaption in the reported racial differences in serum BDNF. Repeated measures ANOVA demonstrated that, as expected and shown in Fig. 3, a quadratic pattern in cortisol was observed (F(1137) = 492.53, p < 0.001), with increases from the 1st and 2nd (p < 0.001) as well as the 2nd and 3rd trimesters (p < 0.001), followed by a decline from 3rd trimester to postpartum (p < 0.001). Moreover, Black women exhibited a different quadratic change over time than Whites (F(1137) = 7.12, p = 0.009). Specifically, Black women exhibited lower serum cortisol than White women at both the 2nd (p = 0.01) and 3rd trimesters (p = 0.002; Fig. 3).

The relationship between cortisol and serum BDNF at each study visit was examined using partial correlations controlling for time of sampling. As shown in Table 3, higher serum cortisol in the 2nd trimester of pregnancy was associated with lower serum BDNF during the 1st trimester (p < 0.05), 2nd trimester (p < 0.05), and marginally at postpartum (p = 0.07). In addition, lower serum BDNF in the 1st trimester was associated with lower serum cortisol during the 3rd trimester (p < 0.05). No other significant associations were observed.

4. Discussion

The current data demonstrate a clear trajectory of change in serum BDNF across the perinatal period, with considerable declines from the 1st through 3rd trimesters and a subsequent increase at postpartum. Our data extend prior, primarily cross-sectional, studies showing markedly lower serum BDNF levels in women dur-

Table 2
Health behaviors.

	Total (n = 139)	Black (n = 77)	White (n = 62)	Black vs. White Comparisons
Smoking Status [n (%)]				p = 0.80
Current	19 (13.7)	10 (13.0)	9 (14.5)	
Not current/Never	120 (86.3)	67 (87.0)	53 (85.5)	
Exercise [n (%)]				p = 0.46
Less than once per month	40 (28.8)	25 (32.5)	15 (24.2)	
Month				
Once per month	18 (12.9)	8 (10.4)	10 (16.1)	
2–3 Times per month	28 (20.1)	18 (23.4)	10 (16.1)	
Once per week	27 (19.4)	14 (18.2)	13 (21.0)	
More than once per week	26 (18.7)	12 (15.6)	14 (22.6)	
Prenatal vitamin use [n (%)]				p < 0.01[a]
Never	29 (20.9)	22 (28.6)	7 (11.3)	
Some days (1–3/week)	17 (12.2)	12 (15.6)	5 (8.1)	
Most days (4–6/week)	22 (15.8)	14 (18.2)	8 (12.9)	
Every day (7/week)	71 (51.1)	29 (37.7)	42 (67.7)	

[a] Black women were more likely to report no prenatal vitamin use than Whites.

ing late pregnancy compared to non-pregnant women (Kim et al., 2012; Lommatzsch et al., 2006). Our findings contrast a prior longitudinal study of 42 women from Bogotá, Columbia which showed increases in serum BNDF from the 1st to 2nd trimester, with no significant change between 2nd and 3rd trimester (Garcés et al., 2014). The reason for this discrepancy is unknown but may relate to differences in assay methodology.

The trajectory observed in the current investigation is consistent with the role of BDNF (Kawamura et al., 2007; Kawamura et al., 2009; Mayeur et al., 2010); declining levels across gestation may, in part, reflect utilization of maternal BDNF by the placenta and fetus. In relation to fetal development, BDNF crosses the utero-placental barrier and animal models show that maternal circulating levels of BDNF correspond with fetal brain levels (Kodomari et al., 2009). Pregnancy-induced hemodilution may also contribute; serum BDNF is stored in platelets, and platelet counts decrease during pregnancy (Fujimura et al., 2002). Thus, this may be a factor in the observed drop in serum BDNF across the course of pregnancy. Lack of data on platelet counts is a limitation; this should be considered in conjunction with serum BDNF levels in future pregnancy studies. In addition, sex hormones may play a role; estradiol and progesterone increase considerably across pregnancy (O'Leary et al., 1991). Some data suggest that fluctuations in circulating BDNF levels during the menstrual cycle correspond with changes in sex hormones (Pluchino et al., 2009). In addition, pregnancy is characterized by robust increases in cortisol. Heighted cortisol as well as overexpression of glucocorticoid receptors has been implicated in reduced BDNF production/mRNA expression in some studies (Issa et al., 2010; Ridder et al., 2005; Smith et al., 1995b). Overall, mechanisms underlying pregnancy-related changes remain to be fully determined.

Notably, in the current study, Black women exhibited higher levels of serum BDNF than White women during the 1st trimester, 2nd trimester, and at postpartum. This effect was not accounted for by racial differences in demographic factors or health behaviors. This finding was opposite of the expected direction; given that BDNF production/mRNA expression is impaired by stressor exposure (Smith et al., 1995a; Yuluğ et al., 2009), it was predicted that Black women would exhibit lower levels than Whites. Genetic factors may contribute to this racial difference; in particular, considerable differences in the frequency of BDNF (Val66Met) variants have been documented among those of European versus African ancestry (Petryshen et al., 2010).

Moreover, in the context of pregnancy, adaptation of multiple interactive aspects of neuroendocrine function may ultimately contribute to serum BNDF levels. Consistent with prior data (Glynn et al., 2007), we found that Black women exhibited less robust pregnancy-induced increases in cortisol across the course of gestation than Whites. As noted above, cortisol may reduce BDNF production. In the current study, higher serum cortisol in the 2nd trimester was associated with lower serum BDNF during the 1st trimester, 2nd trimester, and (marginally) at postpartum. In addition, lower serum BDNF in the 1st trimester was associated with higher serum cortisol in the 3rd trimester. While these relationships were in the expected direction (i.e., inverse associations), they were primarily non-concurrent and not consistently observed. Thus, it is plausible that differential pregnancy-related cortisol adaptation is related to the observed racial difference in serum BDNF, but this requires further investigation.

Table 3
Correlations between serum cortisol and BDNF.

	BDNF 1	BDNF 2	BDNF 3	BDNF 4
Cortisol 1	−0.11	−0.10	0.03	−0.13
Cortisol 2	−0.22***	−0.19**	−0.12	−0.16*
Cortisol 3	−0.18**	−0.03	−0.03	−0.02
Cortisol 4	−0.11	0.03	0.02	−0.10

Note: lg 10 BDNF values used; analyses control for time of sampling.
*p = 0.07.
**p < 0.05.
***p < 0.01.

In relation to mood, a concurrent inverse relationship between depressive symptoms and serum BDNF was observed during the 3rd trimester only. In addition, depressive symptoms during the 3rd trimester were preceded by lower serum BDNF in the 2nd trimester. These data support a temporal relationship between declines in serum BDNF and subsequent onset of depressive symptoms, and suggest that late pregnancy is the period of greatest vulnerability to BDNF-induced depression.

The observed patterns of relationship between serum BDNF and depressive symptoms in late pregnancy were present in women of both races. However, given the significant main effects of race on serum BDNF, this prediction line was shifted upward for Black women. Of note, the higher levels of serum BDNF in Black women did not provide a protective advantage in terms of depressive symptoms; Black and White women exhibited similar level of depressive symptoms at each assessment. Thus, the relationship between serum BDNF and depressive symptoms is best understood in the context of within-race comparisons.

Analyses of CES-D subscales demonstrated that the association between serum BDNF and depressive symptoms in late pregnancy was driven by somatic symptoms as well as depressed mood. Thus,

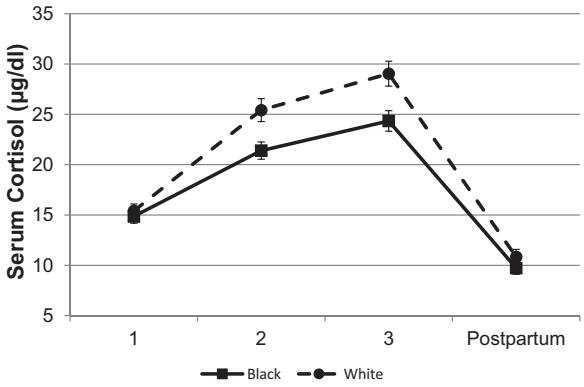

Fig. 3. Serum cortisol across time by race.
In the overall sample, a quadratic change over time was observed ($F(1137) = 482.73$, $p < 0.001$). In addition, a main effect of race was observed ($F(1137) = 9.05$, $p = 0.003$). Black women exhibited lower serum cortisol than White women at both the 2nd ($p = 0.01$) and 3rd trimesters ($p = 0.004$).

although changes in sleep, appetite, and energy level occur within the context of healthy pregnancy, these indicators show relationships with biological correlates of depression. Of note, while the CES-D is commonly administered in perinatal studies (Christian et al., 2009, 2010; Li et al., 2009; Orr et al., 2002; Phillips et al., 2010), the Edinburgh Depression Scale was specifically designed for use in pregnancy and postpartum and is also widely used (Cox et al., 1987). The Edinburgh purposefully excludes somatic symptoms to avoid overlap with typical perinatal experiences. Perhaps relatedly, although it has excellent predictive value for major depression, it is less effective for detecting minor depression (Murray and Cox, 1990). The current findings indicate that somatic symptoms are important in identifying biological pathways to perinatal depression. Thus, assessment method should be carefully considered in future studies.

The current data also support a role for serum BDNF in fetal growth. Women delivering low birth weight infants (<2500 g) showed a considerable drop in serum BDNF in late pregnancy relative to those delivering healthy weight infants. For each 100 pg/ml decrease in serum BDNF in the 3rd trimester, the odds of delivering a low birth weight infant was 3.5 times greater. Effects of serum BDNF on low birth weight remained after controlling for gestational age at delivery, suggesting that fetal growth rather than timing of delivery was a central driver.

In the current study, Black women did not show higher rates of low birth weight than Whites; however this racial disparity is considerable and consistent in the larger U.S. population (March of Dimes Peristats). The lack of effect in the current study may be related to sample size; such effect is likely to emerge more readily in a larger cohort. Similarly, in the current study, we did not observe an association between depressive symptoms during pregnancy and low birth weight, which has been described in prior studies (Grote et al., 2010). Women with low birth weight infants did exhibit higher depressive symptoms at postpartum; this is likely a function of increased stress associated with caring for affected infants (Vigod et al., 2010). It is possible that mediating pathways linking prenatal depressive symptoms to low birth weight via BDNF would emerge in a larger cohort.

Multiple factors, including age, weight, and exercise, affect BNDF levels (Bus et al., 2011; Lommatzsch et al., 2005). In this study, Black and White women did not differ in age, education, smoking, pre-pregnancy BMI, or self-reported exercise. However, they did differ in income, parity, marital status, and prenatal vitamin usage. The sample size precluded examination of the potential mediating roles of these variables in relation to outcomes of interest. In addition, other factors that may correspond with serum BDNF were not measured such as urbanicity; among 1168 adults in the Netherlands, those living in urban versus rural environments exhibited higher serum BDNF (Bus et al., 2011).

Prior research demonstrates that genetic polymorphisms affecting BDNF production and serotonin function moderate the effect of early life adversity on subsequent risk for depressive symptoms (Buchmann et al., 2013). The examination of genetic factors would provide a more nuanced understanding of the associations observed in this cohort. Another important limitation of the current study is that it did not include diagnosis of clinical depression per clinical interview. Although the CES-D is a well-validated measure which includes measurement of multiple domains of depressive symptoms, it does not permit determination of clinical diagnosis. This information would be of value in future investigations. In addition, the ELISA utilized does not distinguish between mature BDNF and its precursor, proBDNF. Of note, prior data suggest that serum levels of mature BDNF are lower in adults with major depression, while serum levels of proBDNF do not differ (Yoshida et al., 2012). In addition, levels of mature BDNF in human serum are approximately 2-fold higher than levels of proBDNF (Yoshida et al., 2012). Thus, we postulate that mature BDNF is driving our observed effects. However, measurement quantifying mature as well as proBDNF would be informative in future studies, particularly as it is possible that differences may be observed specific to pregnancy.

This study did not examine outcomes in infants beyond birth weight. However, a growing literature in human and animal models demonstrates that maternal stress and BDNF exposure during gestation affects BNDF functioning in offspring, which has implications for related cognitive parameters including spatial learning and memory as well as mood and anxiety (Cicchetti et al., 2014; Liu et al., 2000; Perera et al., 2015; Pinheiro et al., 2014; Tozuka et al., 2010). Thus, examination of the extent to which differential maternal BDNF expression affect subsequent life-course development is an important focus for continued studies.

In sum, this study provides novel longitudinal data regarding serum BDNF levels across pregnancy and postpartum in a racially diverse sample of 139 women. Our findings show that serum BDNF declines across gestation in Black as well as White women, with overall higher levels in Blacks. In addition, lower serum BDNF in late pregnancy corresponds with higher depressive symptoms and the onset of these symptoms is preceded by lower BDNF during the 2nd trimester. Finally, women delivering low birth weight infants exhibited significantly different patterns of change in serum BDNF, with substantial declines during the 3rd trimester compared to women delivering healthy weight infants. The marked racial differences observed in BDNF were reflected in shifted patterns of association of BDNF with both mood and birth weight among Blacks versus Whites. Thus, future studies examining the health implications of BDNF in pregnancy should fully consider differential effects by race.

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Contributors

Lisa M. Christian: conceptualized the study, obtained funding, oversaw recruitment, conducted statistical analyses, wrote the majority of the manuscript.

Amanda Mitchell: assisted with literature review, data analyses, and manuscript preparation.

Shannon Gillespie: assisted with manuscript preparation.

Marilly Palettas: assisted with statistical analyses and database management.

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