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Correlates of early pregnancy serum brain-derived neurotrophic factor in a Peruvian population

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Abstract

Purpose—Knowledge about factors that influence serum brain-derived neurotrophic factor (BDNF) concentrations during early pregnancy is lacking. The aim of the study is to examine the correlates of early pregnancy serum BDNF concentrations.

Methods—A total of 982 women attending prenatal care clinics in Lima, Peru, were recruited in early pregnancy. Pearson's correlation coefficient was calculated to evaluate the relation between BDNF concentrations and continuous covariates. Analysis of variance and generalized linear models were used to compare the unadjusted and adjusted BDNF concentrations according to categorical variables. Multivariable linear regression models were applied to determine the factors that influence early pregnancy serum BDNF concentrations.

Results—In bivariate analysis, early pregnancy serum BDNF concentrations were positively associated with maternal age ($r = 0.16$, $P < 0.001$) and early pregnancy body mass index (BMI) ($r = 0.17$, $P < 0.001$), but inversely correlated with gestational age at sample collection ($r = -0.21$, $P < 0.001$) and C-reactive protein (CRP) concentrations ($r = -0.07$, $P < 0.05$). In the multivariable linear regression model, maternal age ($\beta = 0.11$, $P = 0.001$), early pregnancy BMI ($\beta = 1.58$, $P < 0.001$), gestational age at blood collection ($\beta = -0.33$, $P < 0.001$) and serum CRP concentrations ($\beta = -0.57$, $P = 0.002$) were significantly associated with early pregnancy serum BDNF concentrations. Participants with moderate antepartum depressive symptoms (Patient Health

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Compliance with Ethical Standards

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Questionnaire-9 (PHQ-9) score ≥ 10) had lower serum BDNF concentrations compared with participants with no/mild antepartum depressive symptoms (PHQ-9 score <10).

Conclusions—Maternal age, early pregnancy BMI, gestational age and the presence of moderate antepartum depressive symptoms were statistically significantly associated with early pregnancy serum BDNF concentrations in the low-income Peruvian women. Biological changes of CRP during pregnancy may affect serum BDNF concentrations.

Keywords

Peru; Early Pregnancy; Brain-derived neurotrophic factor; C-reactive protein; antepartum depressive symptoms

Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family. It exerts its biological function mainly through the high-affinity tropomyosin-related kinase B (TrkB) receptor. The role of BDNF in neuronal cell growth, survival, and synaptic plasticity has been well established (Warner-Schmidt and Duman 2006). Decreased peripheral BDNF concentrations have been observed in patients with psychiatric disorders, especially those with depression and schizophrenia (Asevedo et al. 2013; Castrén and Rantamäki 2010). In pregnant women, lower serum BDNF concentrations in early pregnancy were associated with symptoms of antepartum depression (Fung et al. 2015). There has been accumulating evidence for the role of BDNF in energy homeostasis. Both BDNF and its receptor, TrkB, are abundantly expressed throughout the hippocampus regions, which are important for maintaining energy balance and normal body weight (Bariohay et al. 2005). A number of studies, which were conducted in non-pregnant adults and children, have found altered BDNF concentrations in obese patients. For instance El-Gharbawy et al found decreased serum BDNF concentration in extremely overweight children (El-Gharbawy et al. 2006), while Suwa et al found that serum BDNF concentration was positively correlated with body mass index (BMI) and the percentage of body fat in newly diagnosed female type 2 diabetes patients (Suwa et al. 2006).

In addition to the central nervous system, BDNF and TrkB receptor have been shown to be expressed in nonneuronal tissues (Ip et al. 1993). For instance, in pregnant mice, BDNF and TrkB receptor are expressed in the ovary, pre-implantation embryos, uterus and trophoblast cells of blastocyst, and are demonstrated to play a vital role in the development of follicles, maturation of oocytes, early embryonic development, proliferation of trophoblast cells and growth and survival of trophoblast cells (Kawamura et al. 2007; Kawamura et al. 2005; Martins da Silva et al. 2005).

In humans, prior studies have documented alterations in BDNF concentrations during pregnancy. Lommatzsch et al, reported decreased serum BDNF concentrations at 37 weeks of gestation and one week after childbirth, compared to non-pregnant women (Lommatzsch et al. 2006). In human placentas affected by intrauterine growth restriction (IUGR), both BDNF and TrkB receptor mRNA expression were up-regulated (Mayeur et al. 2010). Collectively, these findings suggest that BDNF may be essential for placental development

and fetal growth, and are affected by maternal energy status. Results from epidemiologic studies are consistent with findings from clinical studies documenting decreased serum BDNF concentrations in medically complicated pregnancies including preeclampsia and preterm delivery (D'Souza et al. 2014; Malamitsi-Puchner et al. 2004).

Several factors have been found to influence peripheral BDNF concentrations in non-pregnant women and men. In obese subjects, caloric reduction diet (Araya et al. 2008) and participating in aerobic exercise significantly increased serum BDNF concentrations. (Mueller et al. 2015). Plasma BDNF concentrations decreased significantly with increasing age and weight. (Lommatzsch et al. 2005). Kim et al, in their study among 20 tobacco cigarette smokers with diagnosis of nicotine dependence and 20 healthy nonsmokers, found plasma BDNF concentrations in smokers were significantly lower than those in nonsmokers. They also noted that a two-month smoking cessation period resulted in significantly increased BDNF concentrations among smokers (Kim et al. 2007). Joe et al, in their study of 70 in-patients with a diagnosis of alcohol dependence and 75 randomly selected healthy controls, found that plasma BDNF concentrations were decreased in patients with alcohol dependence (Joe et al. 2007).

In addition, increased circulating BDNF concentrations have been observed in some systemic inflammatory conditions, such as asthma (Bonini et al. 1996). Activated lymphocytes and macrophages have been shown to synthesize and secrete BDNF in inflammatory conditions (Kerschensteiner et al. 1999). A well-studied acute-phase inflammatory biomarker is C-reactive protein (CRP). Elevated CRP concentrations during pregnancy were associated with adverse pregnancy outcomes (Catov et al. 2007; Rota et al. 2005). However, CRP concentrations will also increase during normal pregnancy due to the changes in maternal immunity to tolerate the fetus (Mei et al. 2016). A positive correlation between BDNF and CRP concentrations has been reported in patients with type 2 diabetes (Krabbe et al. 2007). Whether biological alterations in CRP concentrations can affect BDNF concentrations during pregnancy is unknown.

Taken together, available evidence suggests that physiological BDNF concentrations during pregnancy may be important for both maternal and fetal health. However, knowledge about factors that influence BDNF concentrations during early pregnancy is lacking. The objective of this study is to examine the influence of maternal age, early pregnancy BMI, parity, gestational age, antepartum depressive symptoms, lifestyle factors (tobacco smoking and alcohol consumption) and CRP concentrations on early pregnancy serum BDNF concentrations.

Material and methods

The sample for the present study was drawn from participants of the ongoing Pregnancy Outcomes, Maternal and Infant Study (ProMIS) Cohort, designed to examine maternal social and behavioral risk factors of preterm birth and other adverse pregnancy outcomes. The ProMIS cohort has been described previously (Barrios et al. 2015). The study population consists of women attending prenatal care clinics at the Instituto Nacional Materno Perinatal (INMP) in Lima, Peru. The INMP is the primary reference establishment

for maternal and perinatal care operated by the Ministry of Health of the Peruvian government. Recruitment began in February 2012. Women eligible for inclusion were those who initiated prenatal care prior to 16 weeks gestation. Women were ineligible if they were younger than 18 years of age, did not speak and read Spanish, or had completed more than 16 weeks gestation. All participants provided written informed consent. The institutional review boards of the INMP, Lima, Peru and the Harvard T. H. Chan School of Public Health Office of Human Research Administration, Boston, MA, USA approved all procedures used in this study.

Analytical Population

The study population for this report is derived from information collected from those participants who were enrolled in the PrOMIS Study between February 2012 and December 2012. During this period, 1327 eligible women were approached, and 1142 (86%) agreed to participate. Of those participating, 982 provided blood samples (86%) and were included in the analysis. Women excluded from this analysis did not differ in regards to sociodemographic and lifestyle characteristics as compared with those included.

Enrolled participants were invited to participate in an interview where trained research personnel used a structured questionnaire to elicit information regarding maternal socio-demographic, lifestyle characteristics, medical and reproductive histories, and early life experiences of abuse and symptoms of mood and anxiety disorders. Height and weight were measured with participants wearing light clothing and no shoes. Gestational age was determined by ultrasound. Antepartum depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9). The total score of PHQ-9 ranged from 0 to 27 and indicated the severity of depressive symptoms. A total score ≥ 10 was considered as presence of moderate antepartum depressive symptoms, and a total score < 10 was considered as no/mild antepartum depressive symptoms (Kroenke et al. 2001).

Other sociodemographic variables included: BMI based on self-reported pre-pregnancy weight and measured early pregnancy BMI (<18.5 , $18.5\text{--}24.9$, $25\text{--}29.9$, $>30\text{ kg/m}^2$), educational attainment (≤ 6 , $7\text{--}12$, >12 years), maternal ethnicity (Mestizos of mixed Amerindian and European descent vs. others), employment status (employed vs. not employed), marital status (married or living with partner vs. other), difficulty in paying medical care (hard vs. not very hard), difficulty in paying basic food (hard vs. not very hard), planned pregnancy (yes vs. no), parity (0, 1, 2, ≥ 3), and gestational age in weeks at the time of interview.

Following structured interviews, maternal non-fasting blood samples were collected in 7 ml plain (red-top) vacutainer tubes. Blood samples were kept on wet ice and processed within 20 minutes of phlebotomy. The samples were centrifuged at 850g for 20 minutes at 4°C. Fractions were aliquoted into cryovials and stored at -80°C until analysis. Serum BDNF concentrations were measured using a competitive enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, Minnesota). Serum CRP concentrations were measured by an ultra-sensitive competitive immunoassay (Dade Behring, Deerfield, Illinois). The intra- and inter-assay coefficients of variation for BDNF and CRP measurement were both $< 8\%$.

Statistical analysis

Characteristics of the study population were expressed as mean $\pm$ standard deviation (SD) for continuous variables and percentage for categorical variables. Visual inspection of quantile-quantile (Q-Q) plot and histogram were used to check for normality. Serum CRP concentrations were right skewed and natural logarithm transformation was made to obtain a normal distribution. Pearson's correlation coefficients were calculated to estimate the correlations between BDNF concentrations and continuous covariates. Continuous covariates were then transformed into categorical variables. We tested the normality and homogeneity of variances assumption, and analysis of variance (ANOVA) was used to compare the unadjusted BDNF concentrations according to categorical variables if the assumptions hold, otherwise we used nonparametric test. Adjusted BDNF concentrations according to each variables were obtained by including all the variables in the generalized linear model and calculating the least square means of BDNF. Tukey-Kramer method was used to adjust for post-hoc pairwise comparisons of adjusted BDNF concentrations. Multivariable linear regression models were used to determine the possible predictors of early pregnancy serum BDNF concentrations. We fitted two models. In the first model, all potential predictors were included. Secondly, we fitted a parsimonious model using stepwise selection with a removal level of 0.10. Least square estimates of β and 95% confidence interval (95%CI) were calculated. Before fitting the model, relationships between variables were examined to check for collinearity. All the analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). A two-tailed P value of < 0.05 was considered to be statistically significant.

Results

Characteristics of the study population are summarized in Table 1. The mean age of the population was 28.0 ± 6.2 years. 36.8% and 49.7% of the participants were overweight with mean pre-pregnancy and early pregnancy BMI of 25.1 ± 3.9 kg/m² and 25.5 ± 4.2 kg/m², respectively. The mean gestational age at blood collection was 9.3 ± 3.5 weeks. The majority of the study population was Mestizo (mixed race, 75.5%) and had more than 7 years of formal education (95.6%). Only 44.1% of the study population were employed and 52.8% of the study population had difficulty in paying basic food during pregnancy. Roughly half of the women were nulliparous. Approximately, 4.6% and 22.3% of the women reported tobacco smoking and alcohol consumption during the current pregnancy, respectively. A total of 28.5% of the participants had moderate antepartum depressive symptoms.

Early pregnancy serum BDNF concentrations were positively correlated with maternal age ($r = 0.16$, $P < 0.001$) and early pregnancy BMI ($r = 0.17$, $P < 0.001$) in the bivariate analysis. The Pearson's correlations were slightly attenuated after adjusting for other variables. Early pregnancy serum BDNF concentrations were negatively correlated with gestational age at blood collection ($r = -0.21$, $P < 0.001$) and serum CRP concentrations ($r = -0.07$, $P < 0.05$). Adjusting for other variables (maternal age, early pregnancy BMI, gestational age at blood collection and antepartum depressive symptoms) did not result in substantial changes in the correlations (Table 2). Results from ANOVA showed statistically significant differences in serum BDNF concentrations in respect to maternal age, early pregnancy BMI, parity,

gestational age and antepartum depressive symptoms. Tobacco smoking and alcohol consumption during pregnancy were not found to be associated with serum BDNF concentrations (Table 3).

The adjusted means (95%CI) of early pregnancy serum BDNF concentrations according to categorical variables were shown in figures (Fig. 1). A gradient increasing trend was observed in adjusted BDNF concentrations with increasing maternal age (Fig. 1a, $P_{trend} = 0.0091$) and early pregnancy BMI (Fig. 1b, $P_{trend} < 0.0001$). A decreasing trend was observed in adjusted BDNF concentrations with increasing gestational age (Fig. 1c, $P_{trend} < 0.0001$). Participants with moderate antepartum depressive symptoms (PHQ-9 score ≥ 10) had lower serum BDNF concentrations compared to participants with no/mild antepartum depressive symptoms (PHQ-9 score < 10) (Fig. 1d, $P = 0.0483$). The difference in adjusted serum BDNF concentrations with respect to difficulty in paying basic food (Fig. 1e) and alcohol consumption (Fig. 1f) status were not statistically significant.

Parity and maternal age were highly correlated, thus we did not include parity in the multivariable model. The parsimonious multivariable linear regression model showed that maternal age ($\beta = 0.11$, $P = 0.001$), early pregnancy BMI ($\beta = 1.58$, $P < 0.001$), gestational age at blood collection ($\beta = -0.33$, $P < 0.001$) and serum CRP concentrations ($\beta = -0.57$, $P = 0.002$) were correlates of early pregnancy serum BDNF concentrations. One year increase in maternal age was associated with a 0.11 ng/ml increase in early pregnancy serum BDNF concentrations. Similarly, one kg/m² increase in early pregnancy BMI was associated with a 1.58 ng/ml increase in early pregnancy serum BDNF concentrations. One week increase in gestational age at blood collection was associated with a 0.33 ng/ml decrease in early pregnancy serum BDNF concentrations. Similarly, one mg/L increase in serum CRP concentrations was associated with a 0.57 ng/ml decrease in early pregnancy serum BDNF concentrations. Similar results were obtained in the full model (Table 4).

Discussion

To the best of our knowledge, this is the first study to explore the correlates of early pregnancy serum BDNF concentrations. Results from our study indicated that maternal age, early pregnancy BMI, gestational age at blood collection, presence of moderate antepartum depressive symptoms (PHQ-9 score ≥ 10) and early pregnancy serum CRP concentrations were cross-sectionally associated with early pregnancy serum BDNF concentrations. BDNF has been reported to cross the blood-brain barrier in both directions (Pan et al. 1998), and a strong correlation ($r = 0.81$, $P < 0.01$) has been found between serum and cortical BDNF concentrations (Karege et al. 2002). Thus, trends in serum BDNF concentrations would be expected to reflect corresponding trends in BDNF concentrations in the brain.

Our study included pregnant women with age of 18–48 years, and found a significant increase in early pregnancy serum BDNF concentrations with increasing age. Our results were supported by findings reported by Webster (Webster et al. 2002). They have found that BDNF mRNA expression in the dorsolateral prefrontal cortex was relatively low during adolescence (14–18 years), peaked during young adulthood (20–24 years), and was maintained at a constant level throughout adulthood (34–43 years) (Webster et al. 2002).

However, our results were inconsistent with findings reported by Lommatzsch et al, in their study of 140 healthy men and non-pregnant women (20–60 years old), they have found that plasma BDNF concentrations were significantly lower in subjects with age of 48–60 years compared to younger subjects (20–47 years old) (Lommatzsch et al. 2005). Apart from the difference in biosamples, the inconsistency of results across studies may be partly explained by the age differences in the different populations studied to date. In addition, our study samples were from women at early pregnancy. BDNF concentrations have been shown to decrease at 37 weeks of gestation, compared to non-pregnant women (Lommatzsch et al. 2006). Thus, pregnancy itself may cause physiological changes of BDNF concentrations and, may explain heterogeneity in findings among pregnant and non-pregnant women.

Since BDNF plays a critical role in neurogenesis and neural plasticity in the central nervous system, the increase of BDNF mRNA during early life period reflects the structurally and functionally maturing process of the human brain, which lasts until adulthood. This can explain the positive correlation between maternal age and early pregnancy serum BDNF concentrations in our population. In addition to the neuron cells, there were several potential sources of circulating BDNF, including vascular endothelial, smooth muscle cells and activated macrophages or lymphocytes (Donovan et al. 1995; Kerschensteiner et al. 1999; Lommatzsch et al. 1999). Functional alterations in these cells during the aging process may also contribute to the decrease in circulating BDNF concentrations in relatively older populations (48–60 years).

Parity was correlated with early pregnancy serum BDNF concentrations in the bivariate analysis. This can be explained by the strong correlation between parity and maternal age.

We found a positive correlation between early pregnancy BMI and serum BDNF concentrations. Our results were consistent with findings among newly diagnosed type 2 diabetes patients. Suwa et al., in their study of 24 newly diagnosed female type 2 diabetes patients, have reported that serum BDNF concentrations were significantly increased, compared to healthy controls and positively associated with BMI (Suwa et al. 2006). However, our results were inconsistent with findings from some other studies that have found an association between decreased serum BDNF concentrations and the risk of diabetes and obesity (El-Gharbawy et al. 2006).

There has been some evidence that BDNF administration to obese diabetic animals reversed their pathophysiological conditions. Intermittent BDNF administration ameliorated glucose metabolism, increased energy expenditure and induced appetite suppression in obese diabetic mice (Yamanaka et al. 2008). This Peruvian population tended to be overweight with a mean pre-pregnancy BMI of $25.1 \pm 3.9 \text{ kg/m}^2$. Increase in weight gain during pregnancy may lead to an increase in BMI. It is possible that BDNF concentrations increase in this population to enhance energy metabolism, thus compensating for the possible pathophysiological conditions caused by being overweight during pre-pregnancy and increasing BMI during pregnancy, and prevent subsequent adverse outcomes.

The inverse correlation between early pregnancy serum BDNF and CRP concentrations was statistically significant though modest in this population. A longitudinal study has shown an

increasing trend in serum CRP concentrations with gestational age from 5–20 weeks in normal pregnancies (Mei et al. 2016), which suggests elevated inflammation during normal pregnancy. Inflammation was considered neurotoxic. For example, inflammatory cytokines interferon- γ (IFN- γ) and tumor necrosis factor- α (TNF- α) have been reported to induce glutamate agonists and nitric oxide (Chao et al. 1995). On the other hand, immune cells have been shown to produce and secrete BDNF in inflammatory conditions (Kerschensteiner et al. 1999). Studies have found that neurons of dorsal root ganglia expressed BDNF after peripheral inflammation (Chao et al. 1995). The expression of BDNF in immune cells and neuron cells may play a neuroprotective role during inflammation. The balance between the inflammatory neurotoxic effect and neuroprotective effect is crucial to the maternal-fetal relation as well as to protection of maternal and fetal neurons from inflammatory injuries.

Results from our study indicated decreased serum BDNF concentrations with increasing gestational age during early pregnancy (range: 4–16 weeks). Animal experiments have demonstrated the transplacental transport of BDNF during pregnancy, which may play a role in fetal brain development (Kodomari et al. 2009). It was speculated that maternal BDNF was transported to the fetal circulation to fulfill the requirements of fetal development during early pregnancy. At as early as the third week of gestation, the fetal brain begins to develop. At 8 weeks of gestation, the nerve cells begin to branch out to connect with one another and form primitive neural pathways. As with fetal brain development, the increasing requirement of BDNF in the fetus may contribute to the decrease in maternal serum BDNF concentrations as pregnancy progresses.

We found no evidence of a statistically significant association between early pregnancy serum BDNF concentrations and severity of antepartum depressive symptoms. However, subjects with moderate antepartum depressive symptoms (PHQ-9 score 10) had lower early pregnancy serum BDNF concentrations, compared to subjects with no/mild antepartum depressive symptoms (PHQ9 score <10). Our previous study has shown that in this Peruvian population, women with serum BDNF concentrations 25.31 ng/ml had 1.61-fold increased odds of antepartum depression as compared with women with BDNF concentrations >25.31 ng/ml (Fung et al. 2015). Previous studies carried out in men and non-pregnant women have shown inconsistent findings in regarding to the association of depression and BDNF concentrations. Azevedo et al. have reported that serum BDNF concentrations was significantly lower in depressed patients compared to healthy controls (de Azevedo Cardoso et al. 2014). However, Jevtovic et al. found that serum BDNF concentrations were not significantly different according to severity of depression (Jevtovic et al. 2011). The results of our study and those of others suggest the potential merits of early identification of antepartum depressive symptoms and effective interventions to avoid the adverse pregnancy outcomes associated with decreased BDNF concentrations.

We found no evidence of associations between tobacco smoking or alcohol consumption during pregnancy with BDNF concentrations. Smoking cessation was associated with weight gain, and increased energy expenditure was observed in smokers during light activity when compared with nonsmokers (Hultquist et al. 1995). Epidemiologic studies also suggested an association between alcohol consumption and lower percentage of body fat in the general population (Liangpunsakul et al. 2010). These findings indicate that both tobacco

smoking and alcohol consumption affect energy metabolism. In addition, findings from animal experiments showed an association between acute nicotine administration and decrease in BDNF mRNA levels in hippocampus (Kim et al. 2007). In alcohol-dependent patients, BDNF concentration was lower compared with non-drinkers (Joe et al. 2007). Given the role of BDNF in regulating energy balance, it is possible that the effect of tobacco smoking and alcohol consumption on energy metabolism is mediated by BDNF. Due to the low prevalence of both alcohol and tobacco use in our study sample, we were not able to test this hypothesis.

The limitations of our study should be addressed. The cross-sectional design does not allow us to evaluate the temporal relationship of the alterations in serum BDNF concentrations and the potential correlates. The study was carried out among a low-income Peruvian population with moderate antepartum depressive symptoms present in 28.5% of the population, which may limit the generalizability of the finding to other populations.

In conclusion, early pregnancy serum BDNF concentrations were positively associated with maternal age and early pregnancy BMI but negatively associated with gestational age at blood collection and early pregnancy serum CRP concentrations. Moderate antepartum depressive symptoms (PHQ-9 score 10) was associated with lower serum BDNF concentrations. These findings suggest that physiological changes during pregnancy may affect serum BDNF concentrations in early pregnancy. Given its role in neurogenesis and energy metabolism, these alterations may impact fetal-placental development. Longitudinal studies are needed to examine alterations of BDNF concentrations during pregnancy and elucidate the role of BDNF in fetal-placental development.

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Fig. 1.

Adjusted early pregnancy serum BDNF concentrations (ng/ml) according to categorical variables, PrOMIS Cohort Study, Lima, Peru (N = 982).

Abbreviations: BDNF, brain-derived neurotrophic factor; BMI, body mass index.

Variables in the adjusted model include maternal age, early pregnancy BMI, gestational age, LnCRP, difficulty in paying basics including food, alcohol consumption, and antepartum depressive symptoms. A total PHQ-9 score ≥ 10 was considered as presence of antepartum depressive symptoms.

Pairwise comparison was adjusted by Tukey-Kramer method.

Table 1

Characteristics of the study population with brain-derived neurotrophic factor (BDNF, ng/ml) measured, PrOMIS Cohort Study, Lima, Peru (N = 982).

Characteristics	N (%) / Mean $\pm$ SD
Maternal age (years)	28.0 $\pm$ 6.2
<25	326 (33.3)
25 – 29	290 (29.5)
30 – 34	195 (19.9)
35	171 (17.4)
Pre-pregnancy body mass index (kg/m ²)	25.1 $\pm$ 3.9
<18.5	12 (1.2)
18.5–24.9	449 (45.7)
25.0–29.9	265 (27.0)
30.0	96 (9.8)
Early pregnancy body mass index (kg/m ²)	25.5 $\pm$ 4.2
<18.50	19 (1.9)
18.50–24.99	467 (47.6)
25.0–29.99	363 (37.0)
30.0	125 (12.7)
Gestational age at blood collection (weeks)	9.3 $\pm$ 3.5
≤ 4	80 (8.15)
5 – 8	401 (40.84)
8 – 12	312 (31.77)
> 12	181 (18.43)
Education (years)	
< 6	39 (4.0)
7–12	560 (57.0)
>12	379 (38.6)
Race	
Mestizo	741 (75.5)
Others	239 (24.3)
Employed during pregnancy	133 (44.1)
Difficulty in paying basic food	519 (52.8)
Unplanned pregnancy	553 (56.3)
Parity	
0	489 (49.8)
1	295 (30.0)
2	146 (14.9)
≥ 3	52 (5.3)
Tobacco smoking during pregnancy	
No	931 (95.4)
Yes	45 (4.6)

Characteristics	N (%) / Mean $\pm$ SD
Alcohol consumption during pregnancy	219 (22.3)
PHQ-9 score	7.60 $\pm$ 5.37
Antepartum depressive symptoms ^a	
No/mild	702 (71.5)
Moderate	280 (28.5)
Serum BDNF (ng/ml)	21.6 $\pm$ 6.3
Serum CRP (mg/L) ^b	3.5 $\pm$ 0.12

Abbreviations: SD, Standard deviation; CRP, C-reactive protein; PHQ-9, Patient health questionnaire-9.

^a A total PHQ-9 score ≥ 10 was considered as presence of moderate antepartum depressive symptoms. A total PHQ-9 score <10 was considered as presence of no/mild antepartum depressive symptoms.

^b Geometric mean.

Table 2

Pearson’s correlation coefficient for early pregnancy serum BDNF Concentrations with covariates, PrOMIS Cohort Study, Lima, Peru (N = 982).

	Maternal age (years)	GA (weeks)	Early pregnancy BMI (kg/m ²)	LnCRP ^a	PHQ-9 score
Unadjusted	0.16 ***	-0.21 ***	0.17 ***	-0.07 *	-0.06
Adjusted for maternal age	---	-0.21 ***	0.13 ***	-0.09 **	-0.05
Adjusted for maternal age and BMI	0.10 **	-0.20 ***	0.13 ***	-0.13 ***	-0.04
Adjusted for maternal age, BMI and GA	0.10 **	-0.20 ***	0.12 ***	-0.09 **	-0.03
Adjusted for maternal age, BMI, GA and PHQ-9 score	0.11 **	-0.21 ***	0.12 ***	-0.09 **	-0.03

Abbreviations: BDNF, brain-derived neurotrophic factor; GA, gestational age; CRP, C-reactive protein; BMI, body mass index; PHQ-9, Patient Health Questionnaire-9.

* $P < 0.05$,
** $P < 0.01$,
*** $P < 0.001$.

^a Natural logarithm transformation was applied to CRP concentrations and LnCRP was used in the correlation analysis.

Table 3

Early pregnancy brain-derived neurotrophic factor concentrations (BDNF, ng/ml) according to categorical variables, PrOMIS Cohort Study, Lima, Peru (N = 982).

Characteristics	N (%)	Mean $\pm$ SD	Median (IQR)	<i>P</i> ^a
Maternal age (years)				
<25	326 (33.3)	20.36 $\pm$ 6.03	19.49 (16.23–23.69)	<0.0001
25 – 29	290 (29.5)	21.61 $\pm$ 6.29	21.25 (17.30–25.37)	
30 – 34	195 (19.9)	22.61 $\pm$ 6.07	22.46 (18.24–26.27)	
35	171 (17.4)	22.56 $\pm$ 6.73	22.11 (18.08–26.95)	
Early pregnancy BMI (kg/m ²)				
<18.5	12 (1.2)	18.61 $\pm$ 6.71	18.06 (14.69–23.62)	<0.0001
18.5–24.9	449 (45.7)	20.66 $\pm$ 5.89	19.75 (16.83–24.19)	
25.0–29.9	265 (27.0)	22.04 $\pm$ 6.41	21.43 (17.66–26.24)	
30.0	96 (9.8)	24.08 $\pm$ 6.60	23.82 (20.95–27.54)	
Parity				
0	489 (49.8)	21.12 $\pm$ 6.04	20.54 (16.98–24.66)	0.016
1	295 (30.0)	22.29 $\pm$ 6.83	21.97 (17.74–26.45)	
2	146 (14.9)	21.03 $\pm$ 6.27	20.77 (17.25–24.96)	
≥ 3	52 (5.3)	23.04 $\pm$ 5.12	22.18 (18.90–27.38)	
GA at blood collection (weeks)				
≤ 4	80 (8.2)	23.40 $\pm$ 6.66	22.73 (18.86–27.10)	<0.0001
5–8	401 (41.2)	22.67 $\pm$ 6.64	22.48 (17.94–26.71)	
9–12	312 (32.0)	20.79 $\pm$ 5.84	20.03 (16.98–24.47)	
≥ 13	181 (18.6)	19.42 $\pm$ 5.22	18.89 (15.73–22.59)	
Tobacco smoking				
No	931 (94.8)	21.65 $\pm$ 6.34	21.11 (17.34–25.56)	0.15
Yes	45 (4.6)	20.25 $\pm$ 5.60	19.47 (16.24–23.32)	
Alcohol consumption				
No	759 (77.3)	21.58 $\pm$ 6.39	20.80 (17.37–25.62)	0.93
Yes	219 (22.3)	21.54 $\pm$ 6.00	21.78 (17.24–25.07)	
Antepartum depressive symptoms ^b				
No/mild	702 (71.49)	21.87 $\pm$ 6.41	21.22 (17.39–25.87)	0.015
Moderate	280 (28.51)	20.79 $\pm$ 5.97	20.31 (17.08 – 24.20)	
Difficulty in paying basic food				
Not very hard	463 (47.2)	21.7 $\pm$ 6.2	21.20 (17.33 – 25.30)	0.62
Hard	519 (52.8)	21.5 $\pm$ 6.4	21.46 (17.32 – 25.40)	

Abbreviations: SD, Standard deviation; IQR, Interquartile range; BMI, Body mass index; GA, Gestational age ; PHQ-9, Patient Health Questionnaire-9.

^a *P*-value was calculated using analysis of variance (ANOVA). A *P*-value of less than 0.05 indicates significant difference in BDNF concentrations across groups.

^b A total PHQ-9 score ≥ 10 was considered as presence of moderate antepartum depressive symptoms; A total PHQ-9 score < 10 was considered as presence of no/mild antepartum depressive symptoms.

Table 4

Parameter estimates (95%CI) using linear regression model for early pregnancy serum brain-derived neurotrophic factor concentrations (BDNF, ng/ml) and predictors, PrOMIS Cohort Study, Lima, Peru (N = 982).

Covariates	Full model			Parsimonious model (stepwise selection)		
	β (SE)	95% CI	P-value	β (SE)	95% CI	P-value
Maternal age (years)	0.10 (0.03)	0.04 – 0.17	0.002	0.11 (0.03)	0.04 – 0.17	0.001
Early pregnancy BMI (kg/m ²)	1.57 (0.29)	0.99 – 2.14	<0.001	1.58 (0.29)	0.99 – 2.14	<0.001
GA at blood collection	-0.33 (0.06)	-0.44 – -0.22	<0.001	-0.33 (0.06)	-0.45 – -0.21	<0.001
LnCRP (mg/L) ^a	-0.57 (0.19)	-0.94 – -.20	0.003	-0.57 (0.19)	-0.94 – -0.20	0.002
Alcohol consumption	0.10 (0.47)	-0.82 – 1.02	0.83			
PHQ-9 score	-0.03 (0.04)	-0.10 – 0.04	0.38			
Difficulty in paying basic food	0.21 (0.40)	-0.56 – 0.99	0.59			

Abbreviations: 95% CI, confidence interval; SE, Standard error; BMI, Body mass index; GA, Gestational age; CRP, C-reactive protein; PHQ-9, Patient Health Questionnaire-9.

^aNatural logarithm transformation was applied to CRP concentrations and LnCRP was used in the model.