Published in final edited form as:

Arch Womens Ment Health. 2016 December ; 19(6): 979–986. doi:10.1007/s00737-016-0638-0.

Serum brain-derived neurotrophic factor (BDNF) concentrations in pregnant women with post-traumatic stress disorder and comorbid depression

Na Yang^{1,2}, Bizu Gelaye¹, Qiuyue Zhong¹, Marta B. Rondon³, Sixto E. Sanchez^{4,5}, and Michelle A. Williams¹

¹Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

²Institute of Reproductive and Child Health, Department of Epidemiology and Biostatistics, Peking University, Beijing, China

³Department of Medicine, Cayetano Heredia Peruvian University, Lima, Peru

⁴Universidad de Ciencias Aplicadas, Lima Peru

⁵Asociación Civil PROESA, Lima, Peru

Abstract

Purpose—There is accumulating evidence for the role of brain-derived neurotrophic factor (BDNF) in the pathophysiology of depression. However, the role of BDNF in the pathophysiology of post-traumatic stress disorder (PTSD) remains controversial; and no study has assessed BDNF concentrations among pregnant women with PTSD. We examined early-pregnancy BDNF concentrations among women with PTSD with and without depression.

Methods—A total of 2,928 women attending prenatal care clinics in Lima, Peru, were recruited. Antepartum PTSD and depression were evaluated using PTSD Checklist-Civilian Version (PCL-C) and Patient Health Questionnaire-9 (PHQ-9) scales, respectively. BDNF concentrations were measured in a subset of the cohort ($N = 944$) using a competitive enzyme-linked immunosorbent assay (ELISA). Logistic regression procedures were used to estimate odds ratios (OR) and 95% confidence intervals (95%CI).

Results—Antepartum PTSD (37.4%) and depression (27.6%) were prevalent in this cohort of low-income pregnant Peruvian women. Approximately 19.9% of participants had comorbid PTSD-depression. Median serum BDNF concentrations were lower among women with comorbid PTSD-depression as compared with women without either condition (Median [Interquartile range]: 20.44 [16.97–24.30] vs. 21.35 [17.33–26.01] ng/ml, $P = 0.06$). Compared to the referent group (those without PTSD and depression), women with comorbid PTSD-depression were 1.52-fold more likely to have low (< 25.38 ng/ml) BDNF concentrations (OR = 1.52; 95%CI 1.00–2.31). We observed no evidence of reduced BDNF concentrations among women with isolated PTSD.

Corresponding author: Dr. Bizu Gelaye, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Ave, K505F, Boston, MA 02115 USA, Telephone: 617-432-6477, Facsimile: 617-566-7805, bgelaye@hsph.harvard.edu.

Conflict of interest: The authors have no competing interests to declare.

Conclusion—BDNF concentrations in early pregnancy were only minimally and non-significantly reduced among women with antepartum PTSD. Reductions in BDNF concentrations were more pronounced among women with comorbid PTSD-depression.

Keywords

Peru; Biomarker; BDNF; Antepartum PTSD; Antepartum depression

Introduction

Post-traumatic stress disorder (PTSD) is a complex syndrome resulting from exposure to life-threatening events such as war, childhood adversity, physical and/or sexual abuse, car accidents, earthquakes or other natural disasters (American Psychiatric Association 2013). The lifetime prevalence of PTSD in the general population is estimated to be between 6% and 8% (Kessler et al. 1995; Kessler et al. 2005; Pietrzak et al. 2011). Women, as compared with men, have a greater risk of PTSD (Kessler et al. 1995; Breslau et al. 1997; Tolin and Foa 2006; Pietrzak et al. 2011); and the risks are particularly elevated during reproductive years. Of note, investigators have reported that PTSD symptoms are likely to peak closer to the time of parturition (Onoye et al. 2013). Overall, the prevalence of PTSD during pregnancy is estimated to be 2%-26% (Ross and Mclean 2006). Maternal antepartum PTSD has been associated with inadequate prenatal care (Kim et al. 2006), smoking during pregnancy (Lopez et al. 2011) and adverse infant outcomes such as preterm birth (Lipkind et al. 2010; Seng et al. 2011; Yonkers et al. 2014; Shaw et al. 2014), and low birth weight (Lipkind et al. 2010; Seng et al. 2011).

Brain-derived neurotrophic factor (BDNF), a neurotrophin that is involved in neuronal cell growth, survival, and synaptic plasticity (Binder and Scharfman 2004), is important for brain development, plasticity, and maintenance of neurons in adult life (Lewin and Barde 1996) and plays a critical role in the formation of long-term memory and other cognitive processes (Ernfors et al. 1990). A growing body of evidence indicates that patients with psychiatric disorders have altered peripheral BDNF concentrations, especially those with schizophrenia (Asevedo et al. 2013), depression (Castren and Rantamaki 2010; Bocchio-Chiavetto et al. 2010) and PTSD (Dell'Osso et al. 2009).

To date, however, no study has examined BDNF concentrations in pregnant women with PTSD. Our group has previously evaluated a sample of pregnant women and showed that BDNF concentrations were reduced in women with antepartum depression (Fung et al. 2015). However, it is currently unknown if BDNF concentrations are altered in women with PTSD symptomology with and without comorbid depression. Therefore, the objectives of this study were to (1) estimate the prevalence of antepartum PTSD among Peru women in early pregnancy and (2) examine the extent to which, if at all, serum BDNF concentrations are associated with antepartum PTSD with and without co-morbid depression.

Methods

The PrOMIS Cohort Study

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 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.

Enrolled participants were invited to participate in an interview where trained research personnel used a structured questionnaire to elicit information regarding maternal sociodemographic, lifestyle characteristics, medical and reproductive histories, and early life experiences of abuse and symptoms of mood and anxiety disorders. 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 March 2014. During this period, 3,541 eligible women were approached, and 3,045 (86%) agreed to participate. Of those enrolled, 117 participants did not complete the interview. Consequently, our estimation of antepartum PTSD prevalence for this cohort is based on a population of 2,928 pregnant women.

Maternal serum samples for a subgroup of the study cohort (i.e., the first 982 participants in study) were selected and BDNF concentrations were measured. After excluding women with missing information concerning PTSD symptoms, a total of 944 women had both PTSD information and BDNF concentrations available for study. Women excluded from these analyses did not differ in regards to sociodemographic and lifestyle characteristics as compared with those included.

Post-traumatic Stress Disorder

The Posttraumatic Stress Disorder Checklist – Civilian Version (PCL-C) was used to assess PTSD symptomatology. The PCL-C assesses PTSD using 17 items designed according to the Diagnostic and Statistical Manual of Mental (DSM-IV) criteria. For each item, participants are asked to indicate how much they have been bothered by each symptom over the past month on a 5-point Likert scale categorized as 1 (not at all), 2 (a little bit), 3 (moderately), 4 (quite a bit) and 5 (extremely) in regards to their most significant life event stressor. The PCL-C total score (i.e., sum of scores for the 17 items) ranges from 17 to 85.

The PCL-C has been shown to have excellent internal consistency, inter-rater reliability, test-retest reliability and convergent validity among both clinical and nonclinical populations (Wilkins et al. 2011; Conybeare et al. 2012; Mueser et al. 2001). The Spanish-language version of the PCL-C has been shown to have psychometric properties roughly similar to those reported for the English-language version (Marshall 2004). Findings from a study in our PrOMIS cohort indicate that a score of 26 will lead to good diagnostic efficiency with a sensitivity of 0.86 and a specificity of 0.63 (Personal Communication). Thus, in the present analysis, we used a score of 26 to denote PTSD.

Antepartum Depression

Antepartum depression was assessed using the Patient Health Questionnaire (PHQ-9), a nine-item, self-reported depression measure from the Primary Care Evaluation of Mental Disorders (Kroenke et al. 2001; Spitzer et al. 1999) diagnostic instrument. The instrument was derived from the criteria of the DSM-IV and assessed nine depressive symptoms, namely, anhedonia, depressed mood, trouble sleeping, feeling tired, change in appetite, guilt or worthlessness, trouble concentrating, feeling slowed down or restless, and suicidal thoughts, experienced over the last two weeks (14 days). The PHQ-9 score was calculated by assigning a score of 0, 1, 2, and 3, to the response categories of “not at all,” “several days,” “more than half the days” and “nearly every day” respectively. As a severity measure, the total score of PHQ-9 ranged from 0 to 27 with possible major depressive disorder (MDD) defined as total score ≥ 10 (Kroenke et al. 2001). The PHQ-9 has been widely used for depression screening in adult primary care settings and hospital settings. It has been translated into at least 25 languages (Furukawa 2010; Flynn et al. 2010) and successfully used to measure depression severity among US African Americans, Asian/Chinese Americans, Latinos, and non-Hispanic Whites (Chen et al. 2006; Huang et al. 2006). The Spanish language version of the PHQ-9 has been shown to be a reliable and efficient screening measure for depression severity in primary care (Wulsin et al. 2002; Zhong et al. 2014) and it has been validated among both prenatal and postpartum women.

Serum BDNF Assessments

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) with intra- and inter-assay coefficients of variation both $<8\%$. All assays were performed without knowledge of maternal PTSD status.

Statistical Analysis

The distribution of maternal socio-demographic characteristics, medical and reproductive histories according to antepartum PTSD status was examined. Since BDNF concentrations were not normally distributed, Wilcoxon sum-rank test was used to compare values across different groups. To estimate the relative association of antepartum PTSD with varying concentrations of BDNF, we categorized each subject according to quartiles determined by the distribution of serum BDNF concentrations among the entire study population. Logistic

regression procedures were used to calculate maximum likelihood estimates of odds ratios (OR) and 95% confidence intervals (95% CI), adjusted for potential confounding factors. Confounders were defined as those factors which altered the unadjusted odds ratios by at least 10%. Maternal age, parity and early pregnancy body mass index (BMI) were considered to be potential confounders. To assess co-morbid antepartum PTSD and depression status in relation to serum BDNF concentrations, we categorized participants into the following four groups based on the combinations of these two disorders: (1) no PTSD and no depression; (2) no PTSD and yes depression (isolated depression); (3) yes PTSD and no depression (isolated PTSD); and (4) PTSD and depression. Women with no PTSD and no depression were used as the referent group. All the analyses were performed using Stata software version 12.0 (StataCorp LP, College Station, TX, USA). A two-tailed P value of <0.05 was considered to be statistically significant.

Results

Antepartum PTSD was prevalent in this cohort of low-income pregnant Peruvian women (37.4%). Characteristics of study participants distributed according to PTSD symptomatology are summarized in Table 1. Briefly, women with antepartum PTSD tended to be younger, to have more difficulty accessing basic foods and report that their pregnancy was unplanned, as compared with women without PTSD. Overall, approximately 27.6% of the cohort had depression and approximately 19.9% of participants had comorbid PTSD-depression. As shown in Table 2, women with comorbid PTSD-depression were younger, less likely to be nulliparous and less likely to have planned the current pregnancy compared to women without either condition.

We observed no significant differences in maternal early pregnancy serum BDNF concentrations with antepartum PTSD status (Median [Interquartile range]: 21.15 [17.33-25.82] vs. 20.67 [17.27-24.70] ng/ml, $P = 0.21$). Estimated associations of antepartum PTSD status in relation to maternal early pregnancy BDNF concentrations are shown in Table 3. The adjusted ORs (95% CIs) for antepartum PTSD were 1.20 (95% CI 0.81-1.78), 1.24 (95% CI 0.84-1.83), 1.38 (95% CI 0.94-2.03) and 1.00 for successive quartiles (lowest to highest quartile), with the highest quartile as the referent group. There was no evidence of a statistically significant linear trend in odds of antepartum PTSD across decreasing quartiles of BDNF (P -value for trend = 0.50 in the adjusted model). As shown in the bottom panel of Table 3, compared to women with BDNF concentrations in the highest quartile (> 25.38 ng/ml), women with lower concentrations (< 25.38 ng/ml, the lowest three quartiles combined) had no clear evidence of an increased odds of antepartum PTSD (OR=1.35; 95% CI 0.98-1.88) after adjustments for confounding factors.

We next evaluated maternal serum BDNF concentrations among women according to their antepartum PTSD and depression status (no PTSD or depression, isolated depression, isolated PTSD, and comorbid PTSD-depression). Median serum BDNF concentrations were lower among women with comorbid PTSD-depression as compared with women without either condition (Median [Interquartile range]: 20.44 [16.97-24.30] vs. 21.35 [17.33-26.01] ng/ml, $P = 0.06$), although the difference did not reach statistical significance. BDNF concentrations were essentially similar for the other three groups (Figure 1). Finally, we

evaluated the odds of low serum BDNF concentrations (< 25.38 vs. 25.38 ng/ml) in relation to isolated depression, isolated PTSD and comorbid PTSD-depression using those with no PTSD and no depression as the referent group. Women with comorbid PTSD-depression had 1.52-fold increased odds of having lower serum BDNF concentration (< 25.38 ng/ml) as compared with women who had neither disorders (OR=1.52; 95% CI 1.00-2.31). Compared with the referent group, women with isolated depression had a 1.83-fold increased odds of having lower serum BDNF concentrations, although this association did not reach statistical significance (OR=1.83; 95% CI 0.96-3.46). We observed no evidence of an association of reduced BDNF concentrations with isolated PTSD (OR=1.20; 95% CI 0.78-1.87) (Table 4).

Discussion and Conclusion

The prevalence of antepartum PTSD and depression in this cohort of pregnant Peruvian women was 37.4% and 27.6%, respectively. The prevalence of comorbid PTSD-depression was 19.9%. This is the first study to take into account the comorbid occurrence of PTSD and depression and to assess serum BDNF concentrations in women with comorbid PTSD-depression. We found BDNF concentrations in early pregnancy were only minimally and non-significantly reduced among women with antepartum PTSD. Reductions in BDNF concentrations were more pronounced among women with comorbid PTSD-depression when compared with women with neither condition.

To the best of our knowledge, this is the first study to examine maternal serum BDNF concentrations in relation to antepartum PTSD while considering co-morbid depression. We found no significant reduction in serum BDNF concentrations in pregnant Peruvian women with antepartum PTSD. Our findings are consistent with some prior studies of BDNF concentrations and PTSD in men, non-pregnant women and children (Su et al. 2015; Simsek et al. 2015; Boone et al. 2011; Molendijk et al. 2012). For example, Bonne, *et al.* in their study of 16 medication-free outpatients with chronic PTSD due to physical and/or sexual abuse or motor vehicle accidents (age: 36 ± 11.4 years), reported similar BDNF concentrations from cerebrospinal fluids between PTSD patients and healthy controls (1.00 ± 0.52 vs. 0.83 ± 0.44 pg/ml; $P = 0.39$) (Bonne et al. 2011). Our results, however, differ from some previous reports that showed decreased BDNF concentrations in PTSD patients (Angelucci et al. 2014; Dell'Osso et al. 2009). Angelucci, *et al.* in their study of 23 drug-free outpatients with PTSD and 19 outpatients with trauma exposure who have not developed PTSD, reported decreased serum BDNF concentrations in PTSD patients as compared to controls (4018.1 ± 359 vs. 4886.6 ± 180 pg/ml, $P < 0.05$) (Angelucci et al. 2014). Dell'Osso, *et al.* reported decreased plasma BDNF concentrations in patients with PTSD ($N=18$) as compared to healthy controls ($N=18$) (5.3 ± 1.1 vs. 7.4 ± 1.5 ng/ml; $P < 0.001$) (Dell'Osso et al. 2009).

Inconsistencies in results across studies may, in part, be attributable to a number of differences in type of assays and tissues (e.g., serum vs. plasma) used to measure BDNF concentrations. Further, differences in the study population characteristics including severity and the presence of co-morbid psychiatric characteristics may account for some variations in results across studies. Lastly, failure to account for demographic, metabolic and lifestyle

characteristics known to be associated with BDNF concentrations may have contributed to residual confounding and variability on associations observed across studies.

Observed associations of antepartum PTSD (and comorbid PTSD-depression) with decreased BDNF concentrations are biologically plausible. Briefly, chronic stress is known to impair various endocrine, physiological and neuronal functions, and is often associated with higher vulnerability to psychiatric disorders and cognitive impairments. Available evidence indicates that BDNF may play a role in stress-related psychiatric disorders. For example, in animal studies BDNF concentrations are decreased after chronic stress (Roceri et al. 2004; Murakamu et al. 2005). Further, serum BDNF concentrations are known to be reduced in stress-related major depressive disorders (Karege et al. 2002; Diniz et al. 2010; Shimizu et al. 2003) and this reduction appears to be mediated partly via stress-induced glucocorticoid release from adrenal glands (Smith et al. 1995). Together, findings from human and animal studies suggest possibly underlying biological mechanisms to support a possible role of altered BDNF synthesis in stress-related psychiatric disorders.

To the best of our knowledge, this is the first study to show that co-morbid PTSD and depression is associated with reduced BDNF concentrations in pregnant women. These findings extend earlier reports and suggest that alterations in BDNF may be involved in the pathogenesis of stress-related mental disorders among pregnant women. BDNF may be a biomarker in stress-related mood disorders, particularly since several earlier studies have found decreased concentrations of serum BDNF in various stress-related mental disorders, such as depression (Karege et al. 2002; Fung et al. 2015) and post-traumatic stress disorder (Bocchio-Chiavetto et al. 2010).

Acknowledgments

This research was supported by an award from the National Institutes of Health (R01-HD-059835). The NIH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. Dr. Na Yang was supported by the China Scholarship Council. The authors wish to thank the dedicated staff members of Asociacion Civil Proyectos en Salud (PROESA), Peru and Instituto Materno Perinatal, Peru for their expert technical assistance with this research.

References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edn.. American Psychiatric Publishing; Arlington, VA: 2013.
- Angelucci F, Ricci V, Gelfo F, Martinotti G, Brunetti M, Sepede G, Signorelli M, Aguglia E, Pettorruso M, Vellante F, Di GM, Caltagirone C. BDNF serum levels in subjects developing or not post-traumatic stress disorder after trauma exposure. *Brain Cogn*. 2014; 84:118–122. [PubMed: 24362070]
- Asevedo E, Gadelha A, Noto C, Mansur RB, Zugman A, Belangero SI, Berberian AA, Scarpato BS, Leclerc E, Teixeira AL, Gama CS, Bressan RA, Brietzke E. Impact of peripheral levels of chemokines, BDNF and oxidative markers on cognition in individuals with schizophrenia. *J Psychiatr Res*. 2013; 47:1376–1382. [PubMed: 23806580]
- Binder DK, Scharfman HE. Brain-derived neurotrophic factor. *Growth Factors*. 2004; 22:123–131. [PubMed: 15518235]
- Blake D, Weathers F, Nagy L, Kaloupek D, Klauminzer G, Charney D, Keane T, Buckley TC. Clinician-administered PTSD scale (CAPS). Boston (Mass). 1990; 7
- Bocchio-Chiavetto L, Bagnardi V, Zanardini R, Molteni R, Nielsen MG, Placentino A, Giovannini C, Rilloso L, Ventriglia M, Riva MA, Gennarelli M. Serum and plasma BDNF levels in major

depression: a replication study and meta-analyses. *World J Biol Psychiatry*. 2010; 11:763–773. [PubMed: 20334574]

Bonne O, Gill JM, Luckenbaugh DA, Collins C, Owens MJ, Alesci S, Neumeister A, Yuan P, Kinkead B, Manji HK, Charney DS, Vythilingam M. Corticotropin-releasing factor, interleukin-6, brain-derived neurotrophic factor, insulin-like growth factor-1, and substance P in the cerebrospinal fluid of civilians with posttraumatic stress disorder before and after treatment with paroxetine. *J Clin Psychiatry*. 2011; 72:1124–1128. [PubMed: 21208596]

Breslau N, Davis GC, Andreski P, Peterson EL, Schultz LR. Sex differences in posttraumatic stress disorder. *Arch Gen Psychiatry*. 1997; 54:1044–1048. [PubMed: 9366662]

Castren E, Rantamaki T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Dev Neurobiol*. 2010; 70:289–297. [PubMed: 20186711]

Chen T, Huang F, Chang C, Chung H. Using the PHQ-9 for depression screening and treatment monitoring for Chinese Americans in primary care. *Psychiatr Serv*. 2006; 57:976–981. [PubMed: 16816282]

Conybeare D, Behar E, Solomon A, Newman MG, Borkovec TD. The PTSD Checklist-Civilian Version: reliability, validity, and factor structure in a nonclinical sample. *J Clin Psychol*. 2012; 68:699–713. [PubMed: 22517497]

Dell'Osso L, Carmassi C, Del Debbio A, Catena Dell'Osso M, Bianchi C, da Pozzo E, Origlia N, Domenici L, Massimetti G, Marazziti D, Piccinni A. Brain-derived neurotrophic factor plasma levels in patients suffering from post-traumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; 33:899–902. [PubMed: 19409951]

Diniz BS, Teixeira AL, Talib LL, Mendonça VA, Gattaz WF, Forlenza OV. Serum brain-derived neurotrophic factor level is reduced in antidepressant-free patients with late-life depression. *World J Biol Psychiatry*. 2010; 11:550–555. [PubMed: 20109109]

Ernfors P, Wetmore C, Olson L, Persson H. Identification of cells in rat brain and peripheral tissues expressing mRNA for members of the nerve growth factor family. *Neuron*. 1990; 5:511–526. [PubMed: 2206535]

Flynn HA, Sexton M, Ratliff S, Porter K, Zivin K. Comparative performance of the Edinburgh Postnatal Depression Scale and the Patient Health Questionnaire-9 in pregnant and postpartum women seeking psychiatric services. *Psychiatry Res*. 2011; 187:130–134. [PubMed: 21122923]

Franklin TB, Perrot-Sinal TS. Sex and ovarian steroids modulate brain-derived neurotrophic factor (BDNF) protein levels in rat hippocampus under stressful and non-stressful conditions. *Psychoneuroendocrinology*. 2006; 31:38–48. [PubMed: 15996825]

Fung J, Gelaye B, Zhong QY, Rondon MB, Sanchez SE, Barrios YV, Hevner K, Qiu C, Williams MA. Association of decreased serum brain-derived neurotrophic factor (BDNF) concentrations in early pregnancy with antepartum depression. *BMC Psychiatry*. 2015; 15:43. [PubMed: 25886523]

Furukawa TA. Assessment of mood: guides for clinicians. *J Psychosom Res*. 2010; 68:581–589. [PubMed: 20488276]

Huang FY, Chung H, Kroenke K, Delucchi KL, Spitzer RL. Using the patient health questionnaire-9 to measure depression among racially and ethnically diverse primary care patients. *J Gen Intern Med*. 2006; 21:547–552. [PubMed: 16808734]

Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res*. 2002; 109:143–148. [PubMed: 11927139]

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry*. 2005; 62:593–602. [PubMed: 15939837]

Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1995; 52:1048–1060. [PubMed: 7492257]

Kim HG, Mandell M, Crandall C, Kuskowski MA, Dieperink B, Buchberger RL. Antenatal psychiatric illness and adequacy of prenatal care in an ethnically diverse inner-city obstetric population. *Arch Womens Ment Health*. 2006; 9:103–107. [PubMed: 16380813]

- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Me.* 2001; 16:606–613.
- Lewin GR, Barde YA. Physiology of the neurotrophins. *Annu Rev Neurosci.* 1996; 19:289–317. [PubMed: 8833445]
- Lipkind HS, Curry AE, Huynh M, Thorpe LE, Matte T. Birth outcomes among offspring of women exposed to the September 11, 2001, terrorist attacks. *Obstet Gynecol.* 2010; 116:917–925. [PubMed: 20859156]
- Lopez WD, Konrath SH, Seng JS. Abuse-related post-traumatic stress, coping, and tobacco use in pregnancy. *Obstet Gynecol.* 2011; 40:422–431.
- Marshall GN. Posttraumatic Stress Disorder Symptom Checklist: Factor structure and English–Spanish measurement invariance. *J Trauma Stress.* 2004; 17:223–230. [PubMed: 15253094]
- McEwen C. Molecular mechanisms of neuroplasticity and pharmacological implications: the example of tianeptine. *Eur Neuropsychopharmacol.* 2004; S5:S497–502.
- Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Prickaerts J, Oude Voshaar RC, Elzinga BM. Gender specific associations of serum levels of brain-derived neurotrophic factor in anxiety. *World J Biol Psychiatry.* 2012; 13:535–543. [PubMed: 21888560]
- Mueser KT, Rosenberg SD, Fox L, Salyers MP, Ford JD, Carty P. Psychometric evaluation of trauma and posttraumatic stress disorder assessments in persons with severe mental illness. *Psychol Assess.* 2001; 13:110–117. [PubMed: 11281032]
- Murakami S, Imbe H, Morikawa Y, Kubo C, Senba E. Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. *Neurosci Res.* 2005; 53:129–139. [PubMed: 16024125]
- Onoye JM, Shafer LA, Goebert DA, Morland LA, Matsu CR, Hamagami F. Changes in PTSD symptomatology and mental health during pregnancy and postpartum. *Arch Womens Ment Health.* 2013; 16:453–463. [PubMed: 23797809]
- Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *J Anxiety Disord.* 2011; 25:456–465. [PubMed: 21168991]
- Roceri M, Cirulli F, Pessina C, Peretto P, Racagni G, Riva MA. Postnatal repeated maternal deprivation produces age-dependent changes of brain-derived neurotrophic factor expression in selected rat brain regions. *Biol Psychiatry.* 2004; 55:708–714. [PubMed: 15038999]
- Ross LE, McLean LM. Anxiety disorders during pregnancy and the postpartum period: A systematic review. *J Clin Psychiatry.* 2006; 67:1285–1298. [PubMed: 16965210]
- Seng JS, Low LK, Sperlich M, Ronis DL, Liberzon I. Post-traumatic stress disorder, child abuse history, birthweight and gestational age: a prospective cohort study. *Brit J Obstet Gynaec.* 2011; 118:1329–1339.
- Shaw JG, Asch SM, Kimerling R, Frayne SM, Shaw KA, Phibbs CS. Posttraumatic stress disorder and risk of spontaneous preterm birth. *Obstet Gynecol.* 2014; 124:1111–1119. [PubMed: 25415162]
- Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, Nakazato M, Watanabe H, Shinoda N, Okada S, Iyo M. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry.* 2003; 54:70–75. [PubMed: 12842310]
- Simsek S, Uysal C, Kaplan I, Yuksel T, Aktas H. BDNF and cortisol levels in children with or without post-traumatic stress disorder after sustaining sexual abuse. *Psychoneuroendocrinology.* 2015; 56:45–51. [PubMed: 25800148]
- Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J Neurosci.* 1995; 15:1768–1777. [PubMed: 7891134]
- Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA.* 1999; 282:1737–1744. [PubMed: 10568646]

- Su S, Xiao Z, Lin Z, Qiu Y, Jin Y, Wang Z. Plasma brain-derived neurotrophic factor levels in patients suffering from post-traumatic stress disorder. *Psychiatry Res.* 2015; 229:365–369. [PubMed: 26160204]
- Tolin DF, Foa EB. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. *Psychol Bull.* 2006; 132:959–992. [PubMed: 17073529]
- Warner-Schmidt JL, Duman RS. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus.* 2006; 16:239–249. [PubMed: 16425236]
- Wilkins KC, Lang AJ, Norman SB. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. *Depress Anxiety.* 2011; 28:596–606. [PubMed: 21681864]
- Wulsin L, Somoza E, Heck J. The feasibility of using the Spanish PHQ-9 to screen for depression in primary care in Honduras. *Prim Care Companion J Clin Psychiatry.* 2002; 4:191–195. [PubMed: 15014707]
- Yonkers KA, Smith MV, Forray A, Epperson CN, Costello D, Lin H, Belanger K. Pregnant women with posttraumatic stress disorder and risk of preterm birth. *JAMA Psychiatry.* 2014; 71:897–904. [PubMed: 24920287]
- Zhong Q, Gelaye B, Fann JR, Sanchez SE, Williams MA. Cross-cultural validity of the Spanish version of PHQ-9 among pregnant Peruvian women: A Rasch item response. 2014; 158:148–53.

Fig.1.

Concentrations of serum brain-derived neurotrophic factor (BDNF, ng/ml) in early pregnancy according to antepartum post-traumatic stress disorder (PTSD) and depression status, Lima, Peru ($N=933^a$)

^a11 participants were excluded due to missing information on the PHQ-9 (Patient Health Questionnaire-9)

Table 1

Characteristics of the total population according to antepartum post-traumatic stress disorder (PTSD) status, PROMIS Cohort Study, Lima, Peru ($N = 2,928$)

Characteristics	No PTSD $N = 1,834$		Any PTSD $N = 1,094$		P^b -value
	N	%	N	%	
Maternal age (years) ^a	28.2 ± 6.2		28.0 ± 6.5		0.364
Maternal age (years)					
18-20	80	4.4	80	7.3	0.008
20-29	1,041	56.8	601	54.9	
30-34	385	21.0	216	19.7	
35	328	17.9	197	18.0	
Gestation age at interview (weeks) ^a	9.3 ± 3.4		9.2 ± 3.5		0.465
Education (years)					
6	67	3.7	56	5.1	0.137
7-12	1,015	55.5	585	53.6	
>12	748	40.9	451	41.3	
Mestizo (Mixed Ancestry)	1,444	78.8	755	69.1	<0.001
Access to basic food					
Hard	825	45.0	628	57.4	<0.001
Not very hard	1,007	55.0	466	42.6	
Married/living with a partner	1,501	82.1	864	79.4	0.072
Planned pregnancy	789	43.3	420	38.7	0.017
Nulliparous	934	51.1	497	45.6	0.005
Early pregnancy body mass index (kg/m ²)					
<25	909	50.1	551	50.8	0.343
25-29.9	667	36.8	412	38.0	
30	237	13.1	122	11.2	

due to missing data, the total sample size may not add up to 2,928

^aMean $\pm$ SD (standard deviation)

^bFor continuous variable, P-value was calculated using Student's t test; For categorical variable, P-value was calculated using Chi-square test

Table 2

Characteristics of the total population according to comorbid antepartum post-traumatic stress disorder (PTSD) and depression symptoms, PrOMIS Cohort Study, Lima, Peru ($N = 2,899^a$)

Characteristics	No PTSD No Depression $N = 1,591$		No PTSD Yes Depression $N = 225$		Yes PTSD No Depression $N = 507$		Yes PTSD Yes Depression $N = 576$		P-value ^c
	N	%	N	%	N	%	N	%	
Maternal age (years) ^b	28.3 ± 6.2		27.6 ± 6.0		28.4 ± 6.3		27.7 ± 6.6		0.005
Maternal age (years)									
18-20	62	3.9	18	7.4	28	5.5	52	8.9	<0.001
20-29	908	57.1	133	54.7	273	53.8	328	55.9	
30-34	327	20.6	58	23.9	116	22.9	100	17.0	
35	294	18.5	34	14.0	90	17.8	107	18.2	
Gestation age at interview (weeks) ^b	9.3 ± 3.5		9.1 ± 3.2		9.2 ± 3.6		9.2 ± 3.5		0.667
Education (years)									
6	59	3.7	8	3.3	27	5.3	29	4.9	0.521
7-12	877	55.2	138	57.0	277	54.9	308	52.5	
>12	652	41.1	96	39.7	201	39.8	250	42.6	
Mestizo (Mixed Race)	1,283	80.7	161	66.3	400	78.9	355	60.7	<0.001
Access to basic food									
Hard	718	45.2	107	44.0	303	59.8	325	55.4	<0.001
Not very hard	871	54.8	136	56.0	204	40.2	262	44.6	
Married/living with a partner	1,302	82.1	199	82.2	396	78.4	468	80.3	0.277
Planned pregnancy	683	43.1	106	44.5	207	41	213	36.8	0.049
Nulliparous	819	51.6	115	47.5	212	42.1	285	48.6	0.003
Early pregnancy									
Body Mass Index (kg/m ²)									
<25	776	49.4	133	55.0	264	52.2	287	49.6	0.369
25-29.9	583	37.1	84	34.7	184	36.4	228	39.4	
30	212	13.5	25	10.3	58	11.5	64	11.1	

^a29 participants were excluded due to missing information on the PHQ-9 (Patient Health Questionnaire-9)

^bMean ± SD (standard deviation)

^cFor continuous variable, P-value was calculated using one-way analysis of variance; For categorical variable, P-value was calculated using Chi-square test

Table 3

Odds ratio (OR) and 95% confidence interval (CI) for maternal serum brain-derived neurotrophic factor (BDNF, ng/ml) concentrations in early pregnancy in relation to post-traumatic stress disorder (PTSD) symptoms, Lima, Peru ($N = 944$)

Serum BDNF concentrations (ng/ml)	PTSD				Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
	Yes (N = 337)		No (N = 607)			
	N	%	N	%		
Quartile 1 (< 17.31)	87	25.8	149	24.5	1.33 (0.91-1.95)	1.20 (0.81-1.78)
Quartile 2 (17.31-20.92)	87	25.8	149	24.5	1.33 (0.91-1.95)	1.24 (0.84-1.83)
Quartile 3 (21.92-25.38)	91	27.0	145	23.9	1.43 (0.98-2.09)	1.38 (0.94-2.03)
Quartile 4 (>25.38)	72	21.4	164	27.0	Reference	Reference
<i>P-value for linear trend</i>					0.21	0.50
Quartile 1-3 (≤ 25.38)	265	78.6	443	73.0	1.36 (0.99-1.87)	1.35 (0.98-1.88)
Quartile 4 (> 25.38)	72	21.4	164	27.0	Reference	Reference

^a Adjusted for maternal age, parity and early pregnancy body mass index

Table 4

Associations between antepartum PTSD and depression and concentrations of serum brain-derived neurotrophic factor (BDNF, ng/ml) in early pregnancy, Lima, Peru ($N = 933^a$)

Antepartum PTSD and depression	Serum BDNF concentrations (ng/ml) ^b				Unadjusted OR (95% CI)	Adjusted OR ^c (95% CI)
	High concentrations (		Low concentrations (<			
	25.38) <i>N</i> = 231		25.38) <i>N</i> = 702			
	<i>N</i>	%	<i>N</i>	%		
No PTSD, No Depression	148	64.1	378	53.9	Reference	Reference
No PTSD, Yes Depression	13	5.6	62	8.8	1.87 (1.00-3.50)	1.83 (0.96-3.46)
Yes PTSD, No Depression	34	14.7	108	15.4	1.24 (0.81-1.91)	1.20 (0.78-1.87)
Yes PTSD, Yes Depression	36	15.6	154	21.9	1.67 (1.11-2.52)	1.52 (1.00-2.31)

Abbreviations: PTSD, post-traumatic stress disorder; OR odds ratio; CI, confidence interval

^a 11 participants were excluded due to missing information on the PHQ-9 (Patient Health Questionnaire-9)

^b High concentrations were defined as “the fourth quartile”; Low concentrations were defined as “the first three quartiles combined”

^c Adjusted for maternal age, parity and early pregnancy body mass index