Blood manganese levels during pregnancy and postpartum depression: A Cohort Study among Women in Mexico

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Abstract

Background—Occupational studies have shown an association between elevated Mn exposure and depressive symptoms. Blood Mn (BMn) naturally rises during pregnancy due to mobilization from tissues, suggesting it could contribute to pregnancy and postpartum depressive symptoms.

Objectives—To assess the association between BMn levels during pregnancy and postpartum depression (PPD), creating opportunities for possible future interventions.

Methods—We studied 561 women from the reproductive longitudinal Programming Research in Obesity, Growth, Environment, and Social Stressors (PROGRESS) cohort in Mexico City. BMn was measured at the 2nd and 3rd trimesters, as well as delivery. The Edinburgh Postnatal Depression Scale (EPDS) was used to assess PPD symptoms at 12-months postpartum. We used a generalized linear model assuming a Poisson distribution to assess the association between BMn levels and PPD, with adjustments for age, stress and depressive symptoms during pregnancy, education, socioeconomic status, and contemporaneous blood lead levels.

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Competing Financial Interests
The authors declare they have no actual or potential competing financial interests.

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**Results**—The mean ± standard deviation (SD) EPDS score at 12-months postpartum was 6.51 ± 5.65, and 17.11% of women met the criteria for possible PPD (score ≥ 13). In adjusted models, BMn during the 3rd trimester (β: 0.13, 95% CI: 0.04–0.21) and BMn levels averaged at the 2nd and 3rd trimester (β: 0.14, 95% CI: 0.02–0.26) had a positive association with EPDS scores at 12 months postpartum. BMn at the 2nd trimester (β: 0.07, 95% CI: −0.09–0.22) and delivery (β: 0.03, 95% CI: −0.04–0.10) had a non-significant positive association with EPDS scores at 12-months postpartum. Stress and depressive symptoms during pregnancy was associated with higher EPDS scores at 12-months postpartum in all of the adjusted models but were only significant when either BMn during 3rd trimester or BMn averaged across 2nd and 3rd trimester was assessed as the exposure.

**Discussion**—Our results demonstrate that elevated BMn levels during pregnancy predict PPD symptoms and could be a potential pathway for intervention and prevention of PPD.

**Keywords**
manganese; pregnancy; postpartum depression; Mexico; cohort study

**Introduction**

Postpartum depression (PPD) is a highly prevalent mood disorder that can have detrimental impacts on the health of a mother and her child, predicting a higher risk of clinical depression and affecting early life parenting. PPD is a treatable clinical illness characterized by extreme sadness, indifference, and anxiety. PPD is defined by major depressive disorder (MDD) symptoms that occur after childbirth such as changes in energy, sleep, and appetite, all of which can negatively impact parenting behaviors (American Psychiatric Association 2017). PPD is the most common complication of childbirth, affecting 10–20% of women (Gaynes et al. 2005) (Postpartum Depression: Action Towards and Treatment 2015) (Fisher et al. 2012) in both developing and developed countries. In addition to its effects on mothers, PPD can harm the development of infants by preventing mothers from engaging in critical social interactions with their children (Ibarra-Yruegas et al. 2018). In extreme cases, PPD can result in suicide or even infanticide (El-Hachem et al. 2014). Despite the emotional, physical, and mental burden it places on mother and child, PPD remains an under examined, underdiagnosed, and undertreated mental disorder (Place et al. 2015) (Postpartum Depression: Action Towards and Treatment 2015).

A better understanding of the etiology of PPD could potentially improve prevention strategies. Established risk factors for PPD include history of depression, inadequate social support, stress during pregnancy, family conflict, socioeconomic status (SES), parity, lack of partner support, and low self-esteem (Norhayati et al. 2015) (Oppo et al. 2009) (Mori et al. 2017) (Almutairi et al. 2017). Neuroactive chemicals, such as manganese (Mn), may play a role as well. Metals (e.g. lead, copper, and iron, among others) have well-known impacts on neurobehavior and have been linked to depressive symptoms (Gonulalan et al. 2013; Li et al. 2018), albeit typically with clinically-relevant levels of high exposure or for some nutrient metals in the setting of mineral deficiency. Mlyniec et al. (2015) suggested that essential elements may contribute to the neurobiology of psychiatric disorders (Mlyniec et al. 2015). Manganese is an essential nutrient with well-known neurobehavioral effects from high
occupational exposures, including depressive symptoms (Horning et al. 2015) (Roels et al. 2012) (Bouchard et al. 2007). Because Mn is mobilized from internal stores in pregnancy, it may rise in the blood to levels that exceed homeostatic levels, raising the possibility that Mn may play a role in PPD (Claus Henn et al. 2017).

Mn is a ubiquitous trace element that naturally occurs in the environment and is an essential nutrient that bioaccumulates in the central nervous system (CNS), particularly in fetal life and infancy. This suggests that it plays a functional role in brain development (Pfalzer and Bowman 2017). Mn acts as a cofactor to anti-oxidant enzymes such as superoxide dismutase and to enzymes involved in neurotransmitter synthesis such as glutamine (Takeda 2003). Common Mn exposure pathways are air, diet, water, and occupation (Wright and Baccarelli 2007). Mn is a transition metal similar to iron and copper that is an anti-oxidant at homeostatic levels (Aschner and Aschner 2005) (Chen et al. 2015) (Horning et al. 2015). However, elevated Mn exposure, such as that from occupational exposure or from contaminated environments, is neurotoxic and can stimulate oxidative stress and neurodegenerative processes by acting as a catalyst for the Fenton reaction (Roels et al. 2012) (Farina et al. 2013). Mn-induced oxidative stress has been associated with MDD (Black et al. 2015) (Liu et al. 2015) (Pulta et al. 2014) (Maes et al. 2011). Most studies on Mn neurotoxicity have examined its detrimental effects on motor and cognitive function (Chen et al. 2015) (Haynes et al. 2015) (Guilarte 2011) but have not focused on emotion regulation or other aspects of mental health.

Research regarding chronic Mn exposure and psychiatric disorders has demonstrated a direct association between higher Mn levels and MDD symptoms (Bouchard et al. 2007) (Shiue 2015). Most relevant to this study are the recent studies which demonstrate that BMn levels rise rapidly in pregnancy to two to three times their baseline (Guy et al. 2018) (Rodrigues et al. 2015) (Eum et al. 2014) (Smargiassi et al. 2002) (Claus Henn et al. 2017). During pregnancy, there is a physiological redistribution of body Mn stores that is likely to facilitate transport of Mn to the fetus, leading to substantial increases in circulating BMn in mothers. If higher brain Mn is a cause of depressive symptoms, then we hypothesize that a relatively modest disruption in maternal Mn homeostasis during pregnancy might cause a threshold to be crossed, predisposing mothers to PPD following delivery. To our knowledge, this is the first study to focus on the association between BMn levels during pregnancy and PPD.

Methods

Study Participants

The Programming Research in Obesity, Growth, Environment, and Social Stressors (PROGRESS) study is an ongoing longitudinal birth cohort study based in Mexico City. Briefly, pregnant women were recruited during prenatal visits at four Mexican Social Security System (IMSS) clinics between July 2007 and February 2011, enrolled in the study in the 2nd trimester, consented and followed longitudinally thereafter. The inclusion criteria required the women to be at least 18 years old, less than 20 weeks pregnant, free of cardiac or renal ailments, have telephone access, and plan to maintain Mexico City residency for at least the following three years. Further details regarding the inclusion criteria have been previously described (Braun et al. 2014). Institutional review boards at the Harvard T.H.
Chan School of Public Health, Icahn School of Medicine at Mount Sinai, the Mexico National Institute of Public Health, the Mexico National Institute of Perinatology, and the IMSS approved the study protocols.

**Postpartum Depression assessment**

The presence of depressive symptoms was assessed during pregnancy as a covariate and at 12 months postpartum as the dependent variable based on scores from the Spanish version of the Edinburgh Postnatal Depression Scale (EPDS) which was been validated in the Mexican population (Cox et al. 1987) (Alvarado-Esquivel et al. 2014). The EPDS is a screening tool for depression and consists of 10 items which query respondents on various symptoms of depression. Responses to each item are scored on a 4-point Likert scale (range 0–3, with higher values representing greater symptom severity). The scores for all 10 items were then summed to produce a total score for each respondent. Higher EPDS scores represented greater severity of depressive symptoms. In the univariate analysis to examine the overall presence of possible depressive symptoms, we dichotomized EPDS scores with a cut-off ≥ 13 as this was previously demonstrated as the correct threshold for identifying cases of possible depressive symptoms (Alvarado-Esquivel et al. 2010). However, in the multivariate analysis, we assessed EPDS scores continuously as it was not significant when it was assessed as a binary variable in the logistic regression model. The time of assessment at 12 months was selected based on the risk period for PPD diagnosis defined by the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention 2008).

**Blood manganese during pregnancy measurements**

Royal Blue top with Ethylene Diamine Tetra-Acetate (EDTA) Vacutainer tubes (Becton-Dickinson and Company, Franklin Lakes, New Jersey) were used to collect venous whole blood samples which were used to measure BMn. Women’s BMn (ug/dl) levels was assessed during the 2nd and 3rd trimesters of pregnancy, as well as at delivery. A dynamic reaction cell-inductively coupled plasma mass spectrometer (ICP-DRC-MS) (Elan 6100; PerkinElmer, Norwalk, CT) was used to measure BMn and BPb. Further details regarding the methods and quality control procedures are described elsewhere (Claus Henn et al. 2010). The sample sizes for BMn measures at 2nd trimester, 3rd trimester, and delivery were 530, 471 and 443, respectively. There were 81% of BMn samples from 2nd trimester which remained at 3rd trimester, and 78% of BMn samples at 2nd trimester overlapped with BMn samples at delivery. BMn measures across these time points were highly correlated with each other and analyzed in separate models to avoid multicollinearity. The 2nd and 3rd trimester BMn measurements were averaged and analyzed in a separate model as well.

**Covariates**

Covariates were selected a priori based on previous scientific literature. BPb (ug/dl) was measured concurrently and with the same ICP-MS technique as for BMn (Claus Henn et al. 2010). BPb was used as a covariate in the adjusted model based on previous literature, which established an association between BPb and depression (Bouchard et al. 2009). Stress during pregnancy was assessed either at 2nd or 3rd trimester using the negative life event (NLE) scores obtained from the Spanish version of the Crisis in Family Systems-Revised (CRISYS-R) survey, which had a test-retest reliability of 0.86 among Spanish speaking...
participants (Tamayo et al. 2017) (Berry et al. 2001). This survey asks respondents to rate the presence and severity of stressful life events spanning 11 domains (e.g. financial struggles, housing challenges, and medical problems) from the past 6 months. Survey responses were summed across domains where respondents reported a NLE to produce a summary score ranging from 0–11. Higher NLE scores indicate greater stress (Tamayo et al. 2017) (Schreier et al. 2015).

Covariates such as socioeconomic status (SES), education, and age were included in the final models based on previous literature on Mn and depressive symptoms during pregnancy (Miyake et al. 2018). Education was divided into three categories: less than high school, high school, and more than high school. SES, which was used as a proxy for income, is an index created by the “Asociación Mexicana de Agencias de Investigación de Mercados y Opinión Pública” (AMAI) which derived thirteen variables from questionnaire results regarding household head’s education and ownership of various household items (Carrasco 2002). The thirteen variables were collapsed into six levels before settling on three levels: low, medium, and high SES (Rodosthenous et al. 2017) (Stroustrup et al. 2016). Age was measured at 2nd trimester and expressed in years.

Statistical Analysis

Descriptive statistics were performed, followed by bivariate (unadjusted) and multivariable (adjusted) analyses. In these analyses, BMn and BPb measures, EPDS and NLE scores, and age were treated as continuous variables, while education and SES were treated as categorical variables. BMn distributions were slightly skewed but we did not perform transformations in the models. The limit of detection (LOD) for BPb and BMn was 0.060. The detection rate was above 99.5% for both BPb and BMn. The bivariate analyses examined the relationship between PPD (quantified by EPDS scores at 12-months postpartum) and each independent variable in separate models. Adjustments for each model included stress during pregnancy, age, SES, education, depressive symptoms during pregnancy, and BPb measures that were concurrent to each BMn time point. EPDS scores at 12-months postpartum were treated as the dependent variable, while BMn measures during pregnancy and covariates were treated as explanatory variables. Because of the discrete nature of EPDS scores, we utilized a Poisson regression model with adjustment for overdispersion. Three separate adjusted models were generated for BMn at each time point; 2nd trimester, 3rd trimester, and delivery. Two additional adjusted models were utilized to assess BMn averaged across both trimesters with and without the inclusion of delivery. We ran a quadratic nonlinear regression to test if a nonlinear model was appropriate but found no significant results. All statistical analyses were performed using SAS 9.4 (SAS, Inc., Cary, NC).

Results

Study Population

Distribution of EPDS scores at 12 months postpartum was right-skewed as shown in Figure 1. Information regarding demographic characteristics, depression and stress measures, and blood metal concentrations are shown in Table 1. Of the 948 women who delivered a live

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birth and were enrolled in the study, 561 provided responses for EPDS at 12-months postpartum. In PROGRESS, 17.11% of women had EPDS scores ≥13. The mean ± standard deviation (SD) for EPDS scores at 12-months postpartum was 6.51 ± 5.65. The mean for BMn at 2nd trimester, 3rd trimester, and at delivery were 1.43 μg/dL ± 0.48, 1.89 μg/dL ± 0.71, and 2.41 μg/dL ± 1.04, respectively. The mean for BMn averaged across 2nd and 3rd trimesters was 1.65 μg/dL ± 0.55. The mean NLE and EPDS scores during pregnancy were 3.26 ± 2.11 and 8.56 ± 5.62, respectively. The average age of the women in the study was 27.64 ± 5.51 years. Approximately, half (52.58%) of the participants had low SES and 41% had less than a high school education.

**Bivariate Analyses**

Moderate to strong correlations were found between second trimester and 3rd trimester BMn (r=0.53, p<0.001), BMn at 2nd trimester and delivery (r=0.39, p<0.001), as well as BMn at 3rd trimester and delivery (r=0.41, p<0.001) (Table 2). BMn trends increased from 2nd trimester to delivery as shown in Figure 2.

Results from the unadjusted models are shown in Table 3. A 1μg/dL increase in 3rd trimester BMn was significantly associated with an increase of 0.10 points in 12-months postpartum EPDS scores (p<0.05). Neither BMn at 2nd trimester nor delivery nor the average of BMn across 2nd and 3rd trimester was associated with 12-months postpartum EPDS scores. Relative to women with less than high school education, women with more than a high school education had a decrease of 0.30 points in 12 months postpartum EPDS scores (p<0.01). A 1 point increase in NLE and EPDS scores during pregnancy were associated with an increase of 0.11 (p<0.0001) and 0.07 (p<0.0001) points, respectively in 12-month postpartum EPDS scores.

**Multivariable Analysis**

Results of the BMn measures and the significant covariates in their respective adjusted models (Models 1–4) are presented in Table 4. Women with higher 3rd trimester BMn levels had higher 12 months postpartum EPDS scores (β: 0.13, 95% CI: 0.04–0.21) after adjusting for covariates. The average of BMn across the 2nd and 3rd trimester showed a positive association with 12 months postpartum EPDS scores (β: 0.14, 95% CI: 0.02–0.26) after adjusting for covariates. BMn levels at delivery (β: 0.03, 95% CI: −0.04–0.10) and 2nd trimester (β: 0.07, 95% CI: −0.09–0.22) had non-significant positive associations with 12-months postpartum EPDS scores.

**Discussion**

We found that women with higher BMn levels during the 3rd trimester of pregnancy had higher EPDS scores at 12-months postpartum after adjusting for previous stressful life events and depression during pregnancy, demographic characteristics, and contemporaneous BPb. This study builds upon the literature on occupational and environmental exposure to Mn that shows associations with depressive symptoms, as the increase BMn in pregnancy is due to physiological changes that mobilize internal Mn stores, rather than environmental exposure. It also adds to the literature by focusing on the role of Mn in postpartum
depression, which is a life stage of heightened sensitivity to this disorder. We note that the primary source of Mn exposure may not be environmental but instead internal, via remobilization of internal Mn tissue stores, in many ways similar to the rise in BPb that also occurs in pregnancy from the mobilization of internal stores.

Environmental sources may still play a role as Mn exposure via air, water, food, etc. may contribute to the rise in BMn levels during pregnancy, perhaps tipping the balance of exposure towards toxic levels. The air pollution in Mexico City contains Mn among various other atmospheric contaminants and may contribute to increased Mn exposure (Genc et al. 2012) (Block and Calderon-Garciduenas 2009). Regardless of the sources, rises in BMn have repeatedly been shown to occur during pregnancy (Tholin et al. 1993; Zota et al. 2009). Our data suggest that relatively minor perturbations in this normal physiological BMn elevation may be contributing to increased risk for PPD. Because environmental Mn exposure has been associated with depressive symptoms in occupational settings (Bouchard et al. 2007) (Bowler et al. 2007), there is a consistency between our findings and the environmental literatures on Mn and depressive symptoms. It may be that the elevations in BMn during pregnancy represent a susceptibility window to PPD that is triggered by other concurrent risk factors such as stress or genetic susceptibility to depression or Mn.

To place our levels of depressive symptoms in PROGRESS in their proper context, the prevalence of PPD symptoms in our cohort was higher than that find in Hispanic women born in the USA (7.14%) but similar to women who migrated from the Dominican Republic and Puerto Rico (17.24%) (Doe et al. 2017). We note that prevalence of PPD symptoms in PROGRESS were similar to Mexican women in the urban area of Monterrey, Mexico (14.3%) (Place et al. 2015). With respect to BMn concentrations in pregnancy, our results were also comparable to other studies which demonstrated that BMn rose during pregnancy. For example, among women in Costa Rica, BMn concentrations had a positive association with gestational age ($\beta = 0.2; 95\%\ CI: 0.1$ to $0.2$) (Mora et al. 2014).

To our knowledge, this is first study to investigate the association between the physiologic rise of BMn during pregnancy and PPD symptoms. In many ways, this illustrates that pregnancy is a sensitive window not only for children, but also for women. The physiologic changes of pregnancy may make women vulnerable to longer term health effects as well as their offspring. The well-described weight retention problems that occur in women post-pregnancy also illustrate this concept (Ruchat et al. 2018) (Nicodemus 2018). Our study extends this vulnerability to neuropsychiatric symptoms. Indeed, it is possible that some of the neurodevelopmental effects from fetal exposures, including Mn exposure, may be due to maternal depressive symptoms that affect parenting, thereby impacting child development (Mughal et al. 2019) (Maruyama et al. 2019) (Aoyagi et al. 2019). If so, then reducing excessive Mn exposure in pregnancy may have benefits directly to the mothers and indirectly to the children. Future research should address this issue. While the exact mechanisms by which Mn produces depressive symptoms is unclear, there are a number of studies showing an association between Mn and MDD symptoms in non-pregnant adults and these results are in agreement with our study. For example, among factory workers whose job consist of producing ferroalloy with high amounts of Mn, subjects in the two highest cumulated exposure indices (CEI) tertiles had higher odds of MDD symptoms compared to the...
reference group (Bouchard et al. 2007). Bouchard et al. measured Mn levels via dust in the air which can not be directly compared to Mn concentrations in our study which measured Mn in the blood.

Among the National Health and Nutrition Examination Surveys (NHANES) study sample, non-institutionalized adults in the United States with higher Mn levels had higher odds of MDD symptoms compared adults with lower Mn levels (Shiue 2015). There was a non-significant positive association between air Mn (0.05 μg/m$^3$) and MDD among 288 adults who were not in engaged in mining work but resided in the mining district Molango in Mexico (Solis-Vivanco et al. 2009). Furthermore, case reports of unusually high levels of exposure to Mn demonstrate that adults with higher levels of Mn report characteristics that correspond to MDD symptoms (Donaldson, 1987) (Sassine et al. 2002). The positive association between Mn and MDD found in the abovementioned studies align with our results which established a positive association between Mn and PPD. It should be noted that a particular strength of our study is that we focused on what is likely a critical window for depression- i.e. the perinatal period. A growing body of literature suggests that Mn exposure during pregnancy is a vulnerable period for the fetus (Claus Henn et al. 2017) (Yamamoto et al. 2019) (Yu et al. 2014) (Zota et al. 2009). Pregnancy is a period of profound physiological changes in women that may make the mother vulnerable to alterations in Mn homeostasis. A very small body of literature exists on this topic for manganese, specifically in regards to lower levels of blood Mn in pregnancy being associated with preeclampsia (Soobramoney et al. 2019) (Liu et al. 2019). Pregnancy induces profound changes in physiology and brain neurotransmitters in mothers, with well-known effects on postpartum mental health and cardiovascular disease risk (Li et al. 2019) (Benschop et al. 2019). A separate body of literature shows that Mn metabolism is related to the same mental health disorders (Jain and Ferrando 2011) (Bowler et al. 2007) and that pregnancy induced physiologic changes include rises in BMn that are not seen at other adult life stages (Ashley-Martin et al. 2018) (Kupsc et al. 2019) (Smargiassi et al. 2002). Given our findings and the existing literature, we believe that the elevation in BMn during pregnancy may be a susceptibility risk factor specific to the pregnancy life stage and that disturbances in Mn metabolism, absorption and/or distribution during pregnancy could contribute to postpartum depression. If so, monitoring BMn in pregnancy may identify women at higher risk for PPD, and create potential opportunities for interventions. Based on our data, the 3rd trimester was more predictive of PPD and not delivery, which is the final day of the 3rd trimester. There are major interventions, and acute factors that occur at delivery that distinguish it from other days in the 3rd trimester such as intravenous hydration, pain from contractions, hormonal changes and physiologic changes that arise from labor. It may be that these profound changes in maternal physiology alter blood Mn sufficiently to obscure associations or it may be that the earlier phases of the 3rd trimester are the true susceptibility window and subsequent elevations in BMn that arise in late 3rd trimester do not pose additional risk.

One of the biological mechanisms that may explain the association between Mn and depressive symptoms involves neurotransmitters, such as dopamine (DA) and serotonin. The dopaminergic and serotonergic systems in the CNS play crucial roles in regulating mental health related behaviors, such as emotion regulation and executive functions. The neurons of
the raphe nuclei are the principal source of serotonin in the CNS. They are located in the brainstem where they form a neurotransmitter system reaching extensively across the central nervous system. These serotonergic receptors regulate mood and work together with dopaminergic neurons found in ventral and dorsal striatal structures, such as the substantia nigra pars compacta (SNpc) and ventral tegmental area (VTA). These brain regions are associated with associative and habit learning, motor and inhibition control, reward motivation and reinforcement, working memory, and attention (Belujon and Grace 2017; Treadway and Zald 2011) (Chinta et al. 2005). These brain regions are also high in tissue Mn levels, and manganese metalloenzymes—including arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, and Mn superoxide dismutase (Mn SOD)—are expressed in these regions. Given Mn in drinking water, rats demonstrate emotional lability and increased levels of striatal 5-hydroxyindoleacetic acid (a serotonin metabolite) in the brain (Krishna et al. 2014). Anhedonia, a lack of motivation and decreased ability to experience pleasure (Belujon and Grace 2017; Treadway and Zald 2011) is mediated in part by DA neurons that create pathways for reward responsiveness. Anhedonia is a core component of severe depression, as patients are less likely to seek pleasurable experiences (Belujon and Grace 2017; Sherdell et al. 2012).

Overall, the neurotransmitter systems regulating depression are complex and involve negative feedback mechanisms and autoregulation functions in CNS. However, a consistent finding is that the underlying basis of depression involves depletion in serotonin, norepinephrine, or dopamine in the CNS. This concept is supported by the mechanisms of common antidepressant drugs, such as monoamine oxidase inhibitors, tricyclic antidepressants or serotonin reuptake inhibitors, all of which increase levels of these neurotransmitters in the brain (Delgado 2000). These same monoamine neurotransmitters are impacted by Mn metabolism (Gordon and Goelman 2016). Among nonhuman primates, chronic Mn exposure altered in vivo dopamine release in the frontal cortex, as measured by positron emission tomography (Guilarte et al. 2019). Another theory of depression involves increases in brain inflammation, particularly at key developmental life stages (Galecki and Talarowska 2018). A transition element such as Mn, which plays a key role in mediating inflammation both at high and low concentrations and which has been associated with monoamine neurotransmitter metabolism, would seem to cross and even unify these two theories of depression. The ability of elevated Mn levels to induce both inflammation and dopamine dysregulation increases the likelihood that it contributes mechanistically to depression.

In addition to the Mn exposures, other covariates in our study were found to have an association with PPD symptoms. In the unadjusted (Table 3) and the adjusted models (Table 4), women with more than a high school education had lower EPDS scores at 12-months postpartum as compared to women with less than a high school education; however, the results were not significant in models 2 and 4 (Table 4). These findings bolster the concept of educational attainment being an important social determinant of health due to higher education being protective against MDD (Shankar et al. 2013) (Bracke et al. 2014). NLE and EPDS scores during pregnancy had positive associations with PPD symptoms in every model presented in Table 4, which concurs with other studies that indicated stress and depressive symptoms during pregnancy as risk factors for PPD (Norhayati et al. 2015).
findings verify that risk factors for PPD can be psychological and social (Bhati and Richards 2015).

**Strengths and Weaknesses**

Our study has many strengths. First, it is a longitudinal study and our measures of BMn precede measures of depressive symptoms. Differential exposure to Mn and/or phenotype misclassification is unlikely, as all assessments were performed without knowledge of BMn levels. Adjustments in the multivariate analysis included important covariates, such as psychosocial and biological measures previously reported to be associated with depression. Our levels of BMn are comparable to those found in pregnancy in the US and Canada (Zota et al. 2009) (Takser et al. 2004). Our focus on perinatal life as a developmental window for depression is also a strength.

Our study has a few limitations. As a screening tool, EPDS is not used to diagnose PPD but is used to assess possible depression, which is a correlate of PPD; as such, we believe our study addresses depressive symptoms but not clinical depression per se. Consequently, our results should be interpreted as an increased risk for depressive symptoms rather than for clinical depression. Still, our findings demonstrate that elevated Mn may increase reported depressive symptoms, and present a danger for women in perinatal life, particularly if they have other risk factors such as genetic vulnerability to depression, high stress levels, and a history of clinical depression, etc. These results may not be generalizable to the United States or other developed countries due to the homogeneity of our Mexican study sample. Nonetheless, we believe the study is internally valid and may be generalizable outside of Mexico, but further research is needed.

**Conclusion**

Higher BMn levels during pregnancy increased the prevalence of PPD symptoms among women in our present study. Our results suggest that the effects of Mn on MDD can be extended to PPD. This study is important as it contributes to developing a better understanding of an understudied mental disorder that is potentially harmful to mothers and children. Because BMn is affected by both exogenous (diet, air, etc.) and endogenous (tissue stores) sources, an increase in blood manganese from either source may contribute to raising BMn levels, potentially increasing risk for PPD. Further research is needed to confirm the sources of the elevated BMn levels in pregnancy and whether a threshold exists that predicts increased risk of PPD. Future research should explore environmental factors that may contribute to excess Mn exposure such as water contamination (Ntihabose et al. 2018), and factors that may regulate mobilization of internal stores, such as iron deficiency (Finley 1999).

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Highlights

• Elevated blood manganese levels during mid to late pregnancy are associated with postpartum depressive symptoms in mothers.

• Manganese is a nutrient critical to brain function, but a toxicant at high levels that can promote oxidative stress.

• This study suggests that dysregulation of the normal rise in blood manganese during pregnancy predicts depressive symptoms.

• Modifiable factors that affect blood manganese levels may be targets to prevent postpartum depressive symptoms.
Figure 1.
Histogram of EPDS Score at 12 Months Postpartum among pregnant women in Mexico City
Figure 2.
Scatter plots with LOESS (Locally Weighted Scatterplot Smoothing) smoother of BMn at each time point and EPDS Score at 12 months postpartum among pregnant women in Mexico City
Table 1.
Demographic, depressive symptoms and Mn exposure characteristics of 561 pregnant women in Mexico City

|                                | Overall          | PPD symptoms (≥3 EPDS) |
|--------------------------------|------------------|------------------------|
|                                | N (%) or mean ± SD | n (%) or mean ± SD     |
| EPDS Score during pregnancy    | 8.56 ± 5.62      | 13.07 ± 6.16           |
| Negative Life Event (NLE) Score during pregnancy | 3.26 ± 2.12      | 4.41 ± 2.35            |
| BMn at 2nd Trimester (μg/dL)   | 1.43 ± 0.48      | 1.43 ± 0.46            |
| BMn at 3rd Trimester (μg/dL)   | 1.89 ± 0.71      | 1.99 ± 0.78            |
| BMn during Delivery (μg/dL)    | 2.41 ± 1.04      | 2.38 ± 0.78            |
| Average of BMn at 2nd & 3rd trimester (μg/dL) | 1.65 ± 0.55      | 1.72 ± 0.55            |
| BPb at 2nd trimester (μg/dL)   | 3.69 ± 2.69      | 3.63 ± 2.51            |
| BPb at 3rd trimester (μg/dL)   | 3.84 ± 2.80      | 3.22 ± 2.13            |
| BPb during delivery (μg/dL)    | 4.14 ± 3.10      | 3.41 ± 2.05            |
| Average of BPb at 2nd and 3rd trimester (μg/dL) | 3.76 ± 2.58      | 3.52 ± 2.37            |
| Age (Years)                    | 27.64 ± 5.51     | 27.13 ± 5.13           |
| Education                      |                  |                        |
| Less Than High School          | 230 (41.00)      | 45 (46.88)             |
| High School                    | 199 (35.47)      | 37 (38.54)             |
| More Than High School          | 132 (23.53)      | 14 (14.58)             |
| Socioeconomic Status (SES)     |                  |                        |
| Low                            | 295 (52.58)      | 51 (53.13)             |
| Medium                         | 210 (37.43)      | 34 (35.42)             |
| High                           | 56 (9.98)        | 11 (11.46)             |
Table 2.
Correlations for BMn at different time points during pregnancy among women in Mexico City

|                  | 2nd trimester | 3rd trimester | Delivery | Average of 2nd and 3rd trimester |
|------------------|---------------|---------------|---------|----------------------------------|
| 2nd trimester    | 1.00          |               |         |                                  |
| 3rd trimester    | 0.53 ***      | 1.00          |         |                                  |
| Delivery         | 0.39 ***      | 0.41 ***      | 1.00    |                                  |
| Average of 2nd and 3rd trimester | 0.84 *** | 0.92 *** | 0.43 *** | 1.00                        |

*p<0.05
**p<0.01
***p<0.001
Table 3.
Unadjusted Poisson regression models for association between EPDS at 12 months postpartum and independent variables among pregnant women in Mexico City (N = 561).

|                                | β (95% CI)       | p value   |
|--------------------------------|------------------|-----------|
| Blood Mn at 2nd Trimester (μg/dL) | 0.01 (−0.14, 0.17) | 0.893     |
| Blood Mn at 3rd Trimester (μg/dL)  | 0.10 (0.01, 0.20)  | 0.036     |
| Blood Mn during Delivery (μg/dL)   | 0.00 (−0.07, 0.08) | 0.928     |
| Average of Blood Mn at 2nd & 3rd trimester (μg/dL) | 0.08 (−0.05, 0.20) | 0.227     |
| NLE Score during pregnancy        | 0.11 (0.08, 0.14)  | <0.0001   |
| EPDS Score during pregnancy       | 0.07 (0.06, 0.08)  | <0.0001   |
| Age (Years)                      | −0.01 (−0.02, 0.01) | 0.287     |
| BPb at 2nd trimester (μg/dL)      | 0.01 (−0.01, 0.04)  | 0.342     |
| BPb at 3rd trimester (μg/dL)      | −0.02 (−0.05, 0.00) | 0.102     |
| BPb during delivery (μg/dL)       | −0.01 (−0.04, 0.02) | 0.434     |
| Average of BPb at 2nd and 3rd trimester (μg/dL) | 0.00 (−0.03, 0.03) | 0.798     |
| Education                        |                  |           |
| Less Than High School             | Reference        |           |
| High School                      | −0.02 (−0.18, 0.13) | 0.779     |
| More Than High School             | −0.30 (−0.50, −0.10) | 0.003     |
| Socioeconomic Status (SES)       |                  |           |
| Low                              | Reference        |           |
| Medium                           | −0.12 (−0.27, 0.04) | 0.141     |
| High                             | 0.05 (−0.18, 0.29)  | 0.661     |
## Table 4.

Adjusted Poisson regression models separated based on time of BMn measure among pregnant women in Mexico City

| Model 1 (n=489) \(^d\) | \(\beta\) Coefficients (95% CI) | \(p\) value |
|-------------------------|---------------------------------|-------------|
| BMn at 2\textsuperscript{nd} Trimester (μg/dL) | 0.07 (−0.09, 0.22) | 0.393 |
| NLE Score during pregnancy | 0.06 (0.03, 0.09) | 0.001 |
| EPDS Score during pregnancy | 0.06 (0.05, 0.07) | <0.0001 |
| More Than High School | −0.23 (−0.44, −0.01) | 0.036 |

| Model 2 (n=465) \(^b\) | \(\beta\) Coefficients (95% CI) | \(p\) value |
|-------------------------|---------------------------------|-------------|
| BMn at 3\textsuperscript{rd} Trimester (μg/dL) | 0.13 (0.04, 0.21) | 0.003 |
| NLE Score during pregnancy | 0.05 (0.02, 0.09) | 0.002 |
| EPDS Score during pregnancy | 0.06 (0.05, 0.08) | <0.0001 |

| Model 3 (n=514) \(^c\) | \(\beta\) Coefficients (95% CI) | \(p\) value |
|-------------------------|---------------------------------|-------------|
| Average of BMn at 2\textsuperscript{nd} & 3\textsuperscript{rd} trimester (μg/dL) | 0.14 (0.02, 0.26) | 0.021 |
| NLE Score during pregnancy | 0.05 (0.02, 0.08) | 0.002 |
| EPDS Score during pregnancy | 0.06 (0.05, 0.07) | <0.0001 |
| More Than High School | −0.20 (−0.41, −0.00) | 0.046 |

| Model 4 (n=410) \(^d\) | \(\beta\) Coefficients (95% CI) | \(p\) value |
|-------------------------|---------------------------------|-------------|
| BMn during delivery (μg/dL) | 0.03 (−0.04, 0.10) | 0.406 |
| NLE Score during pregnancy | 0.06 (0.02, 0.09) | 0.002 |
| EPDS Score during pregnancy | 0.06 (0.05, 0.08) | <0.0001 |

Note: The results of covariates that failed to have a significant association with PPD are not shown in the table.

\(^d\) Adjustments for age, SES, education, stress during pregnancy, depressive symptoms during pregnancy and blood lead at 2\textsuperscript{nd} trimester

\(^b\) Adjustments for all covariates in model 1 and blood lead at 3\textsuperscript{rd} trimester

\(^c\) Adjustments for all covariates in model 1 and blood lead averaged at 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester

\(^d\) Adjustments for all covariates in model 1 and blood lead during delivery

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