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Early pregnancy essential and non-essential metal mixtures and maternal antepartum and postpartum depressive symptoms

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Declaration of interests

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Abstract

Background: Mood disorders are common during and after pregnancy, and environmental metals may contribute to increased risk. Antepartum metal exposures have not been well characterized in relation to maternal depression. We evaluated the extent to which early pregnancy erythrocyte concentrations of essential and non-essential metals were prospectively associated with antepartum and postpartum depressive symptoms.

Methods: Participants were 1226 women in Project Viva, a longitudinal cohort recruited during pregnancy (1999–2002). We measured concentrations of 11 metals in maternal first trimester erythrocytes (arsenic, barium, cadmium, cesium, copper, mercury, magnesium, manganese, lead, selenium, zinc). Using the Edinburgh Postnatal Depression Scale (EPDS), we assessed elevated depressive symptoms (13; 0–30 scale) at mid-pregnancy and at 6 and 12 months postpartum. We applied latent class mixed modeling to identify symptom trajectories. Adjusting for maternal sociodemographics and co-exposures, we examined associations between the metal mixture and depressive symptoms using logistic (for EPDS 13)/multinomial (for symptom trajectories) regression and quantile g-computation.

Results: In this cohort of moderately high socioeconomic status participants (e.g., 72% college graduate), low-level metal concentrations were weakly to moderately correlated (Spearman: -0.24 to 0.59); the prevalence of depressive symptoms ranged from 9% (mid-pregnancy) to 6% (12 months postpartum); and three trajectories (stable low; elevated mid-pregnancy, then decreasing; moderate mid-pregnancy, then increasing) best fit the EPDS data. The early pregnancy erythrocyte metal mixture was not associated with maternal depressive symptoms in logistic, multinomial, or mixture models. For individual metals, most confidence intervals (CI) included the null. There was weak evidence that arsenic, lead, and selenium were moderately associated with elevated odds of depressive symptoms and/or trajectories. However, the odds ratios (95% CI) per doubling of these three metals were imprecise [e.g., arsenic: 1.13 (0.94, 1.40) for EPDS 13 at six months postpartum; lead: 1.19 (0.80, 1.77) for EPDS 13 at mid-pregnancy; selenium: 2.35 (0.84, 6.57) for elevated mid-pregnancy, then decreasing versus stable low trajectory].

Discussion: We did not observe strong, consistent evidence of associations between early pregnancy erythrocyte metal concentrations and subsequent maternal antepartum and postpartum depressive symptoms.

Keywords

environmental exposure; metals; mixtures analysis; pregnancy; maternal depression

1. Introduction

Depression is one of the leading contributors to the burden of disease worldwide, with approximately one in five individuals experiencing a major depressive disorder during their lifetime. Throughout the life course, depression is almost twice as common in women compared to men (Kessler and Bromet, 2013; Malhi and Mann, 2018) and is especially prevalent during and in the first year after pregnancy. The antepartum and postpartum periods may be particularly important times to identify and reduce risk of depression (Van Niel and Payne, 2020). The normal physiological and hormonal changes associated

with pregnancy may serve as a “stress test” that unmasks pre- and sub-clinical disease. Exposure to certain risk factors at this time may heighten susceptibility to health problems (Varshavsky et al., 2019), including depression.

Several psychosocial factors have been implicated in increased risk of antepartum (i.e., prenatal) and postpartum depression (O’Hara and Wisner, 2014), but there has been limited investigation of how exposure to neurotoxicant or endocrine disrupting chemicals, such as metals, impact vulnerability to antepartum and postpartum depressive disorders. In the general population, exposure to metals is ubiquitous, with a major exposure route via consumption of food and water. Elevated exposure to non-essential metals, as well as to essential metals outside of optimal intake, may dysregulate the function of monoaminergic neurotransmitters (e.g., dopamine, serotonin) and the hypothalamic-pituitary-adrenal (HPA) axis (Kala and Jadhav, 1995; Kim et al., 2021; Nehru and Sidhu, 2001; Orisakwe, 2014; van den Bosch and Meyer-Lindenberg, 2019; Wu et al., 2017), and thus increase susceptibility to depression. In adult populations, cross-sectional studies have observed adverse associations of biomarkers of non-essential metals, including arsenic (As), cadmium (Cd), and lead (Pb), with depressive symptoms or diagnosis (Berk et al., 2014; Bouchard et al., 2009; Buser and Scinicariello, 2017; Eum et al., 2012; Mukherjee et al., 2014; Rahman et al., 2020). With respect to antepartum and postpartum depression, there have been individual studies that suggested adverse associations of antepartum inorganic As (Valdés et al., 2017), manganese (Mn) (McRae et al., 2020), and Pb exposures (Li et al., 2017) with depressive symptoms. However, to our knowledge, no single study has used a prospective design; examined mixtures of essential and non-essential metals; and focused specifically on depressive symptoms during and after pregnancy, a period of increased risk for depression and when modest associations may be more easily detected.

In the current study, we evaluated the extent to which early pregnancy erythrocyte concentrations of essential and non-essential metals, considered as a mixture and as independent exposures adjusted for co-exposure confounding, were prospectively associated with antepartum and postpartum depressive symptoms. We assessed depressive symptom outcomes at three timepoints and modeled trajectories from visits at mid-pregnancy to 12 months postpartum. We hypothesized that higher circulating concentrations of non-essential metals, as well as deficient or high concentrations of essential metals (i.e., outside the optimal dose), would be associated with higher odds of elevated depressive symptoms and a trajectory of increasing symptoms.

2. Methods

2.1. Study population

Women included in this study were participants in Project Viva, a longitudinal cohort that, between 1999–2002, recruited women during their first prenatal visit at Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice located in eastern Massachusetts. The cohort was initially established to examine associations of prenatal diet and other factors with maternal and child health. Exclusion criteria for enrollment included multiple gestation, inability to answer questions in English, gestational age ≥ 22 weeks at initial prenatal visit, and/or plans to move from the area prior to delivery (Oken et al., 2015).

Of 2128 live births, there were 28 participants with multiple enrollments from different pregnancies. In this analysis, we included the first enrollment, except for five participants who had more complete exposure and/or outcome data for their second enrollment (of a subsequent pregnancy). Then, of the 2100 individuals with a live birth, we included 1226 women in the current analysis with data on erythrocyte metal concentrations in first trimester blood samples; depressive symptoms assessed during mid-pregnancy, at 6 months postpartum, and/or at 12 months postpartum; and key covariates (see flow-chart: Figure S1). Participants provided written informed consent, and study protocols were approved by the Institutional Review Board at Harvard Pilgrim Health Care.

2.2. Erythrocyte metals exposure assessment

Blood samples were collected at enrollment during early pregnancy [median \pm interquartile range (IQR): 9.6 \pm 2.2 weeks of gestation], then centrifuged at 2000 rpm for 10 minutes at 4°C to separate erythrocytes from plasma and stored at -70°C. Since samples were not stored as whole blood (the predominate biomarker used in clinical tests for blood metal profiles), erythrocyte samples were utilized as a biomarker of metal and metalloid (hereafter referred to as “metals”) concentrations. Metals analyses were performed at the Mount Sinai Children’s Health Exposure Analysis Resource (CHEAR) Network Laboratory using triple quadrupole Inductively Coupled Plasma-Mass Spectrometry (ICP-MS; Agilent 8800 ICP-QQQ) for the assessment of 19 metals on a single run in MS/MS mode, and additionally, using a Direct Mercury Analyzer 80 (Milestone Inc.) for the separate quantification of mercury (Hg) (Zheng et al., 2021). All sample handling was done in an International Organization for Standardization (ISO) class 6 clean room with an ISO class 5 laminar flow clean hood.

For quality control (QC) measures, all machines underwent initial and continuous calibration verification. Each run included procedural blanks, and reproducibility was monitored via repeating analyses for 2% of samples ($n=52$ duplicates). Samples were analyzed in batches of 50 specimens and each batch included certified reference materials for trace element analyses in blood: Seronorm-Blood L3 (Whole blood Level 3, SERO, Billingstad, Norway) and/or NIST SRM 955c (Caprine whole blood, Gaithersburg, MD, U.S.). Additionally, one sample of the Trace Elements CHEAR QC high-level pool and one sample of the low-level pool were run in each batch of the analysis.

For the current analysis, we selected 11 of the 20 measured metals that had >80% detection across samples and whose technical duplicated samples had an intra-class correlation coefficient >0.60, ranging from 0.64 for copper (Cu) to 0.96 for Pb (Table S1). Recoveries of QC standards for these metals were between 90% and 110%. The intra-day coefficient of variation (CV) was <5%, and inter-day CV was <15%, except for concentrations near the limit of detection (LOD). The metals and their respective LODs included in this analysis (units: ng/g erythrocytes) are As, 0.15; barium (Ba), 0.41; Cd, 0.06; cesium (Cs), 0.06; Cu, 1.85; Hg, 0.30; magnesium (Mg), 4.15; Mn, 0.42; Pb, 0.07; selenium (Se), 1.73; and zinc (Zn), 8.74.

2.3. Maternal depressive symptoms

Women's recent depressive symptoms were evaluated via self-reported questionnaire using the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) during mid-pregnancy and at 6 and 12 months postpartum. While the EPDS was initially developed and validated for postpartum depression, this questionnaire has also been validated for use during pregnancy (Kozinszky and Dudas, 2015; Murray and Cox, 1990). The EPDS is a 10-item screening measure that asks about cognitive and affective symptoms in the past week, rated on a 4-point Likert scale (total possible score range 0 to 30), with a higher score indicating greater severity of depressive symptoms. We dichotomized EPDS score, as the EPDS was designed and has been validated to screen for depression risk as a categorical scoring tool, and classified women as having non-elevated or elevated depressive symptoms using a cut-off of 13, which has been shown to indicate elevated depressive symptoms/probable depression (Cox et al., 1987; Matthey et al., 2006). Specifically, the scale at 13 has a sensitivity of 86% and specificity of 78% for the diagnosis of postpartum depression (Cox et al., 1987).

2.4. Covariates

During their initial study visit, participants completed a structured questionnaire, which collected information on sociodemographic information (maternal age, marital status, parity, education, race/ethnicity, household income, immigrant status), pregnancy intention/wantedness, cigarette smoking, pre-pregnancy weight and height, and prenatal diet. We calculated pre-pregnancy body mass index (BMI) from self-reported weight and height. Participants self-reported dietary habits in early pregnancy using a semi-quantitative Food Frequency Questionnaire (FFQ) (Fawzi et al., 2004). A similar FFQ was administered at mid-pregnancy. Additionally, clinical lab values for first trimester hemoglobin levels and hematocrit were abstracted from medical records.

At the mid-pregnancy visit [median \pm IQR: 27.7 \pm 2.0 weeks of gestation], women completed questionnaires that measured social support from family/friends (Turner et al., 1990) and pregnancy-related anxiety (Wadhwa et al., 1993). Additionally, three questions were included on the mid-pregnancy questionnaire to determine pre-pregnancy depression history. As previously described (Rich-Edwards et al., 2006), participants were asked, "Before this pregnancy, was there ever a period of time when you were feeling depressed or down or when you lost interest in pleasurable activities most of the day, nearly every day, for at least 2 weeks?"; if this question was endorsed, and she also reported seeing a health care professional who said she was depressed and/or had been prescribed medication for depression then we categorized that woman as having a history of depression.

2.5. Statistical analysis

In all analyses of associations between early pregnancy metal exposures and odds of elevated depressive symptoms, we \log_2 -transformed skewed concentrations for the 11 metals. Machine-read metal concentration values <LOD were utilized in analysis, to optimize statistical power and avoid biased exposure concentration estimates due to censoring at the detection limit (Kim et al., 1995; Schisterman et al., 2006). However, in cases where machine readings provided values 0 (i.e., $n=20$ for As, $n=4$ for Ba), we

substituted the lowest positive value in our samples of those with erythrocyte biomarkers, prior to \log_2 -transformation. We explored correlations between metals via Spearman's rank correlation coefficients (r_s). All analyses were conducted using R version 4.1.0 (R Foundation for Statistical Computing).

Using directed acyclic graphs (Greenland et al., 1999) and knowledge from prior literature (Bulka et al., 2019; Lin et al., 2021; Rich-Edwards et al., 2006), we identified *a priori* potential confounders, as well as factors that influence erythrocyte metal concentrations or risk of maternal depressive symptoms (see: Figure S1). For those variables that were continuous, we used generalized additive models to evaluate the linearity of associations with log odds of elevated depressive symptoms, and only transformed variables with distinct inflection points. Thus, we selected the following potential confounders for inclusion in all models: maternal age at enrollment (< or \geq 28 years; based on inflection point from generalized additive models), education (college graduate; yes, no), self-identified race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other), parity (nulliparous or multiparous), maternal cigarette smoking status (never, former, during pregnancy), marital status (married/cohabitating or not), annual household income (< or $>$ \$70,000), early pregnancy seafood consumption (continuous servings/week of the sum of canned tuna, shellfish, dark meat fish, and other fish from FFQ), and white rice consumption (continuous servings/week). For seafood and white rice consumption, in cases where early pregnancy data were missing, we used mid-pregnancy information when available ($n=51$, 4% of analytic cohort).

We first assessed the linearity of associations between each exposure and the log odds of elevated depressive symptoms at the mid-pregnancy and 6 and 12 months postpartum visits, using covariate-adjusted generalized additive models. As all associations were linear and our outcome was relatively rare at each timepoint (6–9%), we fit logistic regression models, mutually adjusted for the other metal co-exposures, to estimate the odds of elevated depressive symptoms associated with a doubling of erythrocyte metal concentration. For all three models, we assessed Cook's distance plots and observed no influential outliers to consider for removal.

To evaluate the joint association of metal mixtures with odds of elevated depressive symptoms at single timepoints, we used quantile-based g-computation. Briefly, quantile g-computation, a parametric, generalized-linear-model based implementation of g-computation, provides an effect estimate per simultaneous quantile increase in all metals (i.e., overall mixture effect), as well as weights that represent the importance of individual components of the mixture in the positive or negative direction (Keil et al., 2020). Based on generalized additive models, we assumed linearity in associations, and fit three models for each EPDS timepoint: all metals combined mixture group, non-essential metals mixture group (As, Ba, Cd, Cs, Hg, Pb) adjusted for essential metal co-exposures, and essential metals mixture group (Cu, Mg, Mn, Se, Zn) adjusted for non-essential metal co-exposures. We estimated the odds ratio (OR) and 95% 'pointwise' bounds per quartile increase in the overall mixture using 10,000 bootstraps.

Additionally, we were interested in distinct symptom trajectories from mid-pregnancy through 12 months postpartum. We utilized latent class mixed modeling (Proust-Lima et al., 2017) to model trajectories of depressive symptoms using continuous EPDS scores. Participants included in this analysis were women who had completed the mid-pregnancy EPDS questionnaire and at least one postpartum questionnaire ($n=1010$). We fit separate models assuming 1–6 latent classes and ran models with and without a quadratic term for time and then determined goodness-of-fit based on the Bayesian Information Criteria and entropy. We also ran the latent class mixed modeling with and without including history of depression as an additional fixed term, but as results did not appreciably change, we did not include history of depression in the final model. A model with three latent classes and a quadratic term for time provided the best fit. We assigned participants to the group to which they had the highest probability of belonging. Finally, we ran 1) multinomial logistic regression models, mutually adjusted for the other metal co-exposures, with participants classified as belonging to one of the three trajectories as a categorical outcome, and 2) quantile g-computation models, using two separate binary outcomes (i.e., comparing each trajectory to the referent group).

For sensitivity analyses, we first used inverse probability of censoring weighting (IPCW) to quantify potential selection bias due to cohort attrition, incomplete EPDS questionnaires from mid-pregnancy to 12 months postpartum, and/or exclusion of a small number of participants with missing covariate data in complete case analysis (see flow-chart: Figure S2). Among those eligible for inclusion in our analysis (1392 women with measured early pregnancy erythrocyte metal concentrations), we explored predictors of dropout/exclusion and then calculated stabilized weights (Cole and Hernán, 2008). We additionally truncated the stabilized weights at the 1st and 99th percentiles (Hernán et al., 2004) for use in analyses. Also, in logistic regression models, we additionally adjusted for factors known to influence erythrocyte metal concentrations [gestational week at blood collection for metal measurements (continuous), first trimester hemoglobin levels (continuous)] and risk factors for depressive symptoms [history of depression (yes, no), pre-pregnancy BMI (continuous), mid-pregnancy social support from family/friends (continuous 0–15 scale), immigrant status (U.S. born, foreign born), pregnancy intention (trying, not trying but glad, not now/never), pregnancy-related anxiety (high, low)]. Furthermore, to evaluate possible co-exposure amplification bias due to the inclusion of all exposures in a singular model (Weisskopf et al., 2018), we ran logistic and multinomial models for each metal separately.

Also, we explored the EPDS outcome with a cut-off of 10 (rather than 13) in logistic regression models, as this lower cut-off score is oftentimes used as a marker of possible depression and is more sensitive, although less specific for diagnosis of major depression (Cox et al., 1987; Gibson et al., 2009). Thus, using this less conservative cut-off may capture women experiencing sub-clinical as well as clinical depressive symptoms. Additionally, we examined another exposure window of susceptibility during pregnancy using data from a subset of participants in our analytic cohort who also had metals (Hg, Mn, Pb, Se) measured in mid-pregnancy erythrocyte samples ($n=594$ with at least one EPDS score). To do so, we fit logistic regression models, mutually adjusted for all four co-exposures, to assess the cross-sectional association with mid-pregnancy EPDS 13 and prospective associations with 6- and 12-months postpartum EPDS 13.

3. Results

3.1. Study population characteristics

Among the 1226 study participants, most women were aged 28 years or older at enrollment ($n=1058$, 86%), White ($n=931$, 76%), college graduates ($n=888$, 72%), married or cohabitating ($n=1158$, 94%), had an annual household income $> \$70,000$ ($n=784$, 64%), and reported never smoking ($n=829$, 68%). Half of the participants were nulliparous ($n=607$, 50%) (Table 1).

Compared to Project Viva participants who were excluded from the current analyses (i.e., $n=874$ without early pregnancy erythrocyte metal measures, EPDS measures, and/or covariate data), those included were older and more likely to be non-Hispanic White, a college graduate, married or cohabitating, and have a higher household income (Table S2).

3.2. Metal exposures

The median \pm IQR of erythrocyte metal concentrations (ng/g) are presented in Table 1. Concentrations of essential metals were within reference ranges for measurement of erythrocytes (Quest Diagnostics, 2019), and when adjusting for hematocrit as a proxy estimate of whole blood levels (and further considering a scenario where only 60% of metals were bound to erythrocytes), concentrations of non-essential metals were relatively low compared to whole blood reference values (Quest Diagnostics, 2019). For example, the 99th percentile hematocrit-adjusted Pb concentration is 18.5 ng/g (≈ 1.85 $\mu\text{g/dL}$ assuming equivalency between wet-weight and volumetric-based units), whereas the adult whole blood reference value is < 5 $\mu\text{g/dL}$ (Table S1).

All metals, except for Ba, were positively correlated, although weak to moderately (r_s : 0.00 to 0.59). The negative correlations between Ba and the other ten metals ranged from -0.05 (r_s with Cd) to -0.24 (r_s with Zn). The strongest correlations were between Cu and Zn (r_s : 0.59) and As and Hg (r_s : 0.56) (Figure 1).

3.3. Maternal depressive symptoms

With a cut-off of ≥ 13 for the EPDS, 9% of women had elevated depressive symptoms during mid-pregnancy, 8% at 6 months, and 6% at 12 months postpartum. Overall, 12% of women reported a pre-pregnancy history of depression (Table 1). Compared to those with EPDS < 13 , participants with EPDS ≥ 13 at any given visit were more likely to be younger at enrollment, have a household income $\leq \$70,000$, not be a college graduate, self-identify as Black or Hispanic, report consuming more white rice during early pregnancy, and not be married or cohabitating (Tables 1, S3). On average, erythrocyte metal concentrations were similar when stratified by mid-pregnancy EPDS (Table 1) and by 6 months and 12 months postpartum EPDS categories (Table S3).

Using latent class mixed modeling, three distinct depressive trajectories best fit the EPDS repeat score data from mid-pregnancy to 12 months postpartum. Most participants were categorized with a stable low trajectory ($n=785$, 82%), while 11% ($n=103$) were classified with moderate symptoms at the mid-pregnancy visit that increased in the postpartum period,

and 8% ($n=75$) with elevated symptoms at the mid-pregnancy visit that decreased in the postpartum period (Figure 2).

3.4. Logistic and multinomial regression analyses

After adjustment for *a priori* confounders and metal co-exposures, early pregnancy erythrocyte metal concentrations were largely not associated with odds of elevated depressive symptoms at mid-pregnancy and 6 and 12 months postpartum. For the majority of the 11 metals, the OR was close to the null (i.e., 1.00), and confidence intervals (CI) were imprecise (Figure 3). Erythrocyte Pb concentration was consistently associated with higher odds of elevated depressive symptoms, but CIs included the null for all timepoints [e.g., 1.19 (95% CI: 0.80, 1.77) for mid-pregnancy symptoms per doubling Pb]. In contrast, As and Hg were associated with lower odds of elevated depressive symptoms at one antepartum or postpartum timepoint. Per doubling of its erythrocyte concentration, As was associated with 0.88 (95% CI: 0.77, 1.00) times the odds of elevated depressive symptoms at mid-pregnancy, and Hg was associated with 0.80 (95% CI: 0.68, 0.95) times the odds of elevated depressive symptoms at 12 months postpartum. Similarly, erythrocyte Cd was associated with lower odds of elevated depressive symptoms at 6 months postpartum, although CIs included the null [i.e., 0.75 (95% CI: 0.53, 1.06) per doubling of Cd]. These associations with lower odds of depressive symptoms were not consistent across the three follow-up periods, with, for example, As concentration being associated with higher odds of postpartum depressive symptoms [e.g., 1.13 (95% CI: 0.94, 1.40) for 6 months postpartum symptoms per doubling As]. Erythrocyte concentrations of Ba, Cu, Cs, Mg, Mn, Se, and Zn were not associated, even weakly, with EPDS 13 at any of the three timepoints (Figure 3, Table S4).

Similarly, erythrocyte metals were generally not strongly associated with the maternal depressive symptom trajectories. Erythrocyte As concentration was associated with lower odds of being classified in the elevated depressive symptoms mid-pregnancy followed by decreasing symptom trajectory [e.g., 0.84 (95% CI: 0.73, 0.97) per doubling of As], relative to the stable low trajectory. While CIs included the null, the ORs for Pb and Se were largest in magnitude for being classified with a trajectory other than stable low. For example, a doubling in early pregnancy erythrocyte Pb concentration was associated with 1.37 (95% CI: 0.93, 2.03) times the odds of having a moderate mid-pregnancy, then increasing symptom trajectory and 1.29 (95% CI: 0.81, 2.04) times the odds of having an elevated mid-pregnancy, then decreasing symptom trajectory relative to the stable low trajectory. The largest OR was between erythrocyte Se and the elevated mid-pregnancy then decreasing symptom trajectory relative to a stable low trajectory [i.e., 2.09 (95% CI: 0.74, 5.94) per doubling of Se] (Figure 4, Table S5). When comparing odds of having a moderate mid-pregnancy then increasing symptom trajectory to the elevated mid-pregnancy then decreasing symptom trajectory, there were no associations with these metals (data not shown).

3.5. Quantile g-computation mixtures analyses

The overall mixture of essential and non-essential metals was not associated with odds of elevated mid-pregnancy or postpartum depressive symptoms. Associations were also null when 1) only considering essential or non-essential elements (adjusted for the other set

of exposures), and 2) analyzing the trajectory outcomes in a binary fashion (i.e., stable low versus elevated mid-pregnancy, then decreasing symptom trajectory; stable low versus moderate mid-pregnancy, then increasing symptom trajectory) (Table 2, Figure S3).

3.6. Sensitivity analyses

The use of IPCW (Table S6) and the additional adjustment for factors that influence erythrocyte metal concentrations and risk of depressive symptoms (Table S7) did not appreciably change most results. However, for the association of Pb with odds of elevated depressive symptoms at 12 months postpartum, the OR was slightly strengthened with IPCW, although CIs still included the null [i.e., per doubling of Pb, 1.55 (95% CI: 0.91, 2.62) with IPCW versus 1.36 (95% CI: 0.79, 2.34) with complete case] (Table S6). When comparing single-exposure models to those that were adjusted for metal co-exposures, effect estimates were similar for odds of elevated depressive symptoms at mid-pregnancy and 6 months postpartum (Table S8), as well as for depressive symptom trajectories (data not shown). However, estimates between these two types of models were less stable for the EPDS at 12 months postpartum. Specifically, ORs for As and Pb were somewhat weaker, although in the same direction, for the single-exposure models (Table S8) compared to the models adjusted for co-exposures (Table S4). The directions of association differed for Se and Zn in models adjusted for co-exposures versus single-exposure models, although the CIs were imprecise [e.g., 2.53 (95% CI: 0.51, 14.1) in models adjusted for co-exposures versus 0.86 (95% CI: 0.29, 2.64) in single-exposure models per doubling Zn] (Table S8).

When categorizing the EPDS with a more sensitive binary cut-off of ≥ 10 , directions and magnitude of most associations were similar to the main analyses. The exceptions to this were that As was not associated with (higher or lower) odds of elevated depressive symptoms (EPDS ≥ 10) at any timepoint, while estimates for Se (with mid-pregnancy symptoms) and Pb (with symptoms at 12 months postpartum) were more precise, although CIs still included the null, with EPDS ≥ 10 compared to EPDS ≥ 13 (Table S9). When considering the four metals (Hg, Mn, Pb, Se) measured in mid-pregnancy erythrocyte samples, there were no associations with odds of elevated depressive symptoms at EPDS ≥ 13 (Table S10).

4. Discussion

As previously proposed for maternal health complications such as hypertensive disorders of pregnancy (Varshavsky et al., 2019), physiological and hormonal alterations that occur during pregnancy, including those reflective of the HPA activity, may act as a stress test and possibly shift women towards a threshold of clinically relevant disease for a range of health outcomes. For example, activation of the HPA axis may be correlated with clinical depression (Varghese and Brown, 2001; Varshavsky et al., 2019), making pregnancy a possible opportune time to assess associations of exogenous exposures with depressive symptoms. Despite this context, among a large cohort of women with generally low non-essential metal exposure, essential blood metal levels within recommended ranges, and a relatively low prevalence of depressive symptoms compared to the general population, we observed no prospective associations between early pregnancy erythrocyte

metal concentrations and antepartum and postpartum depressive symptoms. We found null associations with both non-essential and essential metals, whether adjusting for co-exposures or assessing the association of the overall mixture. Furthermore, these associations remained null when looking at the outcome in single time points, trajectories, and with a less stringent cut-off (< 10) that may include sub-clinical symptoms. There was weak but imprecise suggestive evidence that higher early pregnancy As, Pb, and Se concentrations may be associated with more antepartum and/or postpartum depressive symptoms, but CIs included the null. For As and Hg, two non-essential metals that were moderately correlated and for which seafood is a major exposure source, higher erythrocyte concentrations were associated with lower odds of elevated depressive symptoms at certain timepoints.

Most population-based studies of metal exposures and depression in young to middle-aged adults have evaluated individual non-essential metal exposures, have not focused on the pre- and postnatal period with respect to exposures and/or outcomes, and typically have been cross-sectional in design. The most studied metal in these cases has been Pb, which may confer susceptibility to depression via alterations of monoamine neurotransmitters and the HPA axis (Kala and Jadhav, 1995; Nehru and Sidhu, 2001; Orisakwe, 2014; van den Bosch and Meyer-Lindenberg, 2019). Literature utilizing cross-sectional National Health and Nutrition Examination Survey (NHANES) data has reported mixed associations between blood or urinary Pb (biomarkers reflective of short-term exposure) and adult depression, depending on age, sex, and/or NHANES survey year. Specifically, higher blood Pb was associated with increased odds of a major depressive disorder diagnosis in adults aged 20–39 years (NHANES 1999–2004) (Bouchard et al., 2009) and with depressive symptoms among women aged 20–47 years, but not in men or older women (NHANES 2011–2012) (Buser and Scinicariello, 2017). However, Pb levels were not associated with depressive symptoms in adults [NHANES 2005–2010 (Berk et al., 2014); 2005–2006 (Golub et al., 2010); 2011–2012 (Shiue, 2015)], where potential age- and sex-specific differences were not considered. Additionally, when considering concentrations measured in bone, a biomarker of long-term cumulative exposure, tibia bone Pb level was positively associated with elevated depressive symptoms among premenopausal women in the Nurses' Health Study (Eum et al., 2012).

Specific to the antepartum period, in a cross-sectional study of Shanghai women, mid-pregnancy blood Pb had a non-linear relationship with continuous Symptom-Checklist-90-Revised depression scores, in which a positive association was observed only for blood Pb concentrations below 2.57 $\mu\text{g}/\text{dL}$; above this inflection point there was no association (Li et al., 2017). Comparing Pb concentrations across studies, almost all concentration values in our analytic cohort (i.e., 99th percentile adjusted for hematocrit $\approx 1.85 \mu\text{g}/\text{dL}$, assuming wet-weight \approx liquid volume measurements) fell below the previously observed 2.57 $\mu\text{g}/\text{dL}$ threshold. We did not see evidence of non-linearity in our study. The variations in exposure ranges and the use of continuous versus binary outcomes are some possible reasons for different findings.

Most prior studies of other trace elements and depression also have utilized cross-sectional NHANES data. One study found that urinary Ba, Cd, and Cs levels were not associated

with elevated depressive symptoms in adults ≥ 20 years (NHANES 2011–2012) (Shiue, 2015). Blood Cd has been cross-sectionally associated with adult depressive symptoms [NHANES 2005–2010 (Berk et al., 2014), 2011–2012 (Buser and Scinicariello, 2017)], with a stronger association among men aged 20–47 years (Buser and Scinicariello, 2017), whereas blood Hg has been associated with lower odds of depressive symptoms (Berk et al., 2014). In our study, we observed no adverse associations of erythrocyte Ba, Cd, or Cs with maternal depressive symptoms. In fact, directions of association for Cd, as well as Hg, with postpartum depressive symptoms were the opposite of our hypothesized direction (i.e., with lower odds). We adjusted analyses for seafood consumption, as fish is a major source of organic Hg exposure (Sunderland et al., 2018). However, negative residual confounding by healthy diet and other unaccounted for health behaviors may explain the appearance of a protective association (Choi et al., 2008). A main dietary source of Cd is leafy vegetables (Kim et al., 2018), and thus diet could also negatively confound our associations, especially in a cohort with a low prevalence of smoking (the main non-dietary exposure route for Cd). However, a diet-wide association study in Project Viva found no associations between early pregnancy erythrocyte Cd concentrations and dietary items (Lin et al., 2021); therefore, the weak protective association between Cd and depressive symptoms at 6 months postpartum, in which CIs included the null, could reflect of uncertainty in the estimate.

Few prior studies have explored As exposure as a risk factor for adult depression. In our study, metals were measured in erythrocytes, which reflect total As exposure, containing both 1) toxic inorganic and 2) relatively non-toxic organic species present in seafood (Hughes, 2006). Also, in low-exposed populations, erythrocyte As is considered to represent more recent exposures, whereas hair and toenail concentrations may reflect cumulative exposure (Hall et al., 2006; Hughes, 2006). As previously reported in our cohort, seafood intake was highly correlated with erythrocyte As (Lin et al., 2021), and thus this biomarker may be a proxy for recent dietary exposure to non-toxic organic As. Even after adjustment for early pregnancy diet, we observed associations of As with lower depressive symptoms at mid-pregnancy, as well as with lower odds of being in a symptom trajectory other than stable low (i.e., elevated symptoms at some point during the pre- and/or postnatal window); this could be reflective of residual negative confounding, as we hypothesized was the case with Hg. In contrast, higher As was modestly associated with higher odds of elevated postpartum depressive symptoms, but with CIs that included the null. Three cross-sectional studies observed positive associations between different As measures (i.e., urinary arsenous acid $>LOD$, residing in an area with contaminated water, urinary inorganic As) with depressive symptoms, among adults aged ≥ 20 years (NHANES 2015–2016) (Rahman et al., 2020), premenopausal Indian women (Mukherjee et al., 2014), and Chilean women ≥ 25 years and with a history of depression (Valdés et al., 2017). Our findings indicated As may be a potential risk factor for postpartum depressive symptoms, which aligns with these cross-sectional studies (Mukherjee et al., 2014; Rahman et al., 2020; Valdés et al., 2017) and a mouse model in which perinatal exposure to As was associated with dysregulation of markers of HPA activity (e.g., higher corticosterone levels) (Martinez et al., 2008). To better understand this possible association, future prospective studies of As and depressive symptoms should consider use of biomarkers and analytical methods in which arsenic can be speciated.

Literature on associations between essential metals and antepartum, postpartum, or overall adult depression tends to focus on deficiencies (Leung and Kaplan, 2009; Nakamura et al., 2019; Wang et al., 2018). As Project Viva participants were well nourished and had blood concentrations of Cu, Mg, Mn, Se, and Zn within recommended ranges, we did not expect or observe non-linear or protective associations with depressive symptoms. Even within recommended nutrient ranges, certain metals, such as Mn, have been implicated as being neurotoxic at higher levels (Chen et al., 2015). In a prospective study of women in Mexico, late pregnancy, but not mid-pregnancy, blood Mn was positively associated with continuous EPDS scores at 12 months postpartum, but not associated with elevated depressive symptoms as indicated by an EPDS score ≥ 13 (17% prevalence) (McRae et al., 2020). Consistent with these findings, we observed no associations between Mn concentrations and EPDS ≥ 13 at 12 months postpartum. Our cohort had a lower prevalence of postpartum depressive symptoms (i.e., 6% at 12 months postpartum), the timing of exposure measurement during pregnancy varied, and different blood biomarkers were used – distinctions in study population and design that hinder comparability. Like with our Mn findings, we observed no adverse associations between other essential metals and elevated maternal depressive symptoms, although there was weak suggestive evidence that higher erythrocyte Se concentration was associated with increased depressive symptoms in our trajectory and sensitivity analyses. In studies of young adults, the highest levels of serum or toenail Se have been associated with greater depressive symptoms (Colangelo et al., 2014; Conner et al., 2014), highlighting the importance of considering both low and high levels of Se as potential risk factors for depression.

Limitations of our study include potential residual confounding, type II error, selection bias, external generalizability, and lack of power to detect more modest associations. Although we adjusted for sociodemographic and dietary factors, we observed apparent protective associations between non-essential metals (i.e., As, Cd, Hg) and maternal depressive symptoms, which we hypothesize may be due to negative confounding or type II error (i.e., false positives). Additionally, from the visits at mid-pregnancy to 12 months postpartum, we had attrition in responses to the EPDS questionnaires, and thus results were prone to selection bias, which we attempted to address by using IPCW. We did not observe appreciable change with the use of IPCW, supporting the robustness of our findings. However, due to the use of stabilized weights, we were only able to standardize estimates to the sub-population of 1392 Project Viva participants with metals measured in early pregnancy erythrocytes, and residual bias may be present, as these women appear to be sociodemographically different than the overall 2100 women who were enrolled. In our assessment of exposure, some metals have different half-lives in erythrocytes and therefore may reflect short-term exposures and be less suitable biomarkers for cumulative exposure. It is plausible that among populations with low-level exposures, chronic rather than short-term exposure may have a larger impact on decrements to mental health. The quantification of metals in erythrocytes makes results more difficult to compare to prior studies that used whole blood or urine as a biomarker of metal exposure. Also, we measured total As and Hg concentrations, rather than the more neurotoxic and health-relevant species [i.e., inorganic As and methylmercury (MeHg)], although in the case of Hg, total whole blood concentration is a reliable proxy for MeHg in fish eating populations, and approximately 90% of

MeHg is erythrocyte-bound (Berglund et al., 2005; Branco et al., 2017). Furthermore, our study population was primarily of moderately high socioeconomic status, lived in eastern Massachusetts at the time of birth, had health insurance, and had generally low concentrations of toxic metals – all factors that may have contributed to the relatively low prevalence of antepartum and postpartum depressive symptoms compared to recent U.S. estimates (Bauman et al., 2020). Thus, generalizability of our results may be limited; and we were not powered to explore the potential for effect modification by social stressors, as well being underpowered to detect modest main effects.

Despite these limitations, our study has several strengths. First, compared to most prior cross-sectional studies on metal exposures and adult depression, we used a prospective study design that establishes temporality in associations. In addition, rather than only considering a single metal exposure in isolation, we evaluated joint exposures to essential and non-essential metals in relation to depressive symptoms, using regression models adjusted for co-exposure confounding and quantile g-computation. While we cannot discount co-exposure amplification bias in the logistic or multinomial models mutually adjusted for all metals, correlations between these metals were low to moderate, estimates remained null, and, in most cases, ORs only slightly changed from those in single-exposure models. The consistency between directions of the ORs and of quantile g-computation weights, particularly for the EPDS at 12 months postpartum, indicates that the few unstable estimates (e.g., Se and Zn) may be a product of a small event rate and more modest sample size. We also had the advantage of data from multiple EPDS questionnaires during the antepartum and postpartum periods, which allowed for exploration of depressive symptom trajectories from mid-pregnancy to 12 months postpartum as an outcome. Lastly, our study is one of few that has examined exposure to metals exclusively in women during the antepartum period, a time of major physiological and hormonal changes and which has been implicated as a period during which mood disorders may more readily present for women. While most studies of exposure to environmental toxicants during pregnancy focus on neurobehavioral outcomes in children, maternal health is also of great importance, and in fact impacts child development. Routine antepartum care involves more frequent contact with providers who can screen for symptoms and provide recommendations that reduce potential adverse exposures, with the potential to improve intergenerational health outcomes, as maternal depression is associated with adverse consequences for the affected women and their children (Meltzer-Brody, 2011).

In summary, in this prospective study of U.S. women with relatively low levels of non-essential metals and a relatively low prevalence of depressive symptoms, early pregnancy erythrocyte concentrations of essential and non-essential metals were not consistently associated with maternal depressive symptoms. Although we did not find strong associations, studies among cohorts of diverse women, experiencing different degrees of depressive symptoms and with a wider range of metal exposures, will help elucidate whether metals, such as As, Pb, and Se, are risk factors for depression, particularly during the antepartum and postpartum periods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

As	arsenic
Ba	barium
BMI	body mass index
Cd	cadmium
CHEAR	Children's Health Exposure Analysis Resource
CI	confidence interval
Cs	cesium
Cu	copper
CV	coefficient of variation
EPDS	Edinburgh Postnatal Depression Scale
FFQ	Food Frequency Questionnaire
Hg	mercury
HPA	hypothalamic-pituitary-adrenal
IPCW	inverse probability of censoring weighting
IQR	interquartile range
ISO	International Organization for Standardization
LOD	limit of detection
MeHg	methylmercury
Mg	magnesium
Mn	manganese
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio

Pb	lead
r_s	Spearman's rank correlation coefficient
Se	selenium
QC	quality control
Zn	zinc

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Highlights:

- Assessed pregnancy metal exposures and antepartum/postpartum depressive symptoms
- Measured 11 metals in 1st trimester erythrocytes collected from 1226 pregnant women
- Depressive symptoms ascertained by Edinburgh Postnatal Depression Scale
- Blood metal concentrations were overall not associated with depressive symptoms
- As, Pb and Se were weakly, but imprecisely, associated with more depressive symptoms

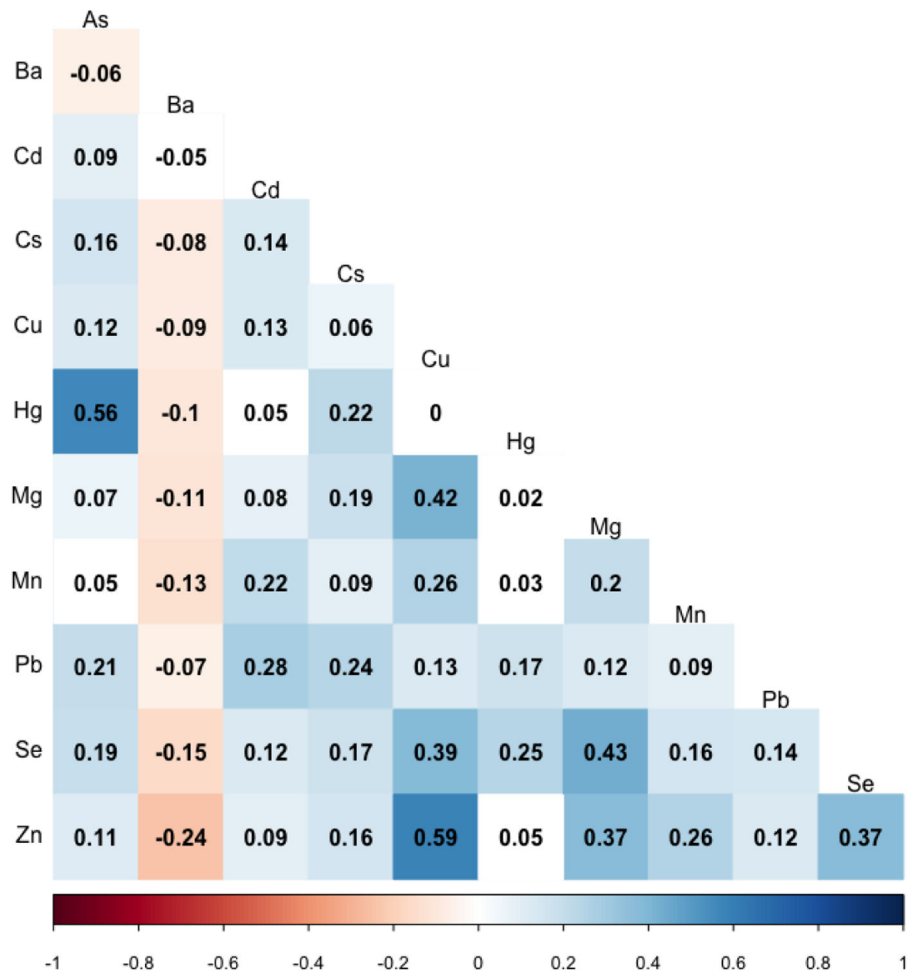


Figure 1. Spearman correlations of erythrocyte concentrations of metals in the analytic cohort ($n=1226$). Notes: Correlations are shown in blue (positive) or red (negative). Abbreviations: As, arsenic; Ba, barium; Cd, cadmium; Cs, Cesium; Cu, Copper; Hg, mercury; Mg, magnesium; Mn, manganese; Pb, lead; Se, selenium; Zn, zinc.

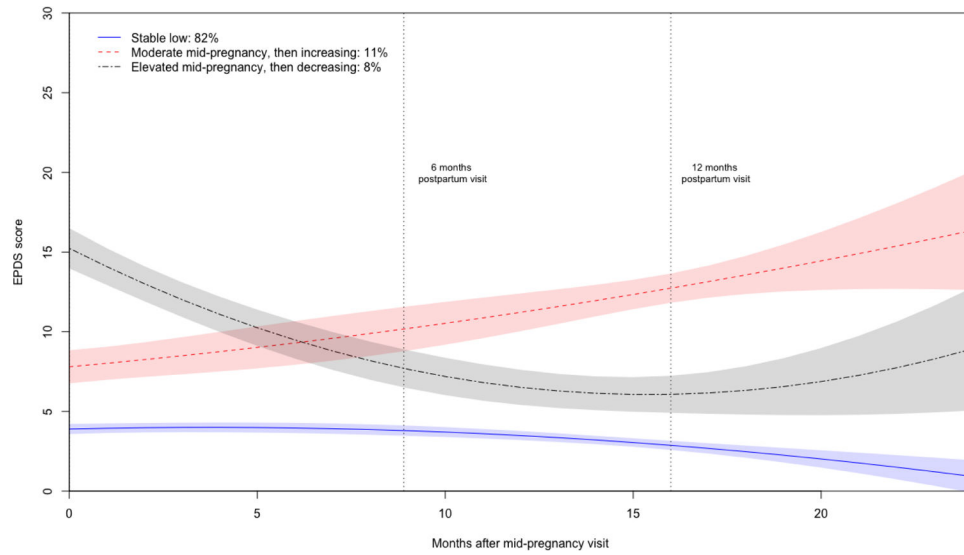


Figure 2. Predicted depressive symptom trajectories from time of the mid-pregnancy to 12 months postpartum questionnaire, based on latent class mixed modeling, among Project Viva participants with data available on early pregnancy erythrocyte metal concentrations, the Edinburgh Postnatal Depression Scale (EPDS) at the mid-pregnancy visit, and the EPDS at 6 months postpartum and/or 12 months postpartum visits

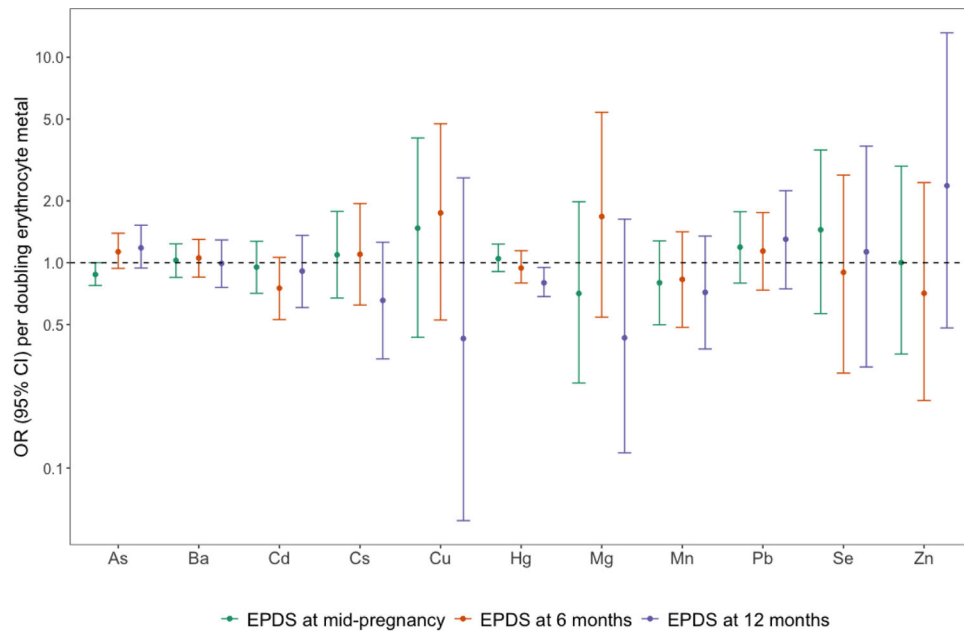


Figure 3.

Adjusted odds ratios (95% confidence intervals) between a doubling of early pregnancy erythrocyte metal concentrations and elevated depressive symptoms, measured via the Edinburgh Postnatal Depression Scale (EPDS), among Project Viva participants. Each of the three models was adjusted for maternal age at enrollment, education, parity, marital status, race/ethnicity, smoking status, household income, early pregnancy seafood consumption, early pregnancy white rice consumption, and metal co-exposures. Numerical values shown in Table S4. Abbreviations: As, arsenic; Ba, barium; Cd, cadmium; CI, confidence interval; Cs, Cesium; Cu, Copper; EPDS, Edinburgh Postnatal Depression Scale; Hg, mercury; Mg, magnesium; Mn, manganese; OR, odds ratio; Pb, lead; Se, selenium; Zn, zinc.

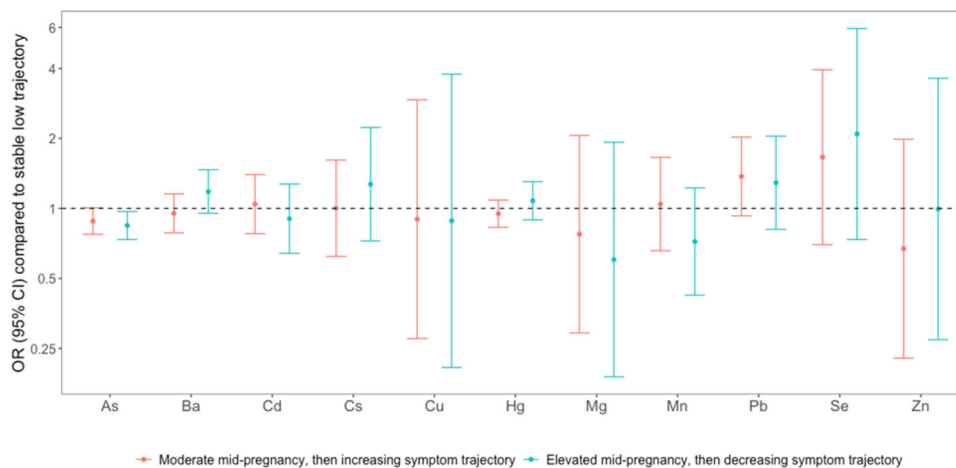


Figure 4. Adjusted odds ratios (95% confidence intervals) between doubling of early pregnancy erythrocyte metal concentrations and 1) elevated mid-pregnancy, then decreasing ($n=103$), and 2) moderate mid-pregnancy, then increasing, depressive symptom ($n=75$) trajectories, compared to a stable low trajectory ($n=785$), among Project Viva participants who completed the Edinburgh Postnatal Depression Scale at mid-pregnancy and at 1 postpartum time-point. The model was adjusted for maternal age at enrollment, education, parity, marital status, race/ethnicity, smoking status, household income, early pregnancy seafood consumption, early pregnancy white rice consumption, and metal co-exposures. Numerical values shown in Table S5. Abbreviations: As, arsenic; Ba, barium; Cd, cadmium; CI, confidence interval; Cs, Cesium; Cu, Copper; EPDS, Edinburgh Postnatal Depression Scale; Hg, mercury; Mg, magnesium; Mn, manganese; OR, odds ratio; Pb, lead; Se, selenium; Zn, zinc.

Table 1.

Characteristics of 1226 women in Project Viva included in this study,^a overall and stratified by depressive symptom status, measured via the Edinburgh Postnatal Depression Scale, at mid-pregnancy

	Overall cohort	Mid-pregnancy depressive symptoms ^b		p-value ^f
	(n=1226) ^c	EPDS 13 (n=96) ^d	EPDS <13 (n=1032) ^e	
	Median ± IQR or N (%)	Median ± IQR or N (%)	Median ± IQR or N (%)	
Maternal and household characteristics				
Early pregnancy seafood consumption (servings/week) ^g	1.5 ± 1.5	1.5 ± 1.5	1.5 ± 1.5	0.24
Early pregnancy white rice consumption (servings/week) ^g	1.0 ± 2.5	1.0 ± 2.5	1.0 ± 2.5	0.08
Age at enrollment (years)	32.6 ± 5.7	32.1 ± 6.2	32.6 ± 5.6	0.03
<28 years	168 (14)	24 (25)	131 (13)	<0.01
College graduate (%)	888 (72)	59 (61)	762 (74)	0.01
Nulliparous (%)	607 (50)	41 (43)	530 (51)	0.13
Married or cohabitating (%)	1158 (94)	80 (83)	987 (96)	<0.01
Annual household income >\$70,000 (%)	784 (64)	43 (45)	681 (66)	<0.01
Race/ethnicity (%)				
Non-Hispanic White	931 (76)	61 (64)	804 (78)	<0.01
Non-Hispanic Black	128 (10)	16 (17)	99 (10)	0.04
Hispanic	73 (6)	9 (9)	58 (6)	0.21
Other	94 (8)	10 (10)	71 (7)	0.28
Smoking status (%)				
Never	829 (68)	66 (69)	692 (67)	0.82
Former	254 (21)	16 (17)	222 (22)	0.32
During pregnancy	143 (12)	14 (15)	118 (11)	0.45
EPDS 13 at mid-pregnancy ^b	96 (9)	-	-	-
EPDS 13 at 6 months postpartum ^{c,d,e}	75 (8)	19 (25)	47 (6)	<0.01
EPDS 13 at 12 months postpartum ^{c,d,e}	53 (6)	14 (20)	34 (5)	<0.01
Pre-pregnancy history of depression ^{c,e}	136 (12)	32 (33)	100 (10)	<0.01
Early pregnancy erythrocyte metal concentrations (ng/g)				
Arsenic	0.9 ± 1.1	0.8 ± 1.3	0.9 ± 1.1	0.47
Barium	3.2 ± 4.0	2.9 ± 3.9	3.2 ± 4.0	0.99
Cadmium	0.4 ± 0.3	0.4 ± 0.3	0.4 ± 0.2	0.96
Cesium	2.6 ± 1.1	2.5 ± 1.3	2.6 ± 1.1	0.24
Copper	564 ± 103	571 ± 120	561 ± 101	0.14
Mercury	3.3 ± 4.9	3.1 ± 5.3	3.4 ± 4.9	0.15
Magnesium	41300 ± 9150	41450 ± 10650	41400 ± 8900	0.98
Manganese	16.3 ± 7.2	15.5 ± 6.4	16.3 ± 7.2	0.41

	Overall cohort	Mid-pregnancy depressive symptoms ^b		
	(<i>n</i> =1226) ^c	EPDS 13 (<i>n</i> =96) ^d	EPDS <13 (<i>n</i> =1032) ^e	
	Median ± IQR or N (%)	Median ± IQR or N (%)	Median ± IQR or N (%)	p-value ^f
Lead	17.6 ± 10.0	18.5 ± 11.3	17.5 ± 10.0	0.36
Selenium	248 ± 61	247 ± 56	248 ± 63	0.95
Zinc	10400 ± 2358	10350 ± 2447	10400 ± 2365	0.89

Abbreviation: EPDS, Edinburgh Postnatal Depression Scale; IQR, interquartile range

^aAmong participants with multiple pregnancies included in the cohort, the first study pregnancy was included except in the case of five women who had more complete exposure and/or outcome data for their second study enrollment (subsequent pregnancy).

^bOf 1226 participants included in at least one analysis, 1128 have mid-pregnancy EPDS.

^cIn the overall cohort (*n*=1226), sample sizes of *n*=963 for EPDS at 6 months postpartum; *n*=872 for EPDS at 12 months postpartum; and *n*=1145 for pre-pregnancy history of depression (all other covariates have no missingness)

^dIn the EPDS 13 strata (*n*=96), sample sizes of *n*=76 for EPDS at 6 months postpartum and *n*=71 for EPDS at 12 months postpartum (all other covariates have no missingness)

^eIn EPDS <13 strata (*n*=1032), sample sizes of *n*=801 for EPDS at 6 months postpartum, *n*=725 for EPDS at 12 months postpartum, and *n*=1030 for pre-pregnancy history of depression (all other covariates have no missingness)

^fP-values comparing EPDS 13 and EPDS<13 groups; Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables

^gWhen available, mid-pregnancy dietary information was used if early pregnancy information was missing

Table 2.

Conditional odds ratios^a (95% confidence intervals) per quartile increase in all metals and depressive symptoms, measured via A) the Edinburgh Postnatal Depression Scale (EPDS) 13 and B) depressive symptom trajectories compared to the stable low referent trajectory, when considering the joint effect in all metals and for subgroups of essential or non-essential metals^b

	Odds ratio (95% confidence interval)		
	All metals	Essential metals ^c	Non-essential metals ^c
A) Elevated depressive symptoms (EPDS 13)^d			
Mid-pregnancy	0.94 (0.54, 1.63)	0.95 (0.69, 1.31)	0.98 (0.60, 1.59)
Six months postpartum	1.08 (0.62, 1.91)	1.09 (0.78, 1.53)	1.02 (0.61, 1.71)
Twelve months postpartum	0.67 (0.34, 1.32)	0.79 (0.51, 1.24)	0.91 (0.50, 1.67)
B) Depressive symptom trajectories compared to stable low^e			
Moderate mid-pregnancy, then increasing symptom trajectory	1.00 (0.62, 1.62)	1.05 (0.77, 1.43)	0.95 (0.61, 1.49)
Elevated mid-pregnancy, then decreasing symptom trajectory	1.00 (0.53, 1.90)	0.83 (0.58, 1.19)	1.17 (0.66, 2.05)

Abbreviation: EPDS, Edinburgh Postnatal Depression Scale

^aAdjusted for maternal age at enrollment, education, parity, marital status, race/ethnicity, smoking status, household income, early pregnancy seafood consumption, and early pregnancy white rice consumption

^bEssential (copper, magnesium, manganese, selenium, zinc) and non-essential (arsenic, barium, cadmium, cesium, mercury, lead) groups selected *a priori* based on toxicology literature on elements integral to metabolic or biochemical processes

^cAdjusted for other subgroup of metal co-exposures

^dSample sizes for EPDS analyses: 1128 at mid-pregnancy; 963 at 6 months postpartum; 872 at 12 months postpartum

^eSample sizes for depressive symptom trajectory analyses: 888 for moderate mid-pregnancy, then increasing ($n=103$) versus stable low ($n=785$); 860 for elevated mid-pregnancy, then decreasing ($n=75$) versus stable low ($n=785$)