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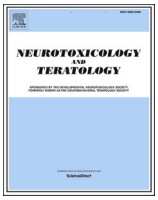

Maternal prenatal lead levels and neonatal brain volumes: Testing moderations by maternal depressive symptoms and family income

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ABSTRACT

There is considerable evidence that prenatal lead exposure is detrimental to child cognitive and socio-emotional development. Further evidence suggests that the effects of prenatal lead on developmental outcomes may be conditional upon exposure to social stressors, such as maternal depression and low socioeconomic status. However, no studies have examined associations between these co-occurring stressors during pregnancy and neonatal brain volumes. Leveraging a sample of 101 mother-infant dyads followed beginning in mid-pregnancy, we examined the main effects of prenatal urinary lead levels on neonatal lateralized brain volumes (left and right hippocampus, amygdala, cerebellum, frontal lobes) and total gray matter. We additionally tested for moderations between lead and depressive symptoms and between lead and family income relative to the federal poverty level (FPL) on the same neurodevelopmental outcomes. Analyses of main effects indicated that prenatal lead was significantly ($ps < 0.05$) associated with reduced right and left amygdala volumes ($\beta s = -0.23$- -0.20). The testing and probing of cross-product interaction terms using simple slopes indicated that the negative effect of lead on the left amygdala was conditional upon mothers having low depressive symptoms or high income relative to the FPL. We interpret the results in the context of trajectories of prenatal and postnatal brain development and susceptibility to low levels of prenatal lead in the context of other social stressors.

1. Introduction

Lead is a toxic metal that serves no biologic function, with higher levels of exposure in utero negatively associated with indices of child development (Bellinger et al., 1987; Hu et al., 2006; Sanders et al., 2009; Sioen et al., 2013; Tchounwou et al., 2012). Extant studies of prenatal lead exposure and child cognitive and socio-emotional development have also demonstrated moderating effects of maternal depression (Stroustrup et al., 2016), socioeconomic status (SES) (Bellinger, 2000), and other maternal psychological or social stressors (Tamayo et al., 2017; Zhou et al., 2017). However, it is not yet known how prenatal lead alone or the combination of prenatal lead and co-occurring non-chemical stressors affect neural correlates associated with cognitive and socio-emotional development. The present study investigates the unique effects of prenatal lead on neonatal brain volumes and whether the effects of prenatal lead are conditional upon maternal prenatal depressive symptoms or family income.

1.1. Lead and neurodevelopment

Lead exposure initially occurs through contaminated drinking water, foods, and dust; over time, lead also accumulates in bones (Sanders et al., 2009). Maternal lead during pregnancy and historical lead from bone stores (which leaches into the bloodstream) crosses the placental barrier into the fetal compartment (Esteban-Vasallo et al., 2012; Goyer, 1990) and through the blood brain barrier into the central nervous

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system (CNS) (Lidsky and Schneider, 2003; Zheng, 2001). Within the CNS, lead induces excitotoxicity and neuronal death (Lidsky and Schneider, 2003), affects cellular energy metabolism (Lidsky and Schneider, 2003), increases inflammatory responses and oxidative stress (Ahamed and Siddiqui, 2007; Ercal et al., 2001; Metryka et al., 2018), causes DNA methylation (Pilsner et al., 2009; Senut et al., 2012), and modulates hypothalamic-pituitary-adrenal (HPA) axis functioning (Braun et al., 2014; Virgolini et al., 2006). Through these and other mechanisms, lead interferes with neurogenesis, dendritic growth and density, and long-term potentiation (Altmann et al., 1994; Senut et al., 2012; Verina et al., 2007; White et al., 2007). Though animal models appear to have more consistently uncovered effects of lead in the hippocampus (Altmann et al., 1994; Stansfield et al., 2012; White et al., 2007), studies have additionally implicated the prefrontal cortex, amygdala, and cerebellum as targets of lead toxicity (Barkur and Bairy, 2016; Sanders et al., 2009).

Considerable evidence suggests that higher prenatal lead levels are associated with poorer cognitive and socio-emotional development across infancy and childhood (e.g., Bellinger et al., 1987; Jedrychowski et al., 2009; Sioen et al., 2013). Affected outcomes include mental development (Bellinger et al., 1987; Hu et al., 2006; Jedrychowski et al., 2009; Schnaas et al., 2006), temperament (Cowell et al., 2021; Stroustrup et al., 2016), executive functions (Fruh et al., 2019), emotional and behavioral problems (Bellinger et al., 1994; Fruh et al., 2019; Sioen et al., 2013; Wasserman et al., 1998), and hyperactivity (Sioen et al., 2013). Considering these and other toxic effects of lead on health, as well as the frequency of exposure, lead was ranked as second on the 2022 Substance Priority list by the Centers for Disease Control and Prevention (Agency for Toxic Substances and Disease Registry, 2022). In fact, the maximum contaminant level goal set for drinking water by the Environmental Protection Agency for lead is zero, corresponding to the fact that there is no known safe level of lead exposure (United States Environmental Protection Agency, 2023).

Exposure to lead occurs across the prenatal and postnatal environments; thus, early indices of neurodevelopment allow us to elucidate the unique effects of prenatal lead exposure on fetal brain development. That is, though some argue for the unique threat of prenatal lead exposure (Ronchetti et al., 2006), others point out the saliency of postnatal lead exposure on child neurodevelopment above the effects of prenatal exposure (Braun and Lanphear, 2007). Neurodevelopmental research with neonatal populations can additionally improve our understanding of the mechanistic effects of prenatal lead on the fetal brain as well as inform the need to mitigate lead exposure prior to and during pregnancy. Though animal models provide some initial evidence for the mechanistic effects of prenatal lead exposure on fetal neurodevelopment, differences between animal and human models in trajectories of fetal neurodevelopment, placenta interface, lead exposure sources and routes, and co-occurring social factors suggest that animal studies may not directly translate to human populations (Pound et al., 2004). Moreover, recent studies suggest that subtle neurological differences observed from neuroimaging studies may precede symptoms of developmental disorders like autism and attention deficit hyperactivity disorder in children (Hazlett et al., 2017; Shaw et al., 2013). Understanding whether prenatal lead levels are associated with fetal neurodevelopmental indices in populations not at a known increased risk for lead exposure may also inform initiatives to screen all pregnant persons for lead exposure as well as advisories for expectant families.

Still, we are aware of only one study that used neuroimaging methods to investigate the main effects of prenatal lead on infant neurodevelopment. Leveraging fetal functional magnetic resonance imaging (fMRI) data in a small sample ($N = 26$), prenatal lead levels were associated with altered patterns of connectivity in fetuses (Thomason et al., 2019). Compared to fetuses with newborn blood spot lead levels below 1 μg/dL ($N = 13$), fetuses with newborn blood spot levels above 1 μg/dL ($N = 13$) exhibited strengthening in connectivity between the superior frontal gyrus and posterior cingulate cortex (Thomason et al., 2019). This differential connectivity may predispose children with higher exposure to prenatal lead to increased risk for psychopathology and poorer executive function (Thomason et al., 2019). This study demonstrates the unique effects of gestational and pre-gestational exposure to lead on fetal brain development. However, to our knowledge, no studies have examined the effects of prenatal lead on neonatal brain volumes.

Neuroimaging studies investigating the effects of lead on the brain have predominantly used prospective designs to evaluate associations between childhood lead and later functional and structural outcomes, demonstrating the long-term effects of childhood lead exposure on brain volumes, neural activation, and white matter integrity (Brubaker et al., 2010; Brubaker et al., 2009; Cecil et al., 2008; Reuben et al., 2020). For example, childhood lead has been negatively associated with adult gray matter volume, with focused reductions in the frontal lobes (Brubaker et al., 2010), particularly areas of the ventrolateral prefrontal cortex and anterior cingulate cortex—regions that are critical to executive functioning, reward-based decision-making, and emotional regulation (Cecil et al., 2008). Increasing childhood blood lead has also been associated with reduced hippocampal volumes, cortical surface area, and white matter integrity in adults (Reuben et al., 2020). While we may assume that prenatal lead would similarly affect fetal gray matter, frontal lobe, and subcortical volumes, differences in brain maturation between pregnancy and childhood and exposure routes (direct vs. placental transfer) requires that we test these expectations directly.

The first goal of this study was to examine the main effects of prenatal lead levels on neonatal brain volumes. Considering the documented effects of prenatal lead on later cognitive and socio-emotional development and affected volumes in animal studies and adults as a function of childhood exposure, we focus on the right and left hippocampus, amygdala, cerebellum, and frontal lobes, and total gray matter. We hypothesized that maternal prenatal lead levels would be negatively associated with neonatal brain volumes, particularly to the hippocampus.

1.2. Lead and non-chemical stressors and neurodevelopment

Lead exposure is not randomly distributed, with lead disproportionally affecting populations who are lower income and racially or ethnically minoritized (Teye et al., 2021; Tyrrell et al., 2013). Therefore, populations who are more likely to be exposed to lead are often disproportionately exposed to psychological and social stressors (Evans and Kantrowitz, 2002; Morello-Frosch and Shenassa, 2006) that could either account for (i.e., confound) or potentiate (i.e., moderate) its effects.

Additionally, psychological and social stressors encountered during pregnancy that are associated with child development (Bergman et al., 2007; Huizink et al., 2003; Madigan et al., 2018; O'Connor et al., 2002; Tarabulsy et al., 2014) like maternal depression and poverty have several common or complementary putative mechanisms as lead (Wright, 2009). For example, chronic psychological distress may also increase reactive oxidative stress and the release of pro-inflammatory cytokines, alter DNA methylation, and program HPA axis functioning (Bellinger, 2018; Gilman et al., 2017; Hantsoo et al., 2019; Viuff et al., 2018; Wright, 2009; Zijlmans et al., 2015). A growing body of research is elucidating the co-occurrence of depressive symptoms with altered inflammatory states (Dowlati et al., 2010; Miller et al., 2009; Schiepers et al., 2005), and a 2020 meta-analysis examining SES and measures of inflammation found that lower SES was associated with increases in inflammatory proteins (Muscatell et al., 2020). Animal studies highlight the role of the HPA axis as a potential mechanism for lead by psychosocial stress exposure interactions (Cory-Slechta et al., 2004; Virgolini et al., 2008). In line with the diathesis-stress model, which proposes that the effect of a predisposition (diathesis; e.g., poverty) on developmental outcomes is potentiated by a later experience (e.g., lead) (Zuckerman, 1999), repeated effects on common or downstream biological systems

by stressors experienced across the social and physical environments may potentiate neurodevelopmental effects. That is, neurobiological effects as a function of exposure to a stressor from one level of the environment (e.g., social) may increase susceptibility or vulnerability to the neurobiological effects incurred as a function of stress experienced from another level of the environment (e.g., physical), such that the layering of these stressors creates a multiplicative, rather than additive, effect. As such, increasing interest has surrounded the "double jeopardy" of joint exposure to chemical and non-chemical stressors (Morello-Frosch and Shenassa, 2006), including the co-occurring effects of prenatal lead with depression and poverty (Bellinger, 2000; Stroustrup et al., 2016).

There is evidence for moderating effects between prenatal lead and psychological or social stressors on infant and child development, such that the presence or strength of an effect of lead on child outcomes is conditional upon levels of psychological or social stress (Bellinger, 2000; Lucchini et al., 2019; Stroustrup et al., 2016; Tamayo et al., 2017; Zhou et al., 2017). In a cohort study following mother-infant dyads from pregnancy through 24 months, infants from higher social classes were protected against the detrimental effects of moderate lead exposure on mental development, whereas infants from lower social classes who were exposed to moderate levels of lead in utero showed decrements to mental development (Bellinger, 2000). Within the high social class group, the effect of lead on infant mental development was only apparent if exposure was high (>10 μg/dL) (Bellinger, 2000). Other studies have observed a higher probability of toddlers having a difficult temperament as a function of prenatal lead if mothers also had high prenatal depressive symptoms (Stroustrup et al., 2016) and that prenatal lead was only associated with toddlers' language, and social and adaptive behavior when mothers additionally had high prenatal stress (Zhou et al., 2017). At least one study found that prenatal lead was only associated with toddler cognitive scores in the absence of maternal stress, with higher levels of prenatal stress masking the effects of co-occurring lead, likely due to a floor effect (Tamayo et al., 2017). With respect to direct measures of neurodevelopment using magnetic resonance imaging (MRI), an analysis of the Adolescent Brain Cognitive Development Study found that risk of lead exposure (i.e., living in census tracts with high lead exposure risk) was associated with reduced brain volumes in children if their families had lower SES (Marshall et al., 2020),

As the synergistic effects of co-exposure to environmental and psychological or social stressors in utero on offspring development are emerging, there is little evidence surrounding their statistical interaction on infant neurodevelopment specifically. The second goal of this study was to examine whether maternal depressive symptoms or family income moderates the effects of prenatal lead on neonatal neurodevelopment. We hypothesized that the effects of prenatal lead on neonatal volumes, particularly the hippocampus, would be stronger when mothers experienced higher levels of depressive symptoms or lower family incomes.

2. Materials and methods

2.1. Participants

The Brain and Early Experience (BEE) Study is a longitudinal study of mother-infant dyads and their families ($N = 203$) (Mills-Koonce et al., 2022). Pregnant mothers were recruited during their second trimester of pregnancy via electronic medical records, social media, flyers, and mailings if they were 18 years or older, spoke English, were pregnant with a singleton, lived within 45 min of the study site, and were planning to remain in the same geographic area for the next three years. At birth, mothers and infants were officially enrolled into the study if the neonate was born at 36 weeks and 4 days of gestation age or older, had a birth weight of at least 5.5 pounds, and had no significant medical complications, and had no metal devices implanted. The current study focuses on an analytic sample of mother-infant dyads who had quality neonatal magnetic resonance imaging (MRI) structural data ($N = 101$). Notably, in-person data collection restrictions due to the COVID-19 pandemic precluded the ability to image neonates beginning in March 2020. All reported study procedures are specific to this analytic sample and were collected prior to the COVID-19 outbreak.

All procedures were approved by the institutional review board (#17–1914) at the University of North Carolina at Chapel Hill. Participants gave written informed consent at each study time point before participating in any data collection activity. As all birthing parents in the analytic sample self-identified their gender as "woman" at the prenatal visit, we refer to the birthing parents as "mothers."

2.2. Procedure

During mid-pregnancy, participants (N = 101) presented to the laboratory at the University of North Carolina at Chapel Hill for a two-hour visit [Mean Gestational Age (GA) = 27.3 weeks; SD = 2.1 weeks]. During this visit, mothers provided multiple biological specimens, including a urine sample, and completed a series of questionnaires. Urine samples were refrigerated immediately after collection, then aliquoted into three 3-mL containers and one 12-mL container and stored in freezers at −80 degrees Celsius until analysis. Mothers were compensated $50 at the end of the prenatal visit.

Mothers were contacted weekly beginning at 37 weeks GA to check on the status of their delivery and, after birth, to gather basic information about their infant and their infant's birth. When infants were approximately two-weeks of age (mean = 14.1 days; SD = 2.0 days), mother-infant dyads returned to the laboratory for an infant scan using 3 T MRI. In total, 123 infant participants completed the visit prior to the onset of the COVID-19 pandemic; however, a subset ($N = 22$) of infant participants' imaging data did not pass quality control checks and were thus removed from the analytic sample. Mothers completed a series of questionnaires about their infant's birth and their own substance use and health behaviors during pregnancy. Mothers were compensated $100 at the end of this visit.

2.3. Measures

Prenatal lead: Mothers provided a urine sample using a Thermo Scientific Samco Wide-Mouth Bio-Tite 90 mL (3 oz.) 53 mm Specimen container. Urine samples were aliquoted in three to 12 mL parts into 15 mL VWR Centrifuge tubes (metal free) using polyethylene pipets within 12 h of collection and stored at −80 degrees Celsius until the time of analysis. Urine samples were analyzed for lead and other metals over the course of two days by quadrupole inductively coupled plasma mass spectrometry (ICP-MS) at RTI International. Samples were prepared by digestion with acid on a graphite heating block. Analysts monitored method blanks to assess background levels of metals from the reagents or sample containers, which indicated that contamination did not play a significant role in the reported results. Limits of quantification and detection were 0.156 and 0.0467 ng/mL for lead respectively, 0.247 and 0.0742 for cadmium, respectively, and 0.499 and 0.150 ng/mL for manganese, respectively. Most (75%) participants had quantifiable levels of urinary lead and nearly all (99%) had detectable urinary lead levels. Fewer participants had quantifiable (19%) or detectable (49%) levels of cadmium or quantifiable (41%) or detectable (65%) levels of manganese. Lead was entered as a continuous measure with values below the level of detection (LOD) set to the LOD divided by the square root of two. Lead values that were detected but not quantifiable remained at the value provided by the laboratory. Exposure to manganese and cadmium were examined as categorical exposures (quantifiable vs. not quantifiable). We adjusted lead levels by urine-specific gravity (SG) using the equation [Metal x ($SG_{median} - 1$) / ($SG_{individual} - 1$)]. Lead was log-10 transformed to approximate a normal distribution. Metals were not significantly associated with the timing of the prenatal

visit in gestation ($ps > 0.05$); therefore, the timing of the prenatal visit was not considered further.

Maternal prenatal depressive symptoms: Mothers completed the Brief Symptom Inventory (BSI) Short Form (Derogatis, 2001) independently during the prenatal laboratory visit. This survey asks respondents to rate the extent to which various symptoms bothered them over the past two weeks using a five-point Likert scale from zero (not at all) to four (extremely often). The BSI Short Form has been validated in a community sample (Derogatis, 2001) and in a sample of pregnant women (Sheikh et al., 2005). Here, we focus on the depressive symptoms subscale, a mean of six items, in which higher scores indicate more frequent or intense depressive symptoms. The internal consistency for the depressive symptom subscale in our sample was good (Cronbach's $\alpha = 0.85$).

Family income relative to the federal poverty level: Mothers self-reported their household income and number of adults and children living in the household with the help of a research assistant during the prenatal laboratory visit. Using the 2018 Census Bureau Poverty Thresholds (U.S. Census Bureau, 2018), an income to needs ratio score was calculated—this score represents their income relative to the federal poverty limit (FPL), which considers the size of their family unit and number of related children in the household.

Neonatal brain volumes: At approximately 2-weeks of age, neonates ($N = 123$) were scanned using a Prisma 3 T MRI. Selected brain region volumes were extracted jointly from T1-weighted and T2-weighted MR images via the UNC MultiSeg pipeline employing three separate multi-template sets: 1) bilateral hippocampus and amygdala volumes (Overfeld et al., 2015), 2) bilateral cerebellum volumes (Hendrickson et al., 2023), and 3) bilateral frontal lobes volumes, and total gray matter volume (Gousias et al., 2012). All regional segmentations were assessed visually. These regions were selected as they provide the biological basis for many cognitive and social-emotional functions, and the decrements in these brain regions have been associated with prenatal and postnatal lead exposures in animal or human studies (Altmann et al., 1994; Barkur and Bairy, 2016; Cecil et al., 2008; Reuben et al., 2020; Sanders et al., 2009; Stansfield et al., 2012; White et al., 2007).

Covariates: We conducted a review of the literature and leveraged directed acyclic graph (DAG) theory to select covariates that included potential confounders between lead effects and neurodevelopmental outcomes as well as variables to increase the precision of the outcome measures. All models adjusted for maternal age at the infant's birth, maternal education, prenatal family income to needs ratio, prenatal diet, prenatal smoking, prenatal alcohol use, prenatal urinary cadmium, and prenatal urinary manganese; these variables were chosen due to their hypothesized confounding role via causal or correlational means for the associations between prenatal lead and neonatal neurodevelopment. The maternal prenatal depressive symptoms score was also included in all models, as this and family income to needs ratio were later examined as moderators. The measure of smoking during pregnancy was a binary indicator representing if the mother never vs. ever smoked during pregnancy, which was ascertained at the first postnatal visit using maternal report. The measure of maternal prenatal alcohol use captured the frequency of alcohol use during pregnancy from 0 (never) to five (a couple of times per week); this measure was also ascertained using maternal report at the first postnatal visit. We adjusted for a continuous measure reflecting the mother's diet quality during pregnancy. Diet quality was assessed using the Nutrition Data System for Research (NDSR) Healthy Eating Index-2015, which was based on up to three days of a maternal diet recall to a research assistant (Krebs-Smith et al., 2018). Models were adjusted for infant's sex, infant's gestation-adjusted age in days at the MRI visit, and the infant's total intracranial volume (ICV) which is common practice in neuroimaging research to control for volumetric differences in regions of interests that are due to the overall size of the brain and not specific to the predictors.

2.4. Analysis

All continuous variables were standardized (mean = 0; SD = 1) to ease interpretability. To examine whether the effects of lead on neonatal brain volumes were moderated by maternal depressive symptoms or family income relative to the FPL, we created cross-product interaction terms between lead and depressive symptoms and between lead and income relative to the FPL (e.g., lead x depressive symptoms). We also created a cross-product interaction term between lead and infant sex.

To address the loss of power and potential for bias when using list-wise deletion, we used the Markov Chain Monte Carlo (MCMC) method of multiple imputation (MI) in SAS 9.4 (Cary, NC) to impute missing data to a full analytic sample of 101 mother-infant pairs. Rates of missing data were as follows: lead, cadmium, and manganese levels (1%), family income to needs ratio (2%), prenatal smoking and alcohol use (3%), amygdala and hippocampus volumes (1%), and prenatal diet (14%). We generated 25 imputed datasets.

In the first step of analyses, we used linear regressions to examine the main effects of prenatal lead, depressive symptoms, family income relative to the FPL, and covariates on each neonatal brain volume. To examine whether the effects of metals on neonatal brain volumes were moderated by maternal depressive symptoms or family income relative to the FPL, we added interaction terms to the model independently. Interaction terms that were statistically significant ($p < 0.05$) were probed at the 10th and 90th percentile of depressive symptoms or income relative to FPL. All analyses were conducted using PROC REG in SAS 9.4 (Cary, North Carolina) by imputation dataset and PROC MI ANALYZE to pool estimates and standard errors across the 25 models.

3. Results

3.1. Descriptive statistics

Mothers were on average 30.7 years old (Standard deviation [SD] = 5.8) at the time of the infant's birth and ranged in age from 19 years to 46 years. The sample tended to be more educated, with 54% of mothers having earned a four-year bachelor's degree or higher. Over half (55%) of the mothers identified their primary race as white, and nearly one in three mothers (31%) identified their race as Black or African American. Another 2% of mothers self-identified as Asian and 11% as another racial group. Only 11% of mothers reported smoking at any point while pregnant, and 20% of mothers reported drinking alcohol at any point while pregnant. Additional descriptive statistics for the analytic sample are presented in Table 1.

3.2. Bivariate correlations

Bivariate correlations between focal predictors and outcomes of interest before standardization and multiple imputation are presented in Table 2. Urinary lead was negatively correlated with left amygdala volume ($r = -0.22$, $p = 0.03$) but positively correlated with left frontal lobe volume ($r = 0.21$, $p = 0.04$) and right frontal lobe volume ($r = 0.20$, $p = 0.05$). There were no significant correlations between depressive symptoms and neonatal brain volumes nor income relative to the FPL and neonatal brain volumes. Lead was not significantly correlated with depressive symptoms nor income relative to the FPL.

3.3. Main effects of lead on neonatal volumes

We first estimated a series of linear regression models to examine the main effects of prenatal urinary lead on neonatal brain volumes while adjusting for covariates (Table 3). We report on standardized results. Log-transformed specific-gravity adjusted urinary lead ("lead") was significantly negatively associated with left and right amygdala volumes in models that explained 25–34% of the variance in the respective volumes. Specifically, a one SD increase in lead was associated with a 0.23

Table 1
Characteristics of the analytic sample.

	N	Mean (SD)	Range
Urinary lead (ng/mL)	100	0.5 (0.6)	0.0–4.3
Specific-Gravity Adjusted Urinary lead	100	0.6 (1.3)	0.1–12.2
Maternal age at child's birth (years)	101	30.7 (5.8)	19.0–46.3
Maternal education (years)	101	15.4 (2.6)	11–19
BSI Depressive Symptoms	101	0.4 (0.5)	0.0–2.7
Income to needs ratio	101	3.5 (2.7)	0.0–13.4
NDSR Healthy Eating Index Score	88	54.8 (13.2)	24.3–83.1
Infant gestational age at MRI visit (weeks)	101	41.4 (1.1)	38.6–44.0
Left hippocampus (mm^3)	100	999 (112)	609–1222
Right hippocampus (mm^3)	100	1047 (112)	712–1324
Left amygdala (mm^3)	100	204 (28)	133–274
Right amygdala (mm^3)	100	216 (26)	135–276
Left cerebellum (mm^3)	101	12,272 (1513)	8463–16,474
Right cerebellum (mm^3)	101	11,770 (1401)	8324–14,775
Left frontal lobe gray matter (mm^3)	101	30,663 (3751)	23,368–40,197
Right frontal lobe gray matter (mm^3)	101	30,613 (3788)	23,684–39,957
Total gray volume (mm^3)	101	259,455 (28012)	201,540–332,066
Total intracranial volume (mm^3)	101	466,330 (49106)	370,892–594,914
	Total N	N (%)	
Urinary cadmium (quantifiable)	100	19 (19%)	
Urinary manganese (quantifiable)	100	24 (24%)	
Report of smoking during pregnancy (yes)	98	11 (11%)	
Report of alcohol use during pregnancy	98		
None		78 (80%)	
One to two times in total		14 (14%)	
Once per month or more		6 (6%)	
Infant sex (female)	101	50 (50%)	

Table 2
Bivariate correlations between predictors and outcomes of interest.

	Urinary Lead[a]	Depressive Symptoms	Income Relative to the FPL
1. Depressive symptoms	0.02	–	
2. Income relative to FPL	−0.07	−0.20	–
3. Urinary cadmium[b]	0.26**	0.09	−0.13
4. Urinary manganese[b]	0.07	−0.12	−0.14
5. Maternal age	0.05	−0.06	0.36***
6. Maternal education	−0.07	−0.32**	0.70***
7. Prenatal smoking-yes	−0.05	0.27**	−0.25*
8. Prenatal alcohol use	0.23**	0.15	0.23*
9. Prenatal healthy diet	0.01	−0.13	0.20
10. L hippocampus	0.00	−0.09	0.17
11. R hippocampus	0.04	−0.15	0.11
12. L amygdala	−0.22*	−0.07	0.11
13. R amygdala	−0.14	−0.05	0.09
14. L cerebellum	0.09	0.02	0.07
15. R cerebellum	0.11	0.04	0.07
16. L frontal lobe	0.21*	−0.04	0.02
17. R frontal lobe	0.20*	−0.04	0.00
18. Total gray volume	0.19	−0.08	0.06

Note.
L = left; R = right; FPL = Federal poverty level.
*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$.
[a] Unrinary lead was adjusted by specific gravity and log transformed.
[b] Urinary metals entered as a binary variable (0 = not quantifiable, 1 = quantifiable).

SD decrease (95% CI [−0.43, −0.03]; $p = 0.03$) in left amygdala volume and a 0.20 SD decrease (95% CI [−0.39, −0.01]; $p = 0.04$) in right amygdala volume. There were no main effects of lead on the left or right hippocampus, cerebellum, or frontal lobes, or total gray matter volumes. There were no substantive differences in the inferences of lead effects when removing ICV as a covariate.

3.4. Testing interaction effects

To test whether the effects of lead on neonatal brain volumes were conditional upon maternal prenatal depressive symptoms or family income, we analyzed cross-product interaction terms (i.e., lead x depressive symptoms or lead x income relative to the FPL) in independent models. When modeling the left amygdala volumes, interaction terms indicated that the lead effects were moderated by both depressive symptoms ($p = 0.02$) and family income ($p = 0.005$). Effects were probed at the 10th and 90th percentile of depressive symptoms and income relative to the FPL (Table 4; Figs. 1 and 2). Among mothers with low depressive symptoms, a one SD increase in lead was associated with a 0.39 SD decrease (95% CI[−0.63, −0.14]; $p = 0.002$) in left amygdala volume, and among mothers with high income relative to the FPL, a one SD increase in lead was associated with a 0.65 SD decrease (95% CI [−1.00, −0.30]; $p < 0.001$) in left amygdala volume. Lead was not significantly associated with left amygdala volume when mothers had high depressive symptoms ($\beta = 0.19$, $p = 0.37$) or low income relative to the FPL ($\beta = 0.12$, $p = 0.45$).

3.5. Sensitivity analyses

Other studies have found that effects of childhood lead on neurodevelopment differ by biologic sex (Cecil et al., 2008). Therefore, we tested whether lead was differentially related to neonatal brain volumes by infant sex by entering cross-product interaction terms (i.e., lead x sex), but none were statistically significant. Finally, we examined the influence of influential cases by removing one participant who was flagged as being an outlier with high leverage according to RStudent plots. Removing this participant minimally weakened the magnitude of the effects of prenatal lead on the left ($\beta = -0.21$, $p = 0.04$) and right amygdala ($\beta = -0.19$, $p = 0.05$) amygdala volume, with effects on the left amygdala continuing to be conditional upon mothers having low depressive symptoms ($\beta = -0.30$, $p = 0.02$) or high family income ($\beta = -0.62$, $p = 0.003$).

4. Discussion

Current findings reveal that maternal prenatal lead levels were negatively associated with neonatal amygdala volumes but not hippocampal, frontal lobe, cerebellum, or total gray matter volumes. Moreover, associations with the left amygdala were conditional upon the mother having low depressive symptoms or high family incomes. Though our study does not confirm causality, it aligns with prior literature finding that prenatal lead exposure, even at low levels, affects neonatal neurodevelopment.

The current study is among the first to test whether prenatal lead is associated with neonatal brain development and the first to demonstrate that pre-gestational and/or gestational exposure to lead is associated with reduced neonatal amygdala volumes. However, the effects of lead on subcortical volumes have been shown in the animal literature and in a study of childhood lead exposure and adult neurodevelopment (Barkur and Bairy, 2016; Reuben et al., 2020). Specifically, a rat model demonstrated that increased lead exposure during pre-gestation and gestation was associated with reduced neurogenesis in rat pups' amygdala, hippocampus, and cerebellum (Barkur and Bairy, 2016). A large ($N = 564$) longitudinal study following children to midlife observed

Table 3
Standardized associations of maternal prenatal lead, depressive symptoms, and family income on neonatal brain volumes.

	L Hippo β (SE)	R Hippo β (95% CI)	L Amygdala β (95% CI)	R Amygdala β (95% CI)	L Cerebellum β (95% CI)	R Cerebellum β (95% CI)	L Frontal Lobe β (95% CI)	R Frontal Lobe β (95% CI)	Total Gray Matter β (95% CI)
Urinary lead[a]	−0.03 (0.10)	−0.09 (0.11)	**−0.23 (0.10)** *	**−0.20 (0.10)** *	−0.05 (0.08)	−0.05 (0.08)	0.01 (0.04)	0.00 (0.04)	0.00 (0.03)
Depressive symptoms	−0.01 (0.10)	−0.09 (0.11)	0.05 (0.11)	0.07 (0.10)	0.10 (0.08)	0.11 (0.08)	0.05 (0.04)	0.05 (0.04)	0.01 (0.03)
Income relative to FPL	0.23 (0.14)	0.06 (0.14)	−0.06 (0.14)	−0.13 (0.13)	0.00 (0.10)	0.00 (0.10)	−0.02 (0.05)	−0.03 (0.05)	0.03 (0.04)
Adjusted R^2	0.26	0.24	0.25	0.34	0.58	0.59	0.90	0.91	0.95

Note. Additional covariates in regression models included maternal age at the target infant's birth, maternal education, maternal prenatal diet quality, prenatal smoking status (binary) and alcohol use, prenatal urinary cadmium and manganese (binary), total intracranial volume, infant gestational age at the neuroimaging visit, and infant sex.
*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$.
FPL = federal poverty limit.
L = left; R = right; Hippo = Hippocampus.
[a] Urinary lead was adjusted for specific gravity and log transformed.

Table 4
Probing interactions between lead x depressive symptoms and lead x income relative to the FPL.

	Left Amygdala Volume β (SE)
Low Depression	
Intercept of lead[a]	0.16 (0.25)
Slope of lead[a]	**−0.39 (0.12)****
High Depression	
Intercept of lead[a]	0.30 (0.29)
Slope of lead[a]	0.19 (0.21)
Low Income relative to FPL	
Intercept of lead[a]	0.24 (0.26)
Slope of lead[a]	0.12 (0.16)
High Income relative to FPL	
Intercept of lead[a]	−0.14 (0.36)
Slope of lead[a]	**−0.65 (0.18)*****

Note.
FPL = federal poverty level. Additional covariates in regression models included maternal age at the target infant's birth, maternal education, maternal prenatal diet quality, prenatal smoking status (binary) and alcohol use, prenatal urinary cadmium and manganese (binary), total intracranial volume, infant gestational age at the neuroimaging visit, and infant sex.
*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$.
[a] Urinary lead adjusted for specific gravity and log transformed.

negative associations between childhood lead and hippocampal volumes and cortical surface area (Reuben et al., 2020). Differences in the affected neural structures as a function of prenatal lead exposure when compared to childhood lead exposure may be due to differences in their sensitive periods of neurodevelopment. Whereas the amygdala develops through early and late childhood for females and males, respectively (Giedd et al., 1996; Tottenham and Sheridan, 2009), most hippocampal growth occurs after early childhood —from middle childhood through adulthood (Tottenham and Sheridan, 2009). Animal models also demonstrate that hippocampal development follows amygdala development (Payne et al., 2010; Tottenham and Sheridan, 2009). Gray matter volume, including frontal gray matter, similarly increases throughout childhood, peaking between middle childhood and early adolescence (Lenroot et al., 2007). Indeed, one study examining childhood blood lead collected yearly from ages one to six years of age and adult gray matter volumes found that lead exposure later in the childhood exposure window (at five to six years of age) was more strongly associated with reduced frontal lobe volumes than lead exposure earlier in the childhood exposure window (Brubaker et al., 2010). This was despite the fact that participants' maximum blood lead levels tended to be in earlier childhood, around age two (Brubaker et al., 2010). Mid-pregnancy may be a more sensitive period for amygdala development, whereas childhood may be a more sensitive period for the development of the hippocampus, the frontal lobes, and cortical volumes more broadly.

Our sample is not at particularly high risk for lead exposure; therefore, it is also possible that our levels of lead exposure were not at a threshold in which we would observe an association with other indices of neurodevelopment. Raw urinary lead levels ranged from being undetectable to 4.3 ng/mL and nearly all mothers (92%) in this study had urinary lead levels <1 ng/mL. These levels are similar to levels found in population-based studies of adults which have observed associations between urinary lead and negative health outcomes (e.g., Li et al., 2018; McElroy et al., 2008). Still, it may be that mothers must be exposed to higher levels of lead during pregnancy to observe associations with the other neonatal neurodevelopmental indices tested here. The lack of significant associations between prenatal lead and other tested brain volumes may also be due to total volumes of structures being too crude of measures to detect more nuanced differences in structure as a function of prenatal lead. It is possible that other structures not tested in this study may be affected by prenatal lead exposure, and/or that the effects of prenatal lead exposure on later developmental outcomes are mediated by differences in brain function rather than structure. The fact that we only observed associations between prenatal lead and neonatal amygdala volumes, whereas longitudinal studies with childhood exposure and adult outcome windows have uncovered associations between lead and other brain volumes, may also support arguments that childhood lead exposure is particularly salient (above and beyond prenatal exposure) for neurodevelopment. It is also possible that there could be a delayed effect of prenatal exposure that becomes more apparent as the brain matures.

We found that prenatal urinary lead was associated with smaller neonatal bilateral amygdala volumes; however, testing two-way interactions revealed that the association with the left amygdala volume was conditional upon mothers having low depressive symptoms or high family income (i.e., low psychological or social risk). This was an interesting and unexpected finding. Plotting of the simple slopes revealed that among mothers with high levels of depressive symptoms and among mothers with low family incomes, the expected amygdala volumes (i.e., the regression line) were within approximately 0.5 standard deviations around the standardized mean. In contrast, at low levels of lead and low depressive symptoms or at low levels of lead and high family incomes, neonates had average amygdala volumes (1.0–1.5 standard deviations above the standardized mean) that decreased with increasing levels of prenatal urinary lead to 1.5–2.5 standard deviations below the mean at the highest level of lead. It may be the case that children of mothers with low psychological or social risk are more sensitive, or biologically susceptible, to the toxic effects of lead. The differential susceptibility hypothesis provides some theoretical support

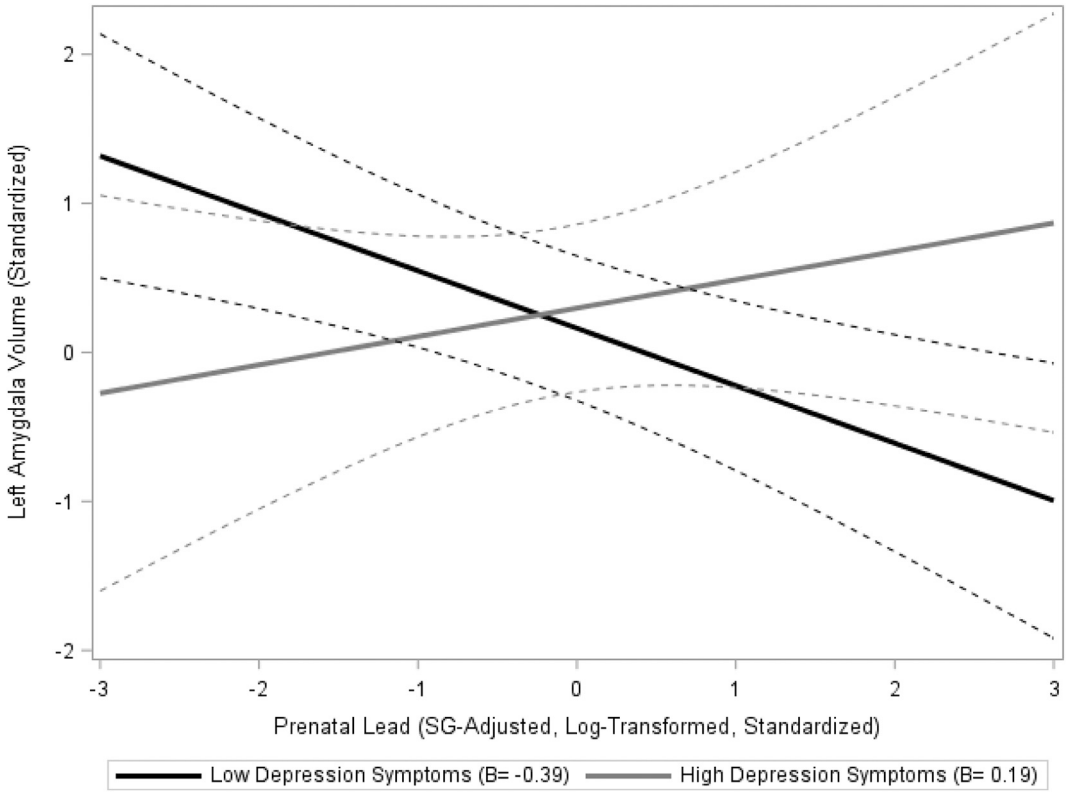

Fig. 1. Probing two-way statistical interactions between prenatal lead and depressive symptoms on left amygdala volumes.
Note.
Lead was adjusted for urine-specific gravity and log-transformed. Solid lines represent the associations of prenatal lead on neonatal left amygdala volume at low (the 10th percentile) and high (the 90th percentile) levels of prenatal depressive symptoms. Dashed lines represent 95% confidence intervals.

for this pattern of results, as the theory proposes that some individuals are more susceptible to negative environments (Belsky, 1997; Hartman and Belsky, 2018). Smaller amygdala volumes as a function of high prenatal urinary lead even in the presence of lower psychological or social risk may demonstrate susceptibility to negative chemical environments. In contrast, neonates of mothers with high depressive symptoms or low family incomes in the sample may be less susceptible to urinary lead at increasing levels.

Relatedly, it is possible that poverty or depressive symptoms co-occur with many other unmeasured risk factors, such as neighborhood deprivation or adverse child experiences, such that one threat (in our case, prenatal lead) has no substantive effect on left amygdala volumes. In contrast, high income or low depressive symptoms may provide a context where prenatal lead, which has well-established neurotoxic effects, becomes a salient stressor with an effect on left amygdala volumes. This explanation aligns with the social distinction model proposed by researchers examining gene by environment interactions on developmental outcomes (Boardman et al., 2014). Under this model, one is more likely to uncover significant associations of a risk factor (e.g., genetic allele or prenatal lead) in protective environments where there is less environmental variation (Boardman et al., 2014). Notably, our results appear incongruent with a masking or swamping effect, like that observed by Tamayo et al. (2017) where prenatal lead and social stress operate in the same direction on child neurodevelopmental outcomes, thereby producing a floor (or ceiling) effect.

Prior studies have observed the effects of prenatal psychological and social stress, including depressive symptoms and family income, on offspring brain volumes including neonatal and infant amygdala volumes (Betancourt et al., 2016; Qiu et al., 2017; Wen et al., 2017). Findings from these studies have also demonstrated conditional effects of prenatal depressive symptoms on lateralized amygdala volumes (Qiu et al., 2017; Wen et al., 2017). That is, other studies have uncovered positive associations between prenatal depressive symptoms in mid-pregnancy and right amygdala volumes that are conditional upon child female sex (Wen et al., 2017) and higher genomic risk for depression (Qiu et al., 2017). Maternal inflammation in mid-pregnancy, a potential mechanism by which chemical and non-chemical stressors affects fetal neurodevelopment, has also been associated with lateralized neonatal amygdala development (Graham et al., 2018). In a sample of African American mother-infant dyads, lower prenatal SES was also associated with smaller cortical gray matter volumes in neonates, with cortical gray matter including volumes of the hippocampus and amygdala (Betancourt et al., 2016). Therefore, current findings combined with prior studies support that the amygdala is susceptible to prenatal psychological and social stress and that the left and right amygdala may be differentially susceptible to these prenatal stressors. Scientists have also proposed potential differences between functions subserved by the left and right amygdala (Baas et al., 2004). Among many other explanations for lateralized functionality (Baas et al., 2004; Murphy et al., 2020), some have proposed that the right amygdala plays a larger role in detecting and automatically responding to emotional stimuli, whereas the left amygdala may have a larger role in evaluating emotional stimuli, sustaining emotion processing, and controlling emotions (Baas et al., 2004; Glascher and Adolphs, 2003; Wright et al., 2001). However, we note that the overall understanding of their distinct functions is still an active area of research, and more studies are needed to clarify the nuances of amygdala lateralization.

Differences in amygdala volume have also been previously associated with mental health and behavioral difficulties (Jones et al., 2019). In comparison to healthy controls, children with anxiety have been shown to have smaller left amygdala volumes (Milham et al., 2005) and children with depression have been shown to have smaller bilateral

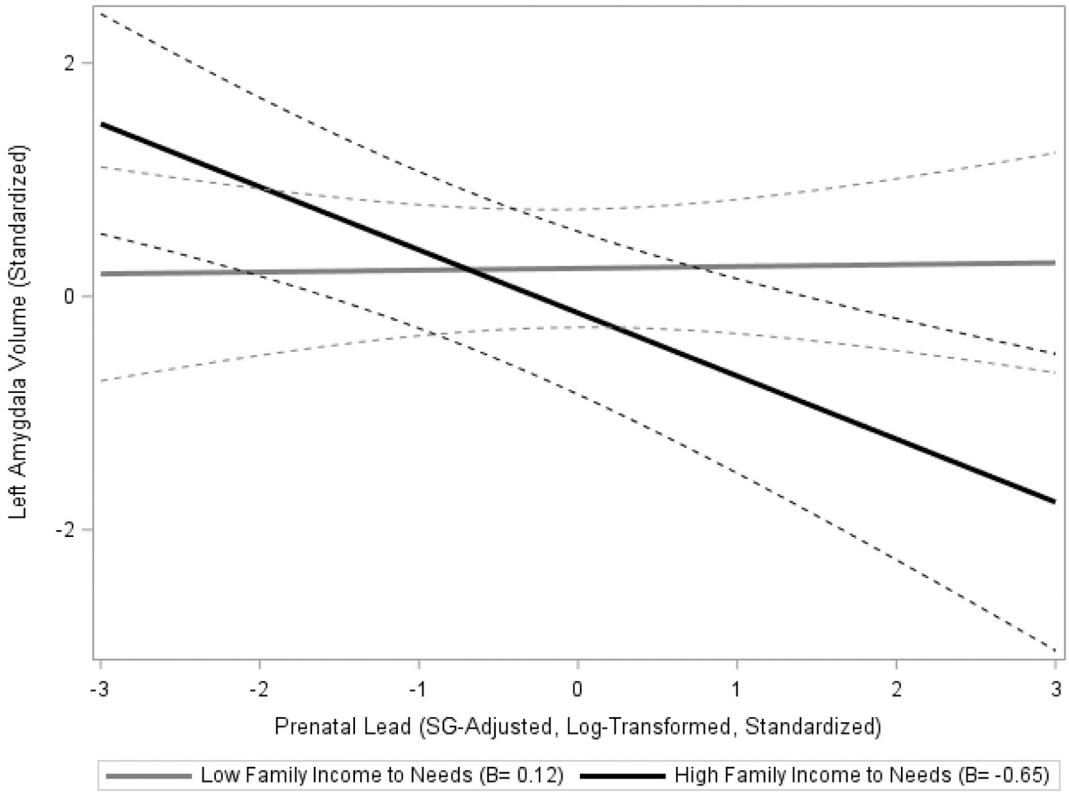

Fig. 2. Probing two-way statistical interactions between prenatal lead and family income relative to FPL on left amygdala volumes.
Note.
Lead was adjusted for urine-specific gravity and log-transformed. Solid lines represent the associations of prenatal lead on neonatal left amygdala volume at low (the 10th percentile) and high (the 90th percentile) levels of family income to needs ratio. Dashed lines represent 95% confidence intervals.

amygdala volumes (Rosso et al., 2005). Smaller total amygdala volumes have also been associated with aggressive behaviors in children (Thijssen et al., 2015) and adults (Pardini et al., 2014). However, other studies have found larger amygdala volumes in children with generalized anxiety disorder (De Bellis et al., 2000) and that larger right amygdala volumes mediated associations between maternal prenatal interleukin-6 and lower impulse control (Graham et al., 2018). Therefore, a future study with this longitudinal cohort will examine whether smaller amygdala volume mediates associations between high prenatal lead with later child internalizing and externalizing symptomatology.

4.1. *Strengths and limitations*

The present study benefits from multiple strengths. First, two of our focal variables utilized objective assessment (i.e., urine analysis of metals and MRI for neonatal brain volumes). Though blood lead is the standard biomarker for lead exposure, urinary lead reflects lead excreted from the blood by the kidneys and is correlated with blood lead (Bergdahl et al., 1997; McElroy et al., 2008). Still, we suggest that replication studies utilize a measure of blood lead to index prenatal lead exposure. Rather than testing a clinical diagnosis of depression as a moderator, we used self-reported depressive symptoms as a continuous measure. Though this captured variability in depressive symptoms and is less prone to bias in clinical diagnosis, this measure may be more appropriate for within-person analysis. Though our sample size may be considered large for MRI studies, larger samples still may be needed to detect smaller effects associated with prenatal lead. Because infants were only eligible to participate in the study if they were not preterm nor low birth weight, eligibility criteria and the live birth bias may underestimate the effects of prenatal lead exposure on neonatal neurodevelopment.

4.2. *Future directions and implications*

As this was the first study to explore prenatal lead exposure and neonatal brain volumes and moderations by non-chemical stressors, replication is needed. Future research should also consider mothers who are at higher risk for lead exposure and social stress as well as chemical and non-chemical mixtures. It is necessary to follow these infants into childhood to test whether effects on neonatal brain volumes mediate associations between prenatal lead exposure, depressive symptoms, and family income and later cognitive or socio-emotional outcomes—that is, whether these subtle neurodevelopmental differences precede later observable differences in child developmental and health outcomes. Additional research into the joint effects of prenatal lead and social and psychological stressor exposures may support lead screening initiatives and advisories in pregnant persons based on their suspected level of exposure to lead and other social and psychological risk factors.

4.3. *Conclusions*

Prenatal lead levels were negatively associated with neonatal bilateral amygdala volumes but not volumes of the hippocampus, frontal lobe, cerebellum, or total gray matter. Moderation analyses demonstrated that associations with the left amygdala were unique to participants with low depressive symptoms or high family income. The amygdala may be a particularly sensitive neural structure to fetal environmental exposures, including lead.

Disclosures

The authors have no biomedical financial interests or potential conflicts of interest.

CRediT authorship contribution statement

Amanda C. Wylie: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sarah J. Short:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **Rebecca C. Fry:** Writing – review & editing, Supervision, Methodology. **W. Roger Mills-Koonce:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition. **Cathi B. Propper:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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