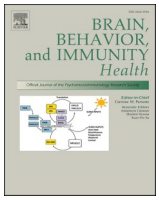
Brain, Behavior, & Immunity - Health 40 (2024) 100846

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



Maternal symptoms of depression and anxiety as modifiers of the relationship between prenatal phthalate exposure and infant neurodevelopment in the Atlanta African American maternal-child cohort

Katherine Springer [a], Jasmin A. Eatman [a,b], Patricia A. Brennan [c], Anne L. Dunlop [d], Dana Boyd Barr [a], Parinya Panuwet [a], P. Barry Ryan [a], Elizabeth Corwin [e], Kaitlin R. Taibl [a], Youran Tan [a], Susan S. Hoffman [f], Donghai Liang [a], Stephanie M. Eick [a,*]

[a] Gangarosa Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA
[b] Emory University School of Medicine, Atlanta, GA, USA
[c] Department of Psychology, Emory University, Atlanta, GA, USA
[d] Department of Gynecology and Obstetrics, School of Medicine, Emory University, Atlanta, GA, USA
[e] School of Nursing, Columbia University, New York City, NY, USA
[f] Department of Epidemiology, Emory University, Atlanta, GA, USA

ARTICLE INFO

Keywords:
Pregnancy
Phthalates
Maternal anxiety
Maternal depression
Birth outcomes
Infant neurodevelopment

ABSTRACT

Background: Prenatal exposure to phthalates, a group of synthetic chemicals widely used in consumer products, has previously been associated with adverse infant and child development. Studies also suggest that maternal depression and anxiety, may amplify the harmful effects of phthalates on infant and child neurodevelopment.
Study design: Our analysis included a subset of dyads enrolled in the Atlanta African American Maternal-Child Cohort (N = 81). We measured eight phthalate metabolites in first and second trimester (8–14 weeks and 24–32 weeks gestation) maternal urine samples to estimate prenatal exposures. Phthalate metabolite concentrations were averaged across visits and natural log-transformed for analysis. Maternal symptoms of depression and anxiety were assessed using validated questionnaires (Edinberg Postnatal Depression Scale and State Trait Anxiety Inventory, respectively) and the total score on each scale was averaged across study visits. The NICU Network Neurobehavioral Scale (NNNS) was administered at two weeks of age. Our primary outcomes included two composite NNNS scores reflecting newborn attention and arousal. Linear regression was used to estimate associations between individual phthalate exposures and newborn attention and arousal. We assessed effect modification by maternal depression and anxiety.
Results: Higher levels of urinary phthalate metabolites were not associated with higher levels of infant attention and arousal, but true associations may still exist given the limited power of this analysis. In models examining effect modification by maternal depression, we observed that an interquartile range increase in mono (2-ethlyhexyl) phthalate (MEHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) was associated with a significant increase in newborn arousal only among those with high depressive symptoms (MEHP: $\beta = 0.71$, 95% confidence interval [CI] = 0.10, 1.32 for high, $\beta = -0.30$, 95% CI = −0.73, 0.12 for low; MEOHP: $\beta = 0.60$, 95% CI = −0.03, 1.23 for high, $\beta = -0.12$, 95% CI = −0.58, 0.33 for low; MEHHP: $\beta = 0.54$, 95% CI = −0.04, 1.11 for high, $\beta = -0.11$, 95% CI = −0.54, 0.32 for low). Similar patterns were observed in models stratified by maternal anxiety, although CIs were wide.
Conclusion: Our results suggest maternal anxiety and depression symptoms may exacerbate the effect of phthalates on infant neurodevelopment. Future studies are needed to determine the optimal levels of attention and arousal in early infancy.

* Corresponding author. Gangarosa Department of Environmental Health, Emory University Rollins School of Public Health, USA.
E-mail address: Stephanie.marie.eick@emory.edu (S.M. Eick).

https://doi.org/10.1016/j.bbih.2024.100846
Received 8 August 2024; Accepted 10 August 2024
Available online 10 August 2024

1. Introduction

Phthalates are a large family of industrial compounds commonly used as plasticizers to increase the flexibility and workability of polymers, and to hold fragrance, shine, and color (Peijnenburg et al., 2008). More than 3,000,000 metric tons of phthalates are produced globally each year, and specific uses of phthalates are dependent on their respective configuration (Schettler, 2006). Low molecular weight phthalates are used in finishing materials such as varnishes, sealants, tiles, and coatings, while high molecular weight phthalates can be found in various plastic toys, food packaging, cosmetics, perfumes, and other common household goods (Zhang et al., 2021). Given that phthalates do not bind to the polymer that they are mixed with, they can easily leach into the environment, (Zhang et al., 2021) resulting in direct human exposure. The primary routes of human exposure include ingestion of food in phthalate-contaminated packaging, inhalation from perfumes, paints, and sprays, and dermal contact from the use of cosmetics and personal care products (Lyche et al., 2011). Phthalates may also be ingested through pharmaceutical coatings (e.g., herbal remedies or nutritional supplements) (Schettler, 2006). Once in the body, phthalates are metabolized into monoesters and other metabolites, which often exhibit stronger biological activity relative to the parent compounds (Zhang et al., 2021).

Phthalates have been shown to have anti-androgen effects and are classified as endocrine disruptors (Zhang et al., 2021). In mice, monoester phthalate metabolites have both fetotoxic and embryotoxic effects, suggesting reproductive and developmental toxicity resulting from exposure to phthalates (Zhang et al., 2021; Lyche et al., 2011). In humans, phthalates can cross the placental-fetal barrier and enter fetal circulation, (Lyche et al., 2011) thus *in utero* exposure to the fetus may impact developmental processes. Epidemiologic studies have shown that prenatal concentrations of specific urinary phthalate metabolites (i.e., mono-n-butyl phthalate (MBP), monoisobutyl phthalate (MiBP), and mono (2-ethyl-5-carboxypentyl) phthalate (MECPP)) are associated with preterm birth (Welch et al., 2022) and fetal growth restriction (Chang et al., 2022; Uldbjerg et al., 2022). Other studies have shown prenatal concentrations of low molecular weight phthalates are associated with attention problems, anxiety, and hyperactivity in children (Hyland et al., 2019). These adverse health outcomes associated with phthalate exposure during pregnancy and early life have garnered the attention of regulatory agencies. As of 2017, the United States Consumer Product Safety Commission passed 16 CFR Part 1307, which added onto the Consumer Product Safety Improvement Act of 2008 to prohibit a total of eight phthalates from being used in children's toys. Additionally, the Food and Drug Administration allows only nine phthalates to be used in polymers that come into contact with food (Indirect Food Additives, 2022). These regulations continue to be challenged and modified, becoming more strict as evidence of health outcomes resulting from phthalate exposures increase.

Pregnant people may also experience psychosocial stressors through many avenues, including poverty, low socioeconomic status, stressful life events, racial discrimination, or place-based chronic stressors (e.g., neighborhood deprivation) (Padula et al., 2020). Previous research, including investigations by our team, indicate that pregnant individuals facing stressful life events, residing in neighborhoods with perceived low quality, and experiencing socioeconomic disadvantages, tend to report heightened symptoms of anxiety and depression (Eick et al., 2020; Barcelona de Mendoza et al., 2018). These maternal anxiety and depression symptoms are psychological and physical manifestations of the stress response, and can occur as the result of other stressors (Williams, 2018). Our work within a prospective cohort of African American mother-child dyads has further shown that elevated levels of maternal stress, including maternal anxiety and depression symptoms, are negatively associated with infant attention (Hendrix et al., 2022). Notably, low infant attention scores assessed via the NNNS have been associated with poor social and communicative behavior later in childhood (Bowers et al., 2019). Findings from the larger Environmental influences on Child Health Outcomes (ECHO) cohort futher show that maternal depression is also be associated with higher levels of infant arousal, (Camerota et al., 2023) and separately a high arousal score is generally considered a "difficult" phenotype (Sucharew et al., 2012). Previous studies have also indicated that high prenatal risk, which can include maternal anxiety and depression, is associated with higher arousal NNNS score (Fink et al., 2012). Separately, maternal anxiety is also further been associated with lower infant attention scores (Hendrix et al., 2022; Hofheimer et al., 2023).

Our team has shown that among pregnant African Americans, increasing phthalate metabolite concentrations are associated with lower birthweight z-scores, and that this association is stronger among those who report higher levels of depression and anxiety symptoms (Eatman et al., 2023). Notably, when assessing cumulative effects, we observed that the effects of phthalate and stressors together where greater what was observed for phthalates alone, providing some evidence of additive effects (Eatman et al., 2023). Our findings of a joint impact between phthalate exposure and psychosocial stressors is supported by findings from a second prospective cohort, The Infant Development and the Environment Study (TIDES), which previously observed a joint impact of phthalates and stressful life events on preterm birth and child behavior at age 4–6 years (Ferguson et al., 2019; Barrett et al., 2024). While prior work has shown a cumulative effect of chemical exposures and stress on birth outcomes, little is known about whether a cumulative effect on infant development exists. In this study, we leveraged a prospective cohort of African American mother-child dyads to examine if prenatal phthalate metabolite levels are associated with alterations in infant neurodevelopment. We hypothesized that phthalate metabolite levels would be inversely and linearly associated with infant attention and positively and linearly associated with infant arousal, and that these associations are stronger in magnitude among those with higher levels of maternal depression and anxiety symptoms.

2. Methods

2.1. Study Design and population

Participants included in this analysis were a subset of the Atlanta African American Maternal-Child Cohort, a prospective birth cohort. The original study was designed to examine the effects of biobehavioral determinants of preterm birth, while chemical exposure biomonitoring and longitudinal infant follow-up were added after. As such, our analytic sample was restricted to mother-child pairs from whom information on prenatal urinary phthalate metabolite levels and infant NNNS measures were available (N = 81). All pregnant persons included in this cohort self-identified as mothers, therefore we use the term 'maternal' throughout. Detailed information regarding recruitment and retention is available elsewhere (Brennan et al., 2019; Corwin et al., 2017). Briefly, participants were recruited between 2016 and 2020 from two metropolitan hospitals (Emory Midtown and Grady Memorial hospitals) in Atlanta, Georgia. Individuals were eligible for inclusion if they self-identified as African American or Black race, were pregnant with a singleton fetus between 8 and 14 weeks gestation and did not have any diagnosed chronic medical conditions (e.g., diabetes mellitus, chronic hypertension, seizure disorders) or chronic use of prescription medication (e.g., anti-diabetic, anti-hypertensive, anti-seizure). This study was approved by the Emory University Institutional Review Board (reference #: 68441) and all participants provided written, informed consent prior to enrollment.

2.2. Measurement of phthalates metabolites

In this cohort, urine samples were collected at up to two points during pregnancy (between 8-14 weeks and 24–32 weeks gestation) and were stored at −80 °C prior to analysis. Levels of eight urinary phthalate

metabolites were quantified at the Laboratory of Exposure Assessment and Development for Environmental Research (LEADER) at Emory University using validated methods that have been previously described (Zhang et al., 2022). Phthalate metabolites included: monoethyl phthalate (MEP), MBP, MiBP, monobenzyl phthalate (MBzP), mono (2-ethlyhexyl) phthalate (MEHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and MECPP. We additionally quantified the molar sum of ∑DEHP using the equation $\sum DEHP = \sum\left(\frac{MEHP}{278.34} + \frac{MEHHP}{294.34} + \frac{MEOHP}{292.33} + \frac{MECPP}{308}\right)$.

All phthalate metabolites were detected in >60% of sample, and values below the limit of detection (LOD) were imputed with $LOD/\sqrt{2}$ (Hornung and Reed, 1990). To obtain a more stable estimate of each urinary phthalate metabolite across gestation, we took the geometric average. Averaged concentrations were right skewed, and natural log-transformed for downstream analysis. If only one measure was available, we used only that measure. We accounted for urinary dilution by including urinary creatinine (as a continuous variable) as a covariate in all models (Barr et al., 2005).

2.3. Assessment of maternal anxiety and depressive symptoms

Symptoms of depression and anxiety were assessed twice during pregnancy (8–14 weeks and 24–32 weeks gestation) using validated, self-reported questionaries (Cox et al., 1987; Spielberger, 2012). As with urinary phthalate metabolites, we calculated an averaged measure of depression and anxiety using scores at both visits. If scores were available at only one timepoint, we used that score.

Self-reported depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987). This 10-item scale is commonly used to measure depressive symptoms experienced within the past week during prenatal and post-partum periods of pregnancy. Scores on the EPDS ranged from 0 to 22, which we then dichotomized into high or low levels of depressive symptoms. Those with an EPDS score >=10 were classified as having experienced high levels of depressive symptoms (Matthey et al., 2006; Teissèdre and Chabrol, 2004).

Self-reported anxiety symptoms were assessed using measured using the State Trait Anxiety Inventory (STAI) (Spielberger, 2012), a commonly used measure to capture anxiety at the moment of assessment. In our analysis, the state anxiety score was utilized to capture current feelings of anxiety. Scores on the STAI ranged from 20 to 69 and were dichotomized into high and low levels of anxiety symptoms, where those with a STAI score >=40 were classified as experiencing high levels of anxiety symptoms (Julian; Womble et al., 2021; Addolorato et al., 1999).

2.4. Infant neurobehavioral assessment

At two weeks of age, the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) (Lester and Tronick, 2005) was administered to newborns by a single, certified, masters-level research specialist. The NNNS is a standardized assessment aimed to comprehensively assess newborns' neurologic integrity, behavioral functioning, and signs of stress. The NNNS assessment results in 13 scores for orientation, habituation, hypertonicity, hypotonicity, excitability, arousal, lethargy, non-optimal reflexes, asymmetric reflexes, stress, self-regulation, quality of movement, and handling.

Our primary outcomes included two composite NNNS summary scores, which were created using principal component analysis (PCA) in this study population (Hendrix et al., 2022). One score measures newborn neurobehavioral arousal and the second captures attention and reflects the newborn's ability to respond to, attend to, and track environmental stimuli. Information regarding the variables comprising the attention and arousal composites are provided elsewhere (Hendrix et al., 2022). These two composite NNNS scores were treated as separate continuous outcomes in individual models in our analysis. In this analysis, we use the terms "attention" and "arousal," to reflect their respective PCA-derived composite scores.

2.5. Confounders and covariates

Maternal age, maternal education, and insurance status were assessed at the first study visit using a self-reported interview questionnaire with verification by medical record review. An income-to-poverty ratio was calculated based on self-reported annual household income and the number of household members. Information on substance use (tobacco, alcohol, and marijuana) in the month prior up to the first visit was also collected. Early pregnancy body mass index (BMI in kg/m^2) was calculated based on maternal height and weight, abstracted from the medical record at the first visit. Infant sex and parity were similarly abstracted from the medical record. Covariates retained in minimally adjusted models included urinary creatinine, infant sex, and infant age at assessment. Infant age at assessment was corrected for preterm deliveries. Fully adjusted models additionally included maternal age, maternal education, and early pregnancy BMI. These covariates were chosen *a priori* via a directed acyclic graph (DAG; Fig. S1) that was informed via a literature review and associations between covariates, exposures, and outcomes in our study population.

2.6. Statistical analysis

The distribution of sociodemographic characteristics and NNNS summary scores in our study population was described using means, standard deviations (SDs), and frequencies and counts for continuous and categorical variables, respectively. The distribution of averaged urinary phthalate metabolite levels was assessed using geometric means (GMs), geometric SDs (GSDs), and select percentiles. We additionally calculated the mean and SDs of averaged phthalate metabolite levels and NNNS summary scores across sociodemographic characteristics. The correlation between averaged phthalate metabolites, depression, and anxiety was quantified using Spearman correlation coefficients.

For our primary analysis, we examined the association between individual, averaged phthalate metabolites and NNNS summary scores using a series of minimally adjusted and fully adjusted linear regression models. Next, we assessed whether these associations were modified by maternal anxiety and depression symptoms using linear regression models that were stratified by levels of depressive and anxiety symptoms. We additionally assessed for interaction by including an interaction term between the averaged phthalate metabolite levels and the continuous measure of maternal anxiety and depression symptoms in models which were not stratified. Across all models, the average of urinary phthalate metabolites was standardized to the populations interquartile range (IQR). Individual phthalate levels and NNNS summary scores were treated as individual exposures and outcomes in separate models.

3. Results

Eighty-one mother-child pairs were included in our analytic sample (Table 1). The average maternal age was 25.25 years (SD = 5.28), and the average early pregnancy BMI was 29.27 kg/m^2 (SD = 8.65) (Table 1). Most participants self-reported being single, not cohabitating with a partner (55.6%) and having completed high school or some college education (55.6%). Nearly two thirds of participants had an income-to-poverty ratio below 150% (67.9%) and most participants had Pregnancy Medicaid as their primary insurance (53.1%). Many participants gave birth at Grady Memorial Hospital (63.0%). Approximately one third of mothers were classified as having experienced high anxiety (33.3%) and depressive symptoms (37.0%) during pregnancy, and 20 mothers (24.7%) reported as having high symptoms of both anxiety and depression (Table 1). The average infant attention summary score was

Table 1
Distribution of sociodemographic characteristics, clinical characteristics, and depression and anxiety symptoms among pregnant people and infants in a subset of the Atlanta African American Maternal-Child Cohort, 2016–2020 (N = 81).

Characteristic	Mean (SD)
Newborn Attention	0.13 (0.95)
Newborn Arousal	−0.01 (0.90)
Infant Birthweight (grams)	3087.32 (485.41)
Gestational Age at Delivery (weeks)	38.73 (1.63)
Infant Age at NNNS Assessment	16.43 (9.96)
Maternal Age (years)	25.25 (5.28)
Early Pregnancy BMI (kg/m^2)	29.27 (8.65)
	N (%)
Marital Status	
Married or Living Together	36 (44.5%)
Single	45 (55.6%)
Maternal Education	
High school or some college or less	45 (55.6%)
College degree or higher	36 (44.4%)
Income to Poverty Ratio	
<150%	55 (67.9%)
≥150%	26 (32.1%)
Tobacco, Alcohol, or Marijuana Use During Pregnancy	
No	43 (53.1%)
Yes	38 (46.9%)
Parity	
No Prior Births	33 (40.7%)
One or More Prior Births	48 (59.3%)
Health Insurance	
Low-Income Medicaid	24 (29.6%)
Right From the Start of Pregnancy Medicaid	43 (53.1%)
Private	14 (17.3%)
Hospital Site	
Emory	30 (37.0%)
Grady	51 (63.0%)
Infant Sex	
Male	42 (51.9%)
Female	39 (48.1%)
Anxiety Symptoms	
Low	54 (66.7%)
High	27 (33.3%)
Depression Symptoms	
Low	51 (63.0%)
High	30 (37.0%)

Abbreviations: SD, standard deviation; BMI, body mass index. Note: Infant age at NNNS assessment was corrected for gestational age. High anxiety symptoms were defined as an STAI score ≥ 40 and high depression symptoms were defined as an EPDS score ≥10.

0.13 (SD = 0.95) and the average infant arousal summary score was −0.01 (SD = 0.9). We note minimal differences in demographic characteristics between our analytic sample and the overall cohort (Table S1) with the most prominent differences being that our analytic sample had a higher proportion of male infants (51.9% versus 48.6%), as well as a higher mean newborn attention summary score (mean 0.13 versus −0.01) relative to the larger cohort (Table 1, Table S1). Additionally, participants included in our analytic sample self-reported higher rates of anxiety and depression symptoms (33.3% versus 26.2% for anxiety symptoms and 37.0% versus 27.4% for depression symptoms) as compared to the overall cohort (Table 1, Table S1).

Among the urinary phthalate metabolites, the highest GM was for MEP (101.12 ng/mL, GSD = 3.18), followed by MBP (8.74 ng/mL, GSD = 3.40) (Table 2). Averaged phthalate metabolite levels were moderately to strongly correlated with one another, with the strongest correlation being between MEOHP and MEHHP (Spearman $\rho = 0.97$) (Fig. S2). Visit specific urinary phthalate metabolite levels were also moderately correlated (Fig. S3), while depression and anxiety were correlated at both timepoints (Fig. S4).

When examining the distribution of phthalate metabolites across sociodemographic characteristics, we observed that levels of all phthalate metabolites were higher among those who were single, had less than a college degree, had an income-to-poverty ratio less than 150%, relative to those who were single, had a college degree or greater, and an income-to-poverty ratio less than 150%, respectively (Table S2). Differences were greatest in magnitude for MEP; for example, the GM of MEP among those who has less than a college degree was 104.83 ng/mL (GSD = 2.58) compared to a GM of 96.75 ng/mL (GSD = 4.00) among those who had at least a college degree. Newborn attention and arousal scores were lower among mothers with a college degree or above and newborn arousal was lower among mothers who self-reported substance use (Table S3).

In the fully adjusted linear regression models, we observed that an IQR increase in averaged phthalate exposure levels was not associated with newborn attention or arousal. For example, an IQR increase in MBP was associated with a non-significant reduction in newborn attention (β = −0.36, 95% confidence interval [CI] = −0.78, 0.05) and almost no difference in newborn arousal (β = −0.08, 95% CI = −0.51, 0.35) (Fig. 1, Table S4). These non-significant associations were also observed in our minimally adjusted linear regression models (Table S4).

In our stratified linear regression models examining effect modification by maternal anxiety, we observed that an IQR increase in levels of all but one phthalate metabolite exposure was associated with a modest increase in newborn attention among those who experienced high anxiety symptoms only (Fig. 2, Table S5). When newborn arousal was the outcome of interest, similar patterns were observed (Fig. 2, Table S5). In models examining the association between averaged phthalate exposures and newborn arousal stratified by maternal depression, we observed that increasing most phthalate exposures was associated with an increase in newborn arousal, only among those with high depression. Effect estimates were greater in magnitude for MEHP (β = 0.71, 95% CI = 0.10, 1.32), MEOHP (β = 0.60, 95% CI = −0.03, 1.23), MEHHP (β = 0.54, 95% CI = −0.04, 1.11), and ΣDEHP (β = 0.47, 95% CI = −0.07, 1.01), where an IQR increase was associated with an increase in newborn arousal among those with high depression, but lower arousal among those with low depression, however all p-values

Table 2
Distributions of averaged, urinary phthalate exposure concentrations in the Atlanta African American Maternal-Child Cohort (ng/mL) (N = 81).

	Geometric Mean (Geometric SD)	Percentile					% above LOD
		5%	25%	50%	75%	95%	
MEP	101.12 (3.18)	13.90	42.7	115.17	178.37	761.04	100%
MBP	8.74 (3.40)	1.28	3.27	9.45	18.60	57.48	78.6%
MiBP	8.17 (2.95)	1.42	3.76	7.61	18.28	51.63	84.8%
MBzP	5.25 (3.65)	0.62	2.09	5.16	13.04	37.38	98.6%
MEHP	1.55 (3.04)	0.14	0.75	1.81	4.00	6.73	87.6%
MEOHP	3.02 (2.47)	0.64	1.65	3.43	5.75	12.90	96.6%
MEHHP	4.57 (2.43)	0.94	2.60	5.28	8.05	16.81	97.9%
MECPP	7.68 (1.81)	3.72	4.94	7.05	11.88	22.41	63.4%
ΣDEHP	0.06 (2.02)	0.02	0.04	0.06	0.09	0.17	–

Abbreviations: SD, standard deviation; LOD, limit of detection. Note: full names for phthalate exposures are provided in the methods section.

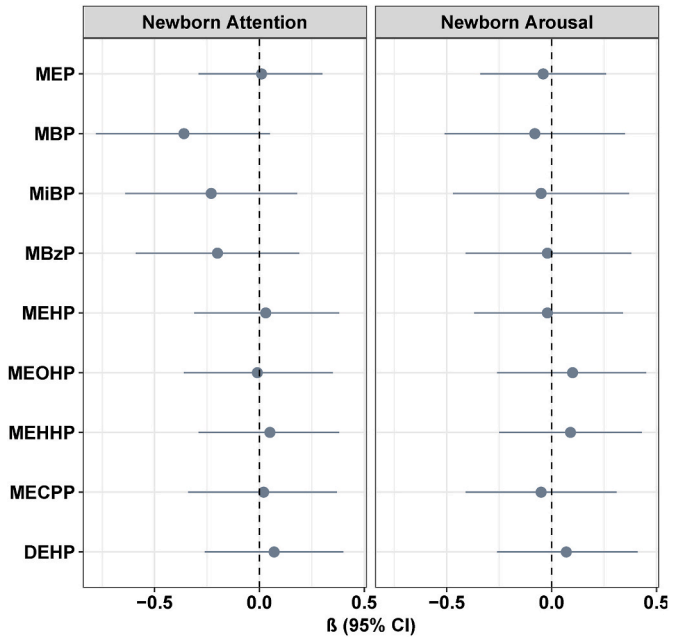


Fig. 1. Associations between an interquartile range increase in of natural log transformed average urinary phthalate exposure (ng/mL) and infant attention and arousal scores among a subset of the African American Maternal-Child Cohort, 2016–2020 (N = 81). Note: Models are adjusted for creatinine, infant sex, infant age at assessment, maternal age, maternal education, and early pregnancy body mass index.

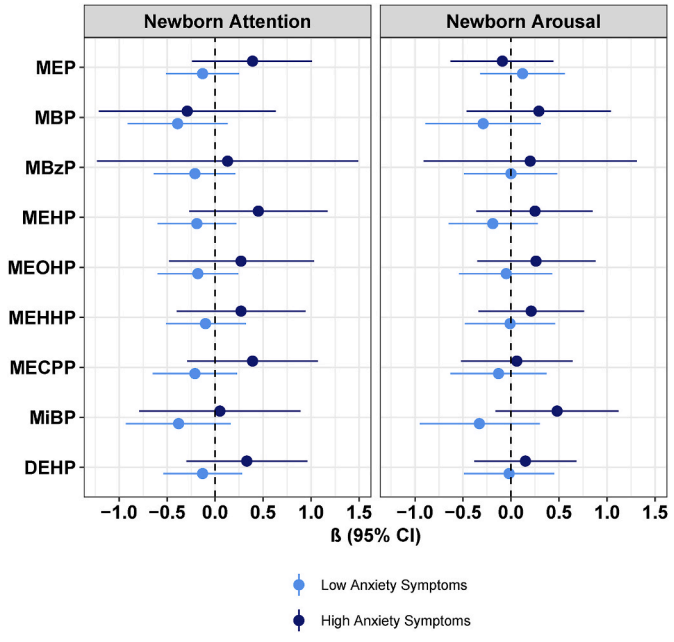


Fig. 2. Associations between an interquartile range increase in natural log transformed average urinary phthalate exposures (ng/mL) and infant attention and arousal scores among a subset of the African American Maternal-Child Cohort, 2016–2020, stratified by averaged anxiety symptoms (N = 54 for low anxiety symptoms, N = 27 for high anxiety symptoms). Note: Models are adjusted for creatinine, infant sex, infant age at assessment, maternal age, maternal education, and early pregnancy body mass index. High anxiety symptoms were defined as an STAI score ≥ 40.

for interaction showed non-significance (Fig. 3, Table S6). When newborn attention was the outcome of interest, there was no evidence of effect modification by depression (Fig. 3, Table S6).

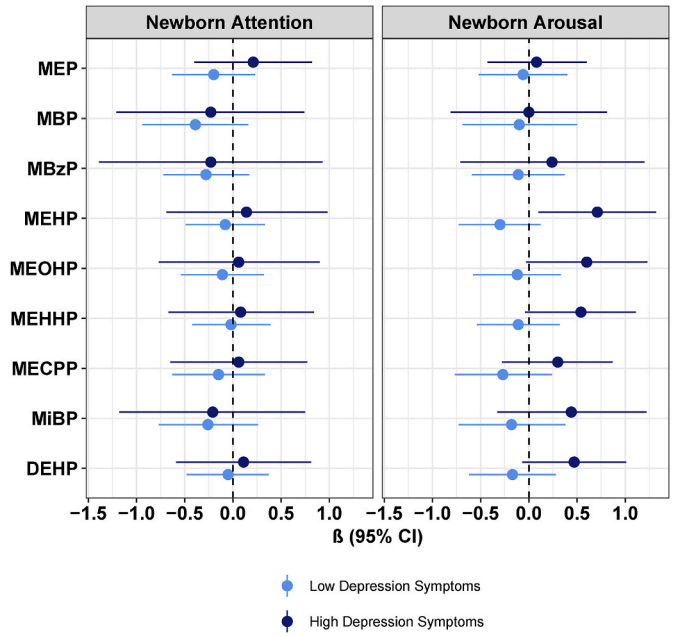


Fig. 3. Associations between an interquartile range increase in natural log transformed average urinary phthalate exposures (ng/mL) and infant attention and arousal scores among a subset of the African American Maternal-Child Cohort, 2016–2020, stratified by averaged depression levels (N = 51 for low depression symptoms, N = 30 for high depression symptoms). Note: Models are adjusted for creatinine, infant sex, infant age at assessment, maternal age, maternal education level, and early pregnancy body mass index. High depression symptoms were defined as an EPDS score ≥ 10.

4. Discussion

Within a prospective cohort of African American mothers and their newborns, we observed a trend that prenatal phthalate exposures were moderately associated with an increase in newborn arousal only among those who reported higher levels of anxiety and depressive symptoms. However, confidence intervals were wide and generally included the null value, suggesting that our study may be underpowered to detect a true difference that may be observed in a larger study. Given that these trends were observed in our limited sample size, future studies are needed to confirm these findings. Our study provides important perspective on how depression and anxiety, which has been shown to be elevated in pregnant people with a history of stressful life events, poor perceived neighborhood quality, and socioeconomic disadvantage, may contribute to offspring neurodevelopment. Prior research on a sample of predominantly African American mother-child pairs finds that newborns born to mothers who report high levels of trait anxiety report higher responses in brain regions that are linked to anxiety disorders in adulthood (Sylvester et al., 2021). In this context, our findings highlight the need for further studies in this area, as the optimal level of newborn attention and arousal during the newborn period is unknown.

Previous studies have established the link between prenatal urinary phthalate levels and adverse impacts on infant development, (Philips et al., 2017; Barrett et al., 2016) and our analysis by high or low anxiety and depression symptoms adds to existing literature supporting the hypothesis that maternal mental health and psychosocial stress functions as a modifier of these relationships. Prior research also finds that experiences of stressful life events can also exacerbate the effects of prenatal phthalate exposure on offspring neurodevelopment (Barrett et al., 2024). Our research finds that the effects may not be exclusive to stressful life events, but maternal mental health in general. Studies also find that individual psychosocial stressors are associated with adverse neurobehavioral outcomes in offspring (Dhaliwal et al., 2023). Also, exposure to specific kinds of phthalates, like DEHP and low molecular

weight phthalates, can lead to adverse neurological outcomes in children such as autism, dementia, (Tran et al., 2023) and attention deficit hyperactivity disorder (Engel et al., 2010). Currently, outcomes describing the impact of composite phthalate exposure on neurodevelopment and behavior in children are inconsistent (Barrett et al., 2024). There is also an increasing body of literature that suggests arousal specifically follows a non-linear pattern, with both hypo and hyper arousal states leading to problems later on in life (Camerota et al., 2023; Liu et al., 2010; McGowan et al., 2022). Additionally, phthalate exposure has been shown to be associated with improved attention and social response, further supporting that the impact of phthalate exposure on neurodevelopment may not be linear (Stroustrup et al., 2018). To obtain a more robust perspective of the mechanisms and effects of these relationships, further research utilizing larger study populations from different geographic regions and sociodemographic groups should be undertaken.

Our results also contribute to a growing body of literature about how perinatal depression and anxiety affects African American women. Importantly, prior literature shows that depression and anxiety symptoms are downstream consequences of racial discrimination, and African American women experience discrimination on the basis of both race and gender (Williams, 2018; Hernandez et al., 2022; Wenzel et al., 2021; Nelson et al., 2023). Our findings demonstrate that environmental exposures during the perinatal period can contribute to adverse birth outcomes in Black communities. Black women are at a higher risk of preterm birth and have higher concentrations of urinary phthalate metabolites as a result of social and structural racism, with disparate industry marketing of chemical-containing beauty products as an example. For example, African American women are more likely to use vaginal douches and fragranced feminine cleansing products, which contain phthalates (Branch et al., 2015). Discrimination against African American women in the media continue to perpetuate damaging sexual stereotypes of Black women, which label them as dirty and devalued (Zota and Shamasunder, 2017). For example, companies that market intimate deodorizing products producing target Black women in advertisement campaigns, capitalizing on disparaging stereotypes that suggest Black women are biologically impure, and must utilize their products at disproportionate rates (Ferranti, 2011). Targeted racial and ethnic marketing of beauty products continues to perpetuate health inequities stemming from Eurocentric standards of beauty. Phthalate exposure and maternal mental health are both issues of environmental justice. In this study, we approach both issues through a lens of intersectionality.

Phthalates exposure and stress response can influence offspring neurodevelopment through a variety of mechanisms. As known endocrine disruptors, phthalates interfere with the hormonal pathways necessary for fetal development, specifically by decreasing maternal thyroid hormones and exhibiting antiandrogenic properties (Nidens et al., 2021). Phthalates can influence thyroid hormone activity during gestation (Nidens et al., 2021). Both maternal and fetal hypothyroidism are associated with adverse effects on fetal brain development (Haddow et al., 1999). Additionally, interference with estrogen receptors, and disruption of such sex hormones can also influence offspring brain development (Nidens et al., 2021). In animal models, DEHP exposure allows transgenerational transmission of allergic airway inflammation. In human models, hypomethylation in placental DNA following maternal DEHP exposure has been shown (Tran et al., 2023). The affected genes are related to neurological symptoms, highlighting possible pathways leading to neurodevelopment. Furthermore, pregnant people with higher exposure to phthalates have higher interferon-γ, a pro-inflammatory cytokine (Taibl et al., 2024). Finally, in research conducted in this cohort on exposure to prenatal phthalate metabolites, perturbations of the newborn metabolome, and infant neurobehavioral functioning, there was evidence that prenatal phthalate exposure disrupts the newborn metabolome, specifically tyrosine and tryptophan metabolism. Within tyrosine metabolism, phthalate metabolites were associated with a downregulation of tyrosine and a subsequent negative association with attention scores. Additionally, within tryptophan metabolism, 5-hydroxytryptophan and serotonin were associated with a decrease in arousal scores. This research provides context for the biological underpinnings of the associations that were highlighted in this work. However, our prior work examining environmental impacts on the newborn metabolome focused only on exposure to phthalates. Future studies could utilize mixture methods to consider psychosocial stressors.

Our results should be interpreted considering its strengths and limitations. First, our analytic sample was relatively small, which limits our statistical power; this imprecision is reflected in our wide confidence intervals, particularly for stratified analysis. Nonetheless, we focused our interpretations of results on trends, as opposed to an over reliance on statistical significance and p-values. Furthermore, studies assessing the joint impact of phthalate exposure and maternal mental health are extremely limited, and this study represents an important first step in understanding these associations. Additionally, we acknowledge that individuals may perceive stressors differently and, in this sense, our self-reported measures of depression and anxiety may be subject to exposure misclassification; however, our measures of depression and anxiety were based on validated questionnaires that are widely used during pregnancy. Using NNNS scores as our outcome measurement also poses some limitations, since it lacks precision when it comes to specific clinical phenomenon; however, these scores allow us to observe general trends for comparability between infants (Salisbury et al., 2005). These general trends still offer important insight while simultaneously warranting further investigation into the minutia and clinical implications of these trends. Additionally, information on maternal medication was not included in this analysis, which may attenuate our effects towards the null if participants taking depression or anxiety mediations report fewer symptoms. Lastly, phthalate metabolites have a short half-life where a single measure reflects very recent exposure. However, exposure is likely consistent given the ubiquity of phthalates in consumer products. We also note that repeated measures of phthalate metabolites were available in our study population, and we averaged these repeated measures to create a robust estimate of phthalate exposure across pregnancy, which is an important strength. Our study has many other strengths. Specifically, we assessed the joint impact of a class of ubiquitous environmental chemicals in combination with maternal anxiety and depression symptoms, which is important as we found trends among mothers that reported high levels of depressive symptoms and anxiety. Non-chemical stressors are often not considered in environmental epidemiology studies, underscoring the importance of this work. Additionally, we leveraged a highly phenotyped cohort of socioeconomically diverse African American women, a population largely underrepresented in previous scientific literature.

5. Conclusions

We observed that prenatal exposure to phthalates may be associated with an increase in newborn arousal only among those with high levels of maternal depressive symptoms during pregnancy. Similarly, we found that phthalates were modestly associated with an increase in newborn attention and arousal among those experiencing anxiety. Our findings provide important insights into how experiences of depression and anxiety by pregnant people can exacerbate associations between environmental exposures and neurodevelopment. Further studies are needed to replicate and validate our results, as our study was limited by a relatively small sample size. Future studies should also assess the influence of other psychosocial and non-chemical stressors, as well as the optimal levels of newborn attention during early life.

Funding

Research reported in this publication was supported by the

Environmental Influences on Child Health Outcomes (ECHO) program, Office of the Director, National Institutes of Health, under Award Numbers UG3/UH3OD023318, the National Institute of Health (NIH) grants [R21ES032117, R01NR014800, R01MD009064, R24ES029490, R01MD009746, P50ES02607, P30ES019776, T32ES012870, K01ES035082], and Environmental Protection Agency (USEPA) center grant [83615301].

CRediT authorship contribution statement

Katherine Springer: Formal analysis, Writing – original draft. **Jasmin A. Eatman:** Conceptualization, Writing – review & editing. **Patricia A. Brennan:** Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Writing – review & editing. **Anne L. Dunlop:** Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Writing – review & editing. **Dana Boyd Barr:** Data curation, Formal analysis, Methodology, Project administration, Writing – review & editing. **Parinya Panuwet:** Data curation, Writing – review & editing. **P. Barry Ryan:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Elizabeth Corwin:** Data curation, Funding acquisition, Investigation, Project administration, Writing – review & editing. **Kaitlin R. Taibl:** Writing – review & editing. **Youran Tan:** Funding acquisition, Writing – review & editing. **Susan S. Hoffman:** Writing – review & editing. **Donghai Liang:** Conceptualization, Project administration, Writing – review & editing. **Stephanie M. Eick:** Conceptualization, Data curation, Formal analysis, Resources, Supervision, Writing – review & editing.

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

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100846.

References

16 CFR Part 1307 – Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates. Accessed January 11, 2024. https://www.ecfr.gov/current/title-16/part-1307.

Addolorato, G., Ancona, C., Capristo, E., et al., 1999. State and trait anxiety in women affected by allergic and vasomotor rhinitis. J. Psychosom. Res. 46 (3), 283–289. https://doi.org/10.1016/S0022-3999(98)00109-3.

Barcelona de Mendoza, V., Harville, E.W., Savage, J., Giarratano, G., 2018. Experiences of intimate partner and neighborhood violence and their association with mental health in pregnant women. J. Interpers Violence 33 (6), 938–959. https://doi.org/10.1177/0886260515613346.

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., Pirkle, J.L., 2005. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 113 (2), 192–200. https://doi.org/10.1289/ehp.7337.

Barrett, E.S., Parlett, L.E., Sathyanarayana, S., Redmon, J.B., Nguyen, R.H.N., Swan, S.H., 2016. Prenatal stress as a modifier of associations between phthalate exposure and reproductive development: results from a multicenter pregnancy cohort study. Paediatr. Perinat. Epidemiol. 30 (2), 105–114. https://doi.org/10.1111/ppe.12264.

Barrett, E.S., Day, D.B., Szpiro, A., et al., 2024. Prenatal exposures to phthalates and life events stressors in relation to child behavior at age 4–6: a combined cohort analysis. Environ. Int. 183, 108425 https://doi.org/10.1016/j.envint.2024.108425.

Bowers, K., Khoury, J., Sucharew, H., et al., 2019. Early infant attention as a predictor of social and communicative behavior in childhood. Int. J. Behav. Dev. 43 (3), 204–211. https://doi.org/10.1177/0165025418797001.

Branch, F., Woodruff, T.J., Mitro, S.D., Zota, A.R., 2015. Vaginal douching and racial/ethnic disparities in phthalates exposures among reproductive-aged women: National Health and Nutrition Examination Survey 2001–2004. Environ. Health 14, 57. https://doi.org/10.1186/s12940-015-0043-6.

Brennan, P.A., Dunlop, A.L., Smith, A.K., Kramer, M., Mulle, J., Corwin, E.J., 2019. Protocol for the Emory University African American maternal stress and infant gut microbiome cohort study. BMC Pediatr. 19 (1), 246. https://doi.org/10.1186/s12887-019-1630-4.

Camerota, M., McGowan, E.C., Aschner, J., et al., 2023. Prenatal and perinatal factors associated with neonatal neurobehavioral profiles in the ECHO Program. Pediatr. Res. 94 (2), 762–770. https://doi.org/10.1038/s41390-023-02540-2.

Chang, C.H., Tsai, Y.A., Huang, Y.F., et al., 2022. The sex-specific association of prenatal phthalate exposure with low birth weight and small for gestational age: a nationwide survey by the Taiwan Maternal and Infant Cohort Study (TMICS). Sci. Total Environ. 806, 151261 https://doi.org/10.1016/j.scitotenv.2021.151261.

Corwin, E.J., Hogue, C.J., Pearce, B., et al., 2017. Protocol for the emory university african American vaginal, oral, and gut microbiome in pregnancy cohort study. BMC Pregnancy Childbirth 17 (1), 161. https://doi.org/10.1186/s12884-017-1357-x.

Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of postnatal depression: development of the 10-item Edinburgh postnatal depression scale. Br. J. Psychiatry 150 (6), 782–786. https://doi.org/10.1192/bjp.150.6.782.

Dhaliwal, S.K., Dabelea, D., Lee-Winn, A.E., Crume, T., Wilkening, G., Perng, W., 2023. Maternal psychosocial stress during pregnancy and offspring neurobehavioral outcomes during early childhood in the Healthy Start Study. Ann. Epidemiol. 86, 16–24.e3. https://doi.org/10.1016/j.annepidem.2023.06.001.

Eatman, J.A., Dunlop, A.L., Barr, D.B., et al., 2023. Exposure to phthalate metabolites, bisphenol A, and psychosocial stress mixtures and pregnancy outcomes in the Atlanta African American maternal-child cohort. Environ. Res. 233, 116464 https://doi.org/10.1016/j.envres.2023.116464.

Eick, S.M., Goin, D.E., Izano, M.A., et al., 2020. Relationships between psychosocial stressors among pregnant women in San Francisco: A path analysis. PLoS One 15 (6), e0234579. https://doi.org/10.1371/journal.pone.0234579.

Engel, S.M., Miodovnik, A., Canfield, R.L., et al., 2010. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. Environ. Health Perspect. 118 (4), 565–571. https://doi.org/10.1289/ehp.0901470.

Ferguson, K.K., Rosen, E.M., Barrett, E.S., et al., 2019. Joint impact of phthalate exposure and stressful life events in pregnancy on preterm birth. Environ. Int. 133, 105254 https://doi.org/10.1016/j.envint.2019.105254.

Ferranti, M., 2011. An odor of racism: vaginal deodorants in african-American beauty culture and advertising. Advert. Soc. Rev. 11 (4). https://muse.jhu.edu/pub/21/article/407304. (Accessed 24 January 2024).

Fink, N.S., Tronick, E., Olson, K., Lester, B., 2012. Healthy newborns' neurobehavior: norms and relations to medical and demographic factors. J. Pediatr. 161 (6), 1073–1079.e3. https://doi.org/10.1016/j.jpeds.2012.05.036.

Haddow, J.E., Palomaki, G.E., Allan, W.C., et al., 1999. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N. Engl. J. Med. 341 (8), 549–555. https://doi.org/10.1056/NEJM199908193410801.

Hendrix, C.L., Brown, A.L., McKenna, B.G., Dunlop, A.L., Corwin, E.J., Brennan, P.A., 2022. Prenatal distress links maternal early life adversity to infant stress functioning in the next generation. J Psychopathol Clin Sci 131 (2), 117–129. https://doi.org/10.1037/abn0000688.

Hernandez, N.D., Francis, S., Allen, M., et al., 2022. Prevalence and predictors of symptoms of perinatal mood and anxiety disorders among a sample of urban Black women in the south. Matern. Child Health J. 26 (4), 770–777. https://doi.org/10.1007/s10995-022-03425-2.

Hofheimer, J.A., McGrath, M., Musci, R., et al., 2023. Assessment of psychosocial and neonatal risk factors for trajectories of behavioral dysregulation among young children from 18 to 72 Months of age. JAMA Netw. Open 6 (4), e2310059. https://doi.org/10.1001/jamanetworkopen.2023.10059.

Hornung, R.W., Reed, L.D., 1990. Estimation of average concentration in the presence of nondetectable values. Appl. Occup. Environ. Hyg 5 (1), 46–51. https://doi.org/10.1080/1047322X.1990.10389587.

Hyland, C., Mora, A.M., Kogut, K., et al., 2019. Prenatal exposure to phthalates and neurodevelopment in the CHAMACOS cohort. Environ. Health Perspect. 127 (10), 107010 https://doi.org/10.1289/EHP5165.

Indirect Food Additives, 2022. Adhesives and components of coatings; paper and paperboard components; polymers; adjuvants, production aids, and sanitizers. Fed. Regist. Published May 20 https://www.federalregister.gov/documents/2022/05/20/2022-10531/indirect-food-additives-adhesives-and-components-of-coatings-paper-and-paperboard-components. (Accessed 12 January 2024).

Lester, B.M., Tronick, E., 2005. NICU Network Neurobehavioral Scale (NNNS) Manual. Paul H. Brookes Pub. Co. http://catdir.loc.gov/catdir/toc/ecip0415/2004004558.html. (Accessed 18 December 2023).

Liu, J., Bann, C., Lester, B., et al., 2010. Neonatal neurobehavior predicts medical and behavioral outcome. Pediatrics 125 (1), e90–e98. https://doi.org/10.1542/peds.2009-0204.

Lyche, J., Lyche, Jan L., 2011. Phthalates. In: Ramesh, C. (Ed.), Reproductive and Developmental Toxicology, vol. 48. Gupta, pp. 637–655, 2011.

Matthey, S., Henshaw, C., Elliott, S., Barnett, B., 2006. Variability in use of cut-off scores and formats on the Edinburgh Postnatal Depression Scale – implications for clinical and research practice. Arch Womens Ment Health 9 (6), 309–315. https://doi.org/10.1007/s00737-006-0152-x.

McGowan, E.C., Hofheimer, J.A., O'Shea, T.M., et al., 2022. Analysis of neonatal neurobehavior and developmental outcomes among preterm infants. JAMA Netw. Open 5 (7), e2222249. https://doi.org/10.1001/jamanetworkopen.2022.22249.

Nelson, T., Tomi, C.L., Gebretensay, S.B., 2023. (Re)Framing strength: how superwoman schema may impact perinatal anxiety and depression among african American

women. Wom. Health Issues 33 (6), 568–572. https://doi.org/10.1016/j.whi.2023.05.003.
Nidens, N., Vogel, M., Körner, A., Kiess, W., 2021. Prenatal exposure to phthalate esters and its impact on child development. Best Pract. Res. Clin. Endocrinol. Metabol. 35 (5), 101478 https://doi.org/10.1016/j.beem.2020.101478.
Padula, A.M., Monk, C., Brennan, P.A., et al., 2020. A review of maternal prenatal exposures to environmental chemicals and psychosocial stressors—implications for research on perinatal outcomes in the ECHO program. J. Perinatol. 40 (1), 10–24. https://doi.org/10.1038/s41372-019-0510-y.
Peijnenburg, W.J.G.M., 2008. Phthalates. In: Jørgensen, S.E., Fath, B.D. (Eds.), Encyclopedia of Ecology. Academic Press, pp. 2733–2738. https://doi.org/10.1016/B978-008045405-4.00419-5.
Philips, E.M., Jaddoe, V.W.V., Trasande, L., 2017. Effects of early exposure to phthalates and bisphenols on cardiometabolic outcomes in pregnancy and childhood. Reprod. Toxicol. 68, 105–118. https://doi.org/10.1016/j.reprotox.2016.08.015.
Salisbury, A.L., Fallone, M.D., Lester, B., 2005. Neurobehavioral assessment from fetus to infant: the NICU Network neurobehavioral scale and the fetal neurobehavior coding scale. Ment. Retard. Dev. Disabil. Res. Rev. 11 (1), 14–20. https://doi.org/10.1002/mrdd.20058.
Schettler, T., 2006. Human exposure to phthalates via consumer products. Int. J. Androl. 29 (1), 134–139. https://doi.org/10.1111/j.1365-2605.2005.00567.x. ; discussion 181-185.
Spielberger, C.D., 2012. State-Trait Anxiety Inventory for Adults. https://doi.org/10.1037/t06496-000. Published online July 9.
Stroustrup, A., Bragg, J.B., Andra, S.S., et al., 2018. Neonatal intensive care unit phthalate exposure and preterm infant neurobehavioral performance. PLoS One 13 (3), e0193835. https://doi.org/10.1371/journal.pone.0193835.
Sucharew, H., Khoury, J.C., Xu, Y., Succop, P., Yolton, K., 2012. NICU Network neurobehavioral scale profiles predict developmental outcomes in a low-risk sample. Paediatr. Perinat. Epidemiol. 26 (4), 344–352. https://doi.org/10.1111/j.1365-3016.2012.01288.x.
Sylvester, C.M., Myers, M.J., Perino, M.T., et al., 2021. Neonatal brain response to deviant auditory stimuli and relation to maternal trait anxiety. Am. J. Psychiatr. 178 (8), 771–778. https://doi.org/10.1176/appi.ajp.2020.20050672.
Taibl, K.R., Dunlop, A.L., Barr, D.B., et al., 2024. Phthalate exposure increases interferon-γ during pregnancy: the Atlanta African American Maternal-Child Cohort. Sci. Total Environ. 916, 170344 https://doi.org/10.1016/j.scitotenv.2024.170344.
Teissèdre, F., Chabrol, H., 2004. Detecting women at risk for postnatal depression using the Edinburgh Postnatal Depression Scale at 2 to 3 days postpartum. Can J Psychiatry Rev Can Psychiatr 49 (1), 51–54. https://doi.org/10.1177/070674370404900108.
Tran, M.T.M.T., Kuo, F.C., Low, J.T., et al., 2023. Prenatal DEHP exposure predicts neurological disorders via transgenerational epigenetics. Sci. Rep. 13 (1), 7399. https://doi.org/10.1038/s41598-023-34661-3.
Uldbjerg, C.S., Lim, Y.H., Krause, M., Frederiksen, H., Andersson, A.M., Bräuner, E.V., 2022. Sex-specific associations between maternal exposure to parabens, phenols and phthalates during pregnancy and birth size outcomes in offspring. Sci. Total Environ. 836, 155565 https://doi.org/10.1016/j.scitotenv.2022.155565.
Welch, B.M., Keil, A.P., Buckley, J.P., et al., 2022. Associations between prenatal urinary biomarkers of phthalate exposure and preterm birth: a pooled study of 16 us cohorts. JAMA Pediatr. 176 (9), 895–905. https://doi.org/10.1001/jamapediatrics.2022.2252.
Wenzel, E.S., Gibbons, R.D., O'Hara, M.W., Duffecy, J., Maki, P.M., 2021. Depression and anxiety symptoms across pregnancy and the postpartum in low-income Black and Latina women. Arch Womens Ment Health 24 (6), 979–986. https://doi.org/10.1007/s00737-021-01139-y.
Williams, D.R., 2018. Stress and the mental health of populations of color:advancing our understanding of race-related stressors. J. Health Soc. Behav. 59 (4), 466–485. https://doi.org/10.1177/0022146518814251.
Womble, M., Jennings, S., Schatz, P., Elbin, R.J., 2021. A-173 clinical cutoffs on the state–trait anxiety inventory for concussion. Arch. Clin. Neuropsychol. 36 (6), 1228. https://doi.org/10.1093/arclin/acab062.191.
Zhang, Y.J., Guo, J.L., Xue, J chuan, Bai, C.L., Guo, Y., 2021. Phthalate metabolites: characterization, toxicities, global distribution, and exposure assessment. Environ. Pollut. 291, 118106 https://doi.org/10.1016/j.envpol.2021.118106.
Zhang, X., Barr, D.B., Dunlop, A.L., et al., 2022. Assessment of metabolic perturbations associated with exposure to phthalates among pregnant African American women. Sci. Total Environ. 818, 151689 https://doi.org/10.1016/j.scitotenv.2021.151689.
Zota, A.R., Shamasunder, B., 2017. The environmental injustice of beauty: framing chemical exposures from beauty products as a health disparities concern. Am. J. Obstet. Gynecol. 217 (4), 418.e1–418.e6. https://doi.org/10.1016/j.ajog.2017.07.020.
Julian LJ. Measures of anxiety: state-trait anxiety inventory (STAI), beck anxiety inventory (bai), and hospital anxiety and depression scale-anxiety (HADS-A). doi: 10.1002/acr.20561.