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Prenatal Exposure to Nonpersistent Environmental Chemicals and Postpartum Depression

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IMPORTANCE Postpartum depression (PPD) affects up to 20% of childbearing individuals, and a significant limitation in reducing its morbidity is the difficulty in modifying established risk factors. Exposure to synthetic environmental chemicals found in plastics and personal care products, such as phenols, phthalates, and parabens, are potentially modifiable and plausibly linked to PPD and have yet to be explored.

OBJECTIVE To evaluate associations of prenatal exposure to phenols, phthalates, parabens, and triclocarban with PPD symptoms.

DESIGN, SETTING, AND PARTICIPANTS This was a prospective cohort study from 5 US sites, conducted from 2006 to 2020, and included pooled data from 5 US birth cohorts from the National Institutes of Health Environmental Influences on Child Health Outcomes (ECHO) consortium. Participants were pregnant individuals with data on urinary chemical concentrations (phenols, phthalate metabolites, parabens, or triclocarban) from at least 1 time point in pregnancy and self-reported postnatal depression screening assessment collected between 2 weeks and 12 months after delivery. Data were analyzed from February to May 2022.

EXPOSURES Phenols (bisphenols and triclosan), phthalate metabolites, parabens, and triclocarban measured in prenatal urine samples.

MAIN OUTCOMES AND MEASURES Depression symptom scores were assessed using the Edinburgh Postnatal Depression Scale (EPDS) or the Center for Epidemiologic Studies Depression Scale (CES-D), harmonized to the Patient-Reported Measurement Information System (PROMIS) Depression scale. Measures of dichotomous PPD were created using both sensitive (EPDS scores ≥10 and CES-D scores ≥16) and specific (EPDS scores ≥13 and CES-D scores ≥20) definitions.

RESULTS Among the 2174 pregnant individuals eligible for analysis, nearly all (>99%) had detectable levels of several phthalate metabolites and parabens. PPD was assessed a mean (SD) of 3 (2.5) months after delivery, with 349 individuals (16.1%) and 170 individuals (7.8%) screening positive for PPD using the sensitive and specific definitions, respectively. Linear regression results of continuous PROMIS depression T scores showed no statistically significant associations with any chemical exposures. Models examining LMW and HMW phthalates and di (2-ethylhexyl) phthalate had estimates in the positive direction whereas all others were negative. A 1-unit increase in log-transformed LMW phthalates was associated with a 0.26-unit increase in the PROMIS depression T score (95% CI, −0.01 to 0.53; $P = .06$). This corresponded to an odds ratio (OR) of 1.08 (95% CI, 0.98-1.19) when modeling PPD as a dichotomous outcome and using the sensitive PPD definition. HMW phthalates were associated with increased odds of PPD (OR, 1.11; 95% CI, 1.00-1.23 and OR, 1.10; 95% CI, 0.96-1.27) for the sensitive and specific PPD definitions, respectively. Sensitivity analyses produced stronger results.

CONCLUSIONS AND RELEVANCE Phthalates, ubiquitous chemicals in the environment, may be associated with PPD and could serve as important modifiable targets for preventive interventions. Future studies are needed to confirm these observations.

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Supplemental content

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Group Information: The members of the Environmental Influences on Child Health Outcomes Consortium appear in Supplement 2.

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Postpartum depression (PPD) is the most common pregnancy complication to occur after delivery, affecting up to 20% of new mothers.[1] It impacts the mother's daily functioning, quality of life, and long-term health, leading to increased risks of chronic mood disorders, weight retention, and cardiovascular disease.[2] Furthermore, PPD is associated with poor mother-infant attachment, which can impact child health and development, resulting in health implications across multiple generations.[3-8]

Although several established risk factors have been identified,[9,10] the underlying pathophysiology of PPD is still under investigation. The endocrine system, and particularly sex-steroid hormone fluctuations during the perinatal period, is of particular interest.[11] Because sex steroids play a central role in neurotransmitter regulation and synthesis, they act as key determinants of mood disorders.[11,12] Further, because of the temporal association between the dramatic changes in hormone concentrations at delivery and the onset of depressive symptoms in the postpartum period, the withdrawal of estrogen and progesterone after delivery is hypothesized to act as a biological trigger for some forms of PPD.[11] Thus, exogenous factors that affect hormones such as exposures to endocrine-disrupting chemicals (EDCs) are plausible contributors to PPD; however, they have not been sufficiently examined.[13] Given that potentially modifiable risk factors for PPD remain elusive,[14] prenatal exposure to EDCs represents a novel interventional target.

Specifically, bisphenols and phthalates, used as plasticizers and in personal care products, have been shown to impact estradiol and progesterone levels in animals and humans[15] and separately have been linked with maternal behavior and anxiety in animal models.[16-18] However, little data exist in humans. These chemicals, along with parabens, triclocarban, and other phenols such as triclosan, are nonpersistent but ubiquitous in the environment, owing to their use in consumer products and the episodic and frequent nature of exposure through diet, dermal absorption, and inhalation. This leads to nearly 100% detection in human urine samples, including those of pregnant individuals.[19-22]

In a 2021 study,[23] we reported that di-n-octyl phthalate (DnOP) metabolites were associated with increased PPD symptoms, after decreased progesterone levels during pregnancy. However, this study was conducted among a small sample of 139 pregnant individuals in a New York City cohort. To build on these findings in a larger and more diverse sample and expand the suite of exposures investigated, this study leverages data from 5 cohorts contributing to the Environmental Influences on Child Health Outcomes (ECHO) consortium. The purpose of this study was to evaluate associations of prenatal exposure to phenols, phthalates, parabens, and triclocarban with PPD symptoms.

Key Points

Question What is the association between prenatal exposure to nonpersistent environmental chemicals (ie, phenols, phthalate metabolites, parabens, and triclocarban) and postpartum depression symptoms?

Findings In this pooled cohort study of 2174 pregnant individuals, there were no associations found between exposure to several nonpersistent environmental chemicals and PPD; however, prenatal phthalate metabolite concentrations were associated with greater postpartum depression symptoms in some analyses.

Meaning Phthalates, nonpersistent chemicals common in the environment, may be associated with postpartum depression, thus representing a potentially modifiable risk factor.

Methods

Participants and Procedures

This study was conducted from 2006 to 2020 among participants from eligible cohorts in the National Institutes of Health's ECHO Research Program. The ECHO program includes over 65 longitudinal birth cohort studies across the US and Puerto Rico, with the overall goal of investigating prenatal and early life environmental exposures in relation to child health and development.[24,25]

Participants in the current analysis included pregnant individuals from cohorts with data on urinary chemical concentrations (phenols, phthalate metabolites, parabens, or triclocarban) from at least 1 time point in pregnancy and a self-reported postnatal depression assessment collected between 2 weeks and 12 months after delivery. Participants from the following self-reported race and ethnicity categories were included: non-Hispanic Black, Hispanic, non-Hispanic multiple or other race, and non-Hispanic White. Written informed consent was obtained for all study participants. Each local institutional review board approved data collection and analysis. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Exposure Assessment

Phenol (bisphenol and triclosan), phthalate metabolite, paraben, and triclocarban concentrations were measured in prenatal urine samples. Chemicals that were measured in at least 3 of the 5 cohorts and in more than 50% of study participants were included. Specifically, this study evaluated 2 bisphenols, 12 phthalate metabolites, 3 parabens, triclosan, and triclocarban.

Quantification of bisphenols, phthalate metabolites, parabens, and triclocarbans was conducted at a Children's Health Exposure Analysis Resource laboratory or the Centers for Disease Control Division for Laboratory Sciences National Center for Environmental Health, depending on cohort. Exposure assessment methods are described in the eMethods in Supplement 1.

Outcome Measures

Depression symptoms assessed between 2 weeks and 12 months after delivery were the primary outcomes. To assess PPD symptoms, 4 of the 5 contributing ECHO cohorts used the Edinburgh Postnatal Depression Scale (EPDS),[26] and 1 cohort used the Center for Epidemiologic Studies Depression Scale

(CES-D).[27] To make scores comparable, these instruments were harmonized to the Patient-Reported Measurement Information System (PROMIS) depression scale (eMethods in Supplement 1).[28-31]

When examining PPD as a dichotomous variable, 2 cutoffs were considered. First, a more sensitive threshold was implemented using EPDS scores of 10 or greater[26,32,33] and CES-D scores of 16 or greater,[27] which corresponded to a uniform cutoff on the PROMIS depression T score scale of 56 or greater.[30,31] This threshold for PPD using the EPDS has been implemented by an international perinatal psychiatry consortium[32] and represents the most sensitive threshold for PPD.[34] Its corresponding score on the CES-D of 16 is the most commonly used cutoff for depression on that scale.[27] The second threshold examined was less sensitive but more specific: EPDS scores of 13 or greater, which is the more stringent cutoff for screening of major depression,[26,33] and CES-D scores or 20 or greater, which has been shown to have better discrimination than 16.[35]

Statistical Analysis

Bisphenols, phthalate metabolites, and parabens were analyzed in groups as molar sums (Σ) based on their use in product categories and/or parent compounds. This included Σ bisphenols, Σ low-molecular-weight (LMW) phthalates (including metabolites <250 Da and typically used in personal care products),[36] Σ high-molecular-weight (HMW) phthalates (including metabolites ≥250 Da and typically used in vinyl plastic manufacturing),[37] Σ di (2-ethylhexyl) phthalate (DEHP), and Σ parabens. Measures representing DnOP and diisononyl phthalate (DiNP) consisted of single metabolites (mono 3-carboxypropyl) phthalate and mono-carboxy isooctyl phthalate, respectively) due to data availability across cohorts. Phthalic acid was examined separately as an individual exposure as it is an end-product metabolite for all phthalates, as were triclosan and triclocarban. Values below the limit of detection (LOD) were imputed by the LOD/$\sqrt{2}$ prior to correction for urinary dilution using the Boeniger method.[38-40] After LOD and urinary dilution correction, all exposures were natural log transformed to reduce skewness and the influence of outliers.

To estimate associations between chemical exposures and PPD, multiple informant models in the form of linear and logistic regression models with generalized estimating equations were fit. These models accommodate repeated exposure measures and generate joint estimates across these multiple windows.[41-43] Linear regression models were fit when the outcome was parameterized as a continuous depressive symptom score variable (ie, the PROMIS depression T score) and logistic models were fit for the dichotomous PPD variable (according to both cutoffs).

All models were adjusted for maternal age, education, race and ethnicity (options defined by investigators and self-reported by participants), prepregnancy body mass index, marital status, and enrollment site/cohort to account for any site-specific clustering of participants. Although prenatal depression could theoretically also be affected by these chemical exposures, it was not included as a covariate in models due to its potential to be on the causal pathway.[9,44] To account for multiple testing, the *P* value was adjusted using a modified Bonferroni approach using the effective number of tests.[23,45] This involved constructing a correlation matrix between all 10 exposures and a subsequent calculation using the resulting eigenvalues. The calculated effective number of comparisons was 5, and the adjusted *P* value was .01 (α = .05/5).

Finally, we conducted several sensitivity analyses. First, exposures were parameterized as subject-specific means of natural log-transformed trimester-specific concentrations.[41] Second, in order to ensure that results were not driven by individual cohort(s), all analyses were repeated on the study population removing 1 cohort at a time. Third, we fitted models stratifying by child sex at birth to yield sex-specific estimates due to data suggesting impacts on PPD[46] and sexually dimorphic effects of EDCs.[47] Fourth, because the distribution of the timing of PPD assessment after birth was bimodal due to different cohort follow-up schedules, analyses were repeated stratifying by early vs later PPD assessment. Finally, because PPD is associated with prenatal depression, we examined associations between chemical exposures and prenatal depression (eMethods in Supplement 1). All statistical analyses were performed using R statistical software, version 4.1.2 (R Core Team). Two-tailed *P* values <.05 were considered statistically significant. Data were analyzed from February to May 2022.

Results

A total of 2174 pregnant individuals from 5 ECHO cohorts eligible for analysis had at least 1 chemical measured during pregnancy and PPD screening within 1 year postpartum (**Table 1** and eTable 1 in Supplement 1). Although less than 15% of the sample had chemical measures in the first trimester, 1273 participants (59%) had at least 2 measures during pregnancy. All chemical species were frequently detected, with 100% having detectable levels of methyl and propyl paraben at all time points in pregnancy and nearly all participants (>99%) having detectable levels of several LMW and HMW phthalate metabolites (eTable 2 in Supplement 1). Both individual and grouped chemical measures exhibited low to moderate reproducibility over time, as shown by intraclass correlation coefficients in the range of 0.27 to 0.60 (Table 1). On average, there was some variation noted across cohorts (eFigure and eTable 3 in Supplement 1). Compared with participants in the other cohorts, persons from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) cohort had greater concentrations of LMW and HMW phthalates (geometric mean [SD], 0.92 [3.0] vs Healthy Start, 0.35 [3.2]; ECHO, 0.35 [3.3]; Archive for Research in Child Health, 0.23 [3.1]; New York University Children's Health and Environment Study, 0.35 [3.2]). In contrast, compared with individuals in the other cohorts, persons from the Healthy Start cohort had greater concentrations of parabens, triclosan, mono (3-carboxypropyl) phthalate, and mono-carboxy isooctyl phthalate (geometric mean [SD], parabens, 1.01 [3.8] nmol/mL; triclosan, 18.27 [6.1] ng/mL; mono

Table 1. Individual and Grouped Chemical Concentration Distributions Across Pregnancy Among 2174 Participants in the Environmental Influences on Child Health Outcomes Program, 2006-2020

		Trimester 1 (<14 wk)		Trimester 2 (≥14-<27 wk)		Trimester 3 (≥27 wk)		
Analyte groups	No.	No.	Median (IQR)	No.	Median (IQR)	No.	Median (IQR)	ICC
Σ Bisphenols, nmol/mL[a]	1059	318	0.01 (0-0.01)	783	0.01 (0-0.01)	562	0.01 (0-0.01)	0.27
Phthalic acid, ng/mL	1438	328	17.85 (9.42-34.12)	1284	44.45 (22.40-88.35)	1242	55.23 (29.67-103.19)	0.41
Σ Low-molecular-weight phthalates, mnol/mL	2112	334	0.29 (0.16-0.63)	1707	0.57 (0.27-1.33)	1551	0.51 (0.25-1.28)	0.50
Σ High-molecular-weight phthalates, nmol/mL	2119	334	0.10 (0.05-0.16)	1717	0.26 (0.11-0.52)	1551	0.16 (0.1-0.29)	0.42
Σ Di-2-ethylhexyl phthalate metabolites, nmol/mL	2036	323	0.06 (0.04-0.11)	1654	0.15 (0.07-0.28)	1513	0.09 (0.05-0.15)	0.33
Mono (3-carboxypropyl) phthalate, ng/mL	2118	333	0.90 (0.54-1.58)	1717	1.59 (0.94-2.85)	1551	1.33 (0.84-2.3)	0.31
Mono-carboxy isooctyl phthalate, ng/mL	1844	332	1.68 (0.85-3.46)	1453	8.59 (3.75-22.6)	1475	2.71 (1.24-7.97)	0.33
Σ Parabens, nmol/mL	671	17	0.44 (0.11-1.72)	406	0.72 (0.20-2.20)	295	0.91 (0.28-2.13)	0.37
Triclocarban, ng/mL	687	<5	0.98 (0.66-1.29)	448	0.24 (0.10-0.64)	293	0.21 (0.09-0.55)	0.60
Triclosan, ng/mL	709	18	6.16 (2.28-13.63)	450	7.53 (2.33-42.7)	297	9.47 (3.43-58.31)	0.39

Abbreviation: ICC, intraclass correlation coefficient.

[a] The Σ symbol represents molar sum.

[3-carboxypropyl] phthalate, 2.26 [3.1] ng/mL; mono-carboxy isooctyl phthalate, 20.43 [3.5] ng/mL) (eTable 3 in Supplement 1).

The study population was racially and ethnically diverse, with 692 non-Hispanic Black (31.9%), 647 Hispanic (29.8%), 124 non-Hispanic multiple or other race (5.7%), and 709 non-Hispanic White (32.6%) participants. In addition, participants were socioeconomically diverse; 884 participants (40.7%) had a high school education or less, and 404 participants (18.6%) had a postgraduate degree (**Table 2**). The distributions of PROMIS depression T scores assessed during pregnancy and postpartum were similar (mean [SD], 47.1 [8.0] and 46.4 [8.9], respectively). PPD was assessed a mean (SD) of 3 (2.5) months after delivery. PPD, as defined by the sensitive definition (≥10 on the EPDS and ≥16 on the CES-D), occurred in 349 participants (16.1%), although reduced to 170 (7.8%) when defined by the specific definition (≥13 on the EPDS and ≥20 on the CES-D).

Those who met sensitive and specific PPD cutoffs, respectively, were more likely to be Hispanic (190 [54.6%]; 99 [58.6%]), from the ECHO in Puerto Rico cohort (161 [46.1%]; 52 [30.6%]), have lower education (133 [38.2%]; 68 [40.8%]), and substantially higher prenatal depression scores (mean [SD], 54.2 [7.7]; 55.5 [8.1]) than those who did not (**Table 3**). Other differences in study participant characteristics across strata of PPD were minimal, although more apparent when examining those with and without the more specific definition. Chemical, specifically LMW and HMW phthalate, concentrations varied by demographic and clinical characteristics including age, education, race and ethnicity, obesity, and marital status (eTable 3 in Supplement 1).

Linear regression results of continuous PROMIS depression T scores showed no statistically significant associations with any chemical exposures (**Table 4**). Models examining LMW and HMW phthalates and DEHP had estimates in the positive direction whereas all others were negative. In particular, 1 observation was suggestive: a 1-unit increase in log-transformed LMW phthalates was associated with a 0.26-unit increase in the PROMIS depression T score (95% CI, −0.01 to 0.53; P = .06), but this increase was not statistically significant. This corresponded to odds ratios (ORs) of 1.08 (95% CI, 0.98-1.19) and 0.98 (95% CI, 0.85-1.13) when modeling PPD as a dichotomous outcome and using the sensitive and specific PPD definitions, respectively. When modeled as a dichotomous outcome, HMW phthalates were associated with increased odds of PPD (OR, 1.11; 95% CI, 1.00-1.23 and OR, 1.10; 95% CI, 0.96-1.27) for the sensitive and specific PPD definitions, respectively. Estimates for other chemicals were similar in magnitude, ranging from 0.94 to 1.08, and consistent with the null; except for mono-carboxy isooctyl phthalate, a metabolite of DiNP, which was associated with decreased odds of PPD using the specific definition (OR, 0.86; 95% CI, 0.76-0.99). When adjusted for multiple comparisons, these estimates did not meet the adjusted P value threshold.

Modeling the exposures as averages across pregnancy yielded consistent results (eTable 4 in Supplement 1). The estimate for the association of LMW phthalates with continuous PROMIS depression T scores became slightly stronger (B = 0.33; 95% CI, 0.01-0.66) as did that for mono-carboxy isooctyl phthalate and specific definition of PPD (OR, 0.74; 95% CI, 0.60-0.92).

Analyses conducted excluding 1 cohort at a time showed substantially different results only when models were fit without the CANDLE cohort (eTable 5 in Supplement 1). In particular, LMW phthalates were associated with higher PROMIS depression T scores (B = 0.39; 95% CI, 0.03-0.75) and increased odds of PPD using the sensitive definition (OR, 1.14; 95% CI, 1.00-1.29). Similarly, when this cohort was excluded, HMW phthalates were associated with increased depression symptoms (B = 0.42; 95% CI, 0.02-0.82) and OR of 1.21 (95% CI, 1.05-1.40) and 1.21 (95% CI, 1.01-1.44) using the sensitive and specific PPD definitions, respectively. Furthermore, the previously

Table 2. Participant Characteristics Among 2174 Participants in the Environmental Influences on Child Health Outcomes (ECHO) Program, 2006-2020

Characteristic	No. (%)
Cohorts	
Archive for Research in Child Health (ARCH)	24 (1.1)
Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE)	1027 (47.2)
ECHO in Puerto Rico (PROTECT)	329 (15.1)
Healthy Start	401 (18.4)
The NYU Children's Health and Environment Study	393 (18.1)
Age, y	
16-25	658 (30.3)
26-34	1083 (49.8)
≥35	432 (19.9)
Missing	<5
Prepregnancy body mass index	
Underweight	94 (4.5)
Normal weight	905 (43.6)
Overweight	520 (25.1)
Obese	555 (26.8)
Missing	100
Race/ethnicity	
Non-Hispanic Black	692 (31.9)
Hispanic	647 (29.8)
Non-Hispanic multiple or other race	124 (5.7)
Non-Hispanic White	709 (32.6)
Missing	<5
Education	
≤High school	884 (40.7)
Some college	370 (17.0)
Bachelor's degree	513 (23.6)
Postgraduate degree	404 (18.6)
Missing	<5
Marital status	
Married or living with partner	1537 (71.0)
Single (never married, widowed, divorced)	629 (29.0)
Missing	8
Child sex	
Male	1114 (51.2)
Female	1060 (48.8)
Parity	
0	967 (45.5)
1	753 (35.5)
≥2	403 (19.0)
Missing	51
Postpartum PROMIS T score	
Mean (SD)	46.4 (8.9)
Median (IQR) [range]	45.9 (38.1-53.4) [33.0-76.0]
PPD sensitive definition[a]	
No	1825 (83.9)
Yes	349 (16.1)
PPD specific definition[b]	
No	2004 (92.2)
Yes	170 (7.8)
Postpartum timing of PPD assessment (mo after delivery)	
Mean (SD)	3.0 (2.5)
Median (IQR) [range]	1.6 (1.1-4.4) [0.5-12.0]
Prenatal PROMIS T score	
Mean (SD)	47.1 (8.0)
Median (IQR) [range]	45.9 (38.7-53.4) [33.0-76.0]
Missing	124

Abbreviations: NYU, New York University; PPD, postpartum depression; PROMIS, Patient-Reported Measurement Information System.

[a] Sensitive definition (EPDS ≥10 or CES-D ≥16).

[b] Specific definition (EPDS ≥13 or CES-D ≥20).

protective association with mono-carboxy isooctyl phthalate changed direction when this cohort was excluded (OR, 1.19; 95% CI, 0.99-1.43). Only the estimate for HMW phthalates and sensitive PPD definition met the adjusted *P* value threshold (*P* = .008). There were still no associations with other chemicals. Notably, no differences were noted when other cohorts were excluded, including the PROTECT cohort, which was the only cohort to use the CES-D.

Although some variation was observed when stratifying by child sex, findings remained consistent (eTable 6 in Supplement 1). In addition, stratifying by timing of PPD assessment did not result in any measurable differences independent from those due to excluding the CANDLE cohort (eTable 7 in Supplement 1). Lastly, chemical exposures were not associated with prenatal depression (eTable 8 in Supplement 1).

Discussion

In a prospective pooled cohort study leveraging 5 US birth cohorts, nonpersistent chemical exposures assessed throughout pregnancy were examined in association with PPD symptomatology. Linear regression results of continuous PROMIS depression T scores showed no statistically significant associations with any chemical exposures. Models examining LMW and HMW phthalates and DEHP had estimates in the positive direction whereas all others were negative. Prenatal HMW phthalate concentrations were associated with increased odds of PPD, and this observation was stronger when excluding 1 contributing cohort. Additional sensitivity analyses using different strategies for modeling time-varying exposures and considering heterogeneity of effects by infant sex and timing of PPD assessment suggested that results were robust. Lastly, analyses of prenatal depression suggested that these associations were specific to PPD.

Results varied across contributing cohorts but were largely consistent with results of the pooled analyses. Specifically, when we excluded the CANDLE cohort, the largest contributor to this study's sample size, associations

Table 3. Participant Characteristics by Postpartum Depression (PPD) (Defined By Edinburgh Postnatal Depression Scale [EPDS] and Center for Epidemiologic Studies Depression Scale [CES-D] Scores) Among 2174 Participants in the Environmental Influences on Child Health Outcomes Program, 2006-2020

Characteristic	Sensitive PPD definition[a]			Specific PPD definition[b]		
	PPD (%)	Non-PPD (%)	*P* value	PPD (%)	Non-PPD (%)	*P* value
Cohorts	n =349	n = 1825		n = 170	n = 2004	
Archive for Research in Child Health (ARCH)	<5	21 (1.2)		<5	23 (1.1)	
Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE)	112 (32.1)	915 (50.1)	<.01[c]	52 (30.6)	975 (48.7)	<.01[c]
ECHO in Puerto Rico (PROTECT)	161 (46.1)	168 (9.2)		87 (51.2)	242 (12.1)	
Healthy Start	<30	372 (20.4)		<15	390 (19.5)	
The NYU Children's Health and Environment Study (CHES)	44 (12.6)	349 (19.1)		19 (11.2)	374 (18.7)	
Age, y						
16-25	113 (32.5)	545 (29.9)		60 (35.3)	598 (29.9)	
26-34	166 (47.7)	917 (50.2)	.60[c]	82 (48.2)	1001 (50.0)	.26[c]
≥35	69 (19.8)	363 (19.9)		28 (16.5)	404 (20.2)	
Prepregnancy body mass index						
Underweight	15 (4.4)	79 (4.6)		8 (4.9)	86 (4.5)	
Normal weight	149 (44.0)	756 (43.6)	.66[c]	63 (38.7)	842 (44.1)	.34[c]
Overweight	77 (22.7)	443 (25.5)		39 (23.9)	481 (25.2)	
Obese	98 (28.9)	457 (26.3)		53 (32.5)	502 (26.3)	
Race/ethnicity						
Non-Hispanic Black	81 (23.3)	611 (33.5)		41 (24.3)	651 (32.5)	
Hispanic	190 (54.6)	457 (25.1)	<.01[c]	99 (58.6)	548 (27.4)	<.01[c]
Non-Hispanic multiple or other race	14 (4.0)	110 (6.0)		5 (3.0)	119 (5.9)	
Non-Hispanic White	63 (18.1)	646 (35.4)		24 (14.2)	685 (34.2)	
Education						
≤High school	133 (38.2)	751 (41.2)		68 (40.0)	816 (40.8)	
Some college	85 (24.4)	285 (15.6)		51 (30.0)	319 (15.9)	
Bachelor's degree	80 (23.0)	433 (23.8)	<.01[c]	29 (17.1)	484 (24.2)	<.01[c]
Postgraduate degree	50 (14.4)	354 (19.4)		22 (12.9)	382 (19.1)	
Missing						
Marital status						
Married or living with partner	251 (72.5)	1286 (70.7)	.48[c]	118 (70.2)	1419 (71.0)	.83[c]
Single (never married, widowed, divorced)	95 (27.5)	534 (29.3)		50 (29.8)	579 (29.0)	
Child sex						
Male	176 (50.4)	938 (51.4)	.74[c]	80 (47.1)	1034 (51.6)	.26[c]
Female	173 (49.6)	887 (48.6)		90 (52.9)	970 (48.4)	
Parity						
0	149 (45.6)	818 (45.5)		70 (44.0)	897 (45.7)	
1	117 (35.8)	636 (35.4)	.98[c]	60 (37.7)	693 (35.3)	.82[c]
≥2	61 (18.7)	342 (19.0)		29 (18.2)	374 (19.0)	
Postpartum PROMIS T score						
Mean (SD)	59.9 (4.2)	43.8 (7.1)		63.1 (3.8)	45.0 (7.7)	
Median (IQR) [range]	58.3 (57.0-62.2) [55.6-76.0]	43.7 (38.1-49.5) [33.0-55.5]	<.01[d]	62.2 (59.7-65.3) [58.6-76.0]	45.9 (38.1-51.2) [33.0-58.3]	<.01[d]
Postpartum timing of PPD assessment (mo after delivery)						
Mean (SD)	3.2 (2.9)	3.0 (2.4)		3.2 (3.0)	3.0 (2.5)	
Median (IQR) [range]	1.5 (1.1-4.7) [0.5-12.0]	1.6 (1.1-4.4) [0.5-12.0]	.25[d]	1.6 (1.1-5.0) [0.5-12.0]	1.6 (1.1-4.4) [0.5-12.0]	.25[d]
Prenatal PROMIS T score						
Mean (SD)	54.2 (7.7)	45.7(7.3)		55.5 (8.1)	46.3 (7.6)	
Median (IQR) [range]	55.6 (50.2-59.1) [33.0-76.0]	45 (38.7-50.6) [33.0-70.1]	<.01[d]	56.8 (50.6-60.8) [33.0-76.0]	45.9 (38.7-52.5) [33.0-70.1]	<.01[d]

Abbreviations: NYU, New York University; PROMIS, Patient-Reported Measurement Information System.

[a] Sensitive definition (EPDS ≥10 or CES-D ≥16).

[b] Specific definition (EPDS ≥13 or CES-D ≥20).

[c] Pearson χ^2 test.

[d] Analysis of variance or 2-sample *t* test.

of phthalate metabolites with PPD were stronger and statistically significant. The CANDLE cohort is a longitudinal pregnancy cohort study in Shelby County, Tennessee.[48] Compared with participants from other cohorts, partici-

Table 4. Associations Between Prenatal Chemical Concentrations and Patient-Reported Measurement Information System (PROMIS) T Scores and Postpartum Depression (PPD) From Multiple Informant Models Among 2174 Participants in the Environmental Influences on Child Health Outcomes Program, 2006-2020

Chemical	PROMIS T score, B (95% CI)	OR (95% CI)	
		PPD (Sensitive definition)[a]	PPD (Specific definition)[b]
Σ Bisphenol[c]	−0.21 (−0.67 to 0.24)	0.94 (0.81 to 1.10)	1.04 (0.83 to 1.31)
Phthalic acid	−0.04 (−0.40 to 0.32)	1.02 (0.89 to 1.17)	0.97 (0.82 to 1.15)
Σ Low molecular weight	0.26 (−0.01 to 0.53)	1.08 (0.98 to 1.19)	0.98 (0.85 to 1.13)
Σ High molecular weight	0.13 (−0.15 to 0.41)	1.11 (1.00 to 1.23)	1.10 (0.96 to 1.27)
Σ DEHP	0.08 (−0.24 to 0.40)	1.06 (0.94 to 1.20)	1.11 (0.94 to 1.31)
Mono-carboxy isooctyl phthalate	−0.14 (−0.36 to 0.07)	0.98 (0.89 to 1.08)	0.86 (0.76 to 0.99)
Mono (3-carboxypropyl) phthalate	−0.12 (−0.43 to 0.20)	0.97 (0.86 to 1.10)	0.96 (0.81 to 1.14)
Σ Parabens	−0.14 (−0.47 to 0.20)	0.96 (0.83 to 1.10)	1.01 (0.85 to 1.22)
Triclocarban	−0.01 (−0.26 to 0.24)	1.06 (0.95 to 1.19)	1.02 (0.88 to 1.17)
Triclosan	0.14 (−0.08 to 0.36)	1.06 (0.95 to 1.17)	1.03 (0.91 to 1.16)

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; DEHP, di (2-ethylhexyl) phthalate; EPDS, Edinburgh Postnatal Depression Scale; OR, odds ratio.

[a] Sensitive definition (EPDS ≥10 or CES-D ≥16).

[b] Specific definition (EPDS ≥13 or CES-D ≥20).

[c] The Σ symbol represents molar sum.

pants in CANDLE had greater concentrations of several chemicals including phthalate metabolites, although not a greater PPD burden. These participants were also more likely to be non-Hispanic Black and had lower educational attainment compared with other cohorts. This aligns with other studies that have documented greater environmental chemical exposures and psychosocial stressors in this cohort, which may be due to differences in lifestyle, region, or sociodemographic factors.[49] Given these observations of both the physical and psychosocial environment, it was unexpected that the prevalence of PPD was not greater. Potential explanations for this could be different cultural norms in reporting or more widespread resilience-promoting factors.[50-52] Differences in the mechanisms that drive (or protect from) PPD could explain the heterogeneity in associations between phthalates and PPD across cohorts.

This study joins the mounting body of literature examining prenatal exposure to EDCs and its association with perinatal psychopathology.[13] Although other studies have examined chemical classes such as polybrominated diphenyl ethers,[53] heavy metals,[54] and phthalates[23] in relation to PPD, this is the largest study to date, to our knowledge. Although our study included cohorts that assessed exposures and outcomes at different times in pregnancy and postpartum, respectively, we detected signals for LMW and HMW phthalates associated with PPD. Given that we observed heterogeneity by contributing cohort, future work with large sample sizes is needed to understand what may be driving this, such as regional differences in exposures and potential interactions with social factors, which are known contributors to PPD.

Strengths and Limitations

In this study, PPD was based on screening instruments. This is both a strength and limitation. Because PPD is underrecognized and undertreated in clinical practice,[55] using a screening tool vs relying on medical record diagnoses is a strength because it captures subclinical symptoms and undiagnosed PPD. However, screening tools are not diagnostic tests. Another potential limitation is that spot urine samples were used for exposure assessment, and the chemicals evaluated are nonpersistent and rapidly metabolized. Indeed, several studies have documented large within-person variability and poor reliability over time.[56,57] However, we leveraged serial measurements over pregnancy and implemented analytic strategies using these longitudinal measures.[41] In addition, we examined associations with several chemicals, which led to multiple testing and may have introduced uncertainty in conclusions drawn from statistical tests. In an effort to address this, we implemented a modified Bonferroni approach,[45] which leverages the correlations among these chemical exposures. Lastly, as is the case with all observational research, our study may be vulnerable to unmeasured confounding. Although we adjusted for several demographic and clinical characteristics, we were likely not able to completely control for all potential confounders, such as psychosocial stress, which may be correlated with environmental exposures and is associated with PPD.[9] This may be another reason we observed variation in associations when excluding the CANDLE cohort.

Although this study presents a mixed picture for the association between prenatal concentrations of nonpersistent chemicals and PPD, one plausible avenue for EDCs to affect PPD is through sex-steroid hormone perturbation. For example, bisphenol A (BPA) has shown estrogenic activity in vitro and in vivo,[58,59] and phthalates have antiandrogenic effects,[60] with monoethyl phthalate and mono(carboxy-isooctyl) phthalate associated with decreased progesterone in animals and humans.[61-63] In parallel, experimental studies in animals have shown that exposure to BPA and phthalates during gestation induces anxietylike behavior in dams (ie, female parent of an animal) and reduces the frequency of maternal behavior and care after parturition, including less frequent nursing, licking, and grooming of pups and more time spent outside the nest.[16-18] These 2 lines of evidence provide a compelling case for these chemicals to plausibly affect PPD.

From a public health perspective, any avenues for PPD prevention would be important, given that established risk factors for PPD such as genetics, psychiatric history, and stressful life events are not readily alterable. In contrast, exposures to synthetic environmental chemicals are potentially modifiable by dietary and behavioral interventions.[64-66]

Conclusions

Despite variation by cohort, results suggest that prenatal phthalate metabolite concentrations in maternal urine during pregnancy were associated with PPD. Given the ubiquitous nature of phthalates in the environment, future studies are needed to confirm these observations. This work underscores the importance of considering pregnancy a critical window of exposure to exogenous agents for maternal health outcomes after delivery, including psychiatric conditions.

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