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Endocrine-Disrupting Chemicals and Persistent Nausea among Pregnant Women Enrolled in the Illinois Kids Development Study (I-KIDS)

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Background: Pregnant women are exposed to numerous endocrine-disrupting chemicals (EDCs). Pregnancy-related nausea likely has hormonal etiology and may persist beyond the first trimester.

Objectives: Therefore, we aimed to determine the relationship between EDC biomarkers and pregnancy nausea characteristics.

Methods: Illinois Kids Development Study (I-KIDS) pregnant women ($n = 467$) reported nausea symptoms monthly from conception to delivery. We categorized women as never having nausea (9%) or as having typical (ends by 17 wk gestation; 42%), persistent (ends after 17 wk gestation; 25%), or irregular (24%) nausea. Women provided five urine samples across pregnancy, which we pooled and analyzed for phthalate/replacement, phenol, and triclocarban biomarkers. Using covariate-adjusted logistic regression, we evaluated relationships of EDCs with nausea and used quantile-based g-computation (QGComp) and Bayesian kernel machine regression (BKMR) to evaluate joint associations of EDCs with nausea symptoms. We also considered differences in associations by fetal sex.

Results: Only the sum of urinary biomarkers of di(isononyl) cyclohexane-1,2-dicarboxylate (ΣDiNCH) was associated with higher risk of persistent nausea compared to typical nausea [odds ratio (OR) = 1.18; 95% CI: 1.01, 1.37] in all women. However, using QGComp, a 10% higher concentration of the EDC mixture was associated with 14% higher risk of persistent nausea [relative risk (RR) = 1.14; 95% CI: 1.01, 1.30], due to ΣDiNCH, ethylparaben, and the sum of di-2-ethylhexyl phthalate (ΣDEHP) metabolites. Similarly, using BMKR, the EDC mixture was associated with greater odds of persistent nausea in all women. In women carrying male offspring, ethylparaben was associated with persistent nausea, and a 10% higher concentration of the QGComp mixture was associated with 26% higher risk of persistent nausea (RR = 1.26; 95% CI:1.13, 1.41), driven by ethylparaben and ΣDiNCH. Consistently, using BKMR, EDCs were positively associated with persistent nausea in women carrying males. We did not identify associations between EDC biomarkers and persistent nausea in women carrying females or between EDC biomarkers and other nausea patterns.

Discussion: Nonpersistent EDCs, modeled as a mixture, are associated with persistent nausea in pregnancy, primarily in women carrying males. Future work should explore possible mechanisms, clinical implications, and interventions to reduce exposures and symptoms. https://doi.org/10.1289/EHP15547

Introduction

Nausea is the most common symptom women experience in pregnancy.[1–4] In 2012, the cost of medically managing one symptomatic woman was estimated at nearly $2,000,[5] and pregnancy nausea symptoms can result in hundreds of hours of lost work, which may have other long-term impacts.[6] In many women, nausea occurs in the first trimester, with peak symptoms at 9 wk and symptomatic improvement by 16 to 18 wk[1,7]; however, up to 40% of women have symptoms that continue later into pregnancy.[8,9] Although persistent nausea may not require hospitalization, as is frequently observed with the most severe form of nausea during pregnancy [hyperemesis gravidarum (HG)],[10–12] persistent nausea is nonetheless an understudied health condition that may negatively impact the pregnant woman and her developing fetus. While the exact mechanisms are not fully understood, pregnancy-related hormonal changes are hypothesized to be the leading cause of nausea.[2] Specifically, early epidemiologic studies linked higher levels of beta human chorionic gonadotrophin (β-hCG) with early pregnancy nausea,[13] whereas later studies identified associations of sex steroid and placental hormones with both early and later symptoms.[14–17] Because of the substantial impacts of nausea during pregnancy, particularly persistent nausea, and the hesitance for pharmacological treatment of pregnant women,[18] it is imperative to identify possible modifiable factors that individuals and clinicians can target to decrease persistent nausea in pregnancy.

Exposure to environmental contaminants is one possible modifiable and hormonally mediated risk factor of nausea in pregnancy, but to our knowledge, only one study has considered this relationship. In a study of women from Bangladesh, higher arsenic exposure from drinking water was associated with higher odds of self-reported nausea and vomiting in pregnancy.[19] However, to date, no studies have investigated pregnancy nausea within the context of chronic exposure to contaminants from daily use consumer products, including nonpersistent contaminants such as phthalates and phenols used in food packaging materials, medications, and cosmetics.[20–22] Virtually all women in the US have detectable concentrations of urinary biomarkers of these chemicals despite their rapid metabolism and excretion from the body.[20,23] Importantly, certain phthalates and phenols are known endocrine-disrupting chemicals (EDCs) based on experimental and epidemiologic studies.[24–26] Specifically, these EDCs can decrease or increase circulating sex steroid and thyroid hormones. In addition, epidemiologic

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studies have reported that EDCs are associated with other hormonally mediated pregnancy conditions, including hypertension, preeclampsia, gestational diabetes, and inappropriate gestational weight gain (both insufficient and excessive).[27–29] One difficulty in investigating the roles of EDCs in health outcomes is that chemicals frequently share exposure sources and are therefore highly correlated. To address this issue, various statistical mixtures methods have been developed to identify joint associations, toxic agents, nonlinear relationships, and chemical–chemical interactions.[30–32] Further research is needed to understand whether EDCs, individually or jointly, play a role in nausea etiology in pregnancy, particularly in relation to symptoms that persist beyond the first trimester.

Because persistent nausea in pregnancy is likely due to hormonal changes, and because pregnant women are frequently exposed to various chemicals with hormone-disrupting properties, our objective was to evaluate the relationship between ubiquitous, nonpersistent, EDC biomarkers (phthalates and phenols) with nausea that persists throughout pregnancy using information from the Illinois Kids Development Study (I-KIDS). I-KIDS is a prospective pregnancy and birth cohort of women whose phthalate/replacement and phenol exposure profiles were previously found to be similar when compared to reproductive-age women in the nationally representative National Health and Nutrition Examination Survey (NHANES).[33] Because EDCs are known to impact pregnancy hormones that have been linked to nausea symptoms, we hypothesized that higher levels of EDCs would be related to higher risk of persistent nausea. As a secondary analysis, we considered differences in associations by fetal sex because prior research suggests that both nausea characteristics and previously explored associations of EDCs with some hormones differ by fetal sex.[25,34]

Materials and Methods

I-KIDS Study Design and Analytic Sample

Pregnant women were recruited into I-KIDS, a prospective pregnancy and birth cohort, from two local obstetric clinics in Champaign-Urbana, Illinois, to evaluate associations of prenatal environmental chemical exposures with neurodevelopment. Recruitment, enrollment, and eligibility criteria have been previously detailed.[24,27,33] Briefly, eligibility criteria included the following: women had to be ≤15 weeks pregnant at enrollment, 18–40 years old, fluent in English, in a low-risk pregnancy (determined by a medical provider), with singleton pregnancy, residing within 30 min of the study site, and planning not to change residences before their child's first birthday. I-KIDS initially enrolled 688 women (of whom, 660 completed the first visit). Our current study includes 467 women with live births, who enrolled in I-KIDS between 2013 and 2019, remained in the study through their child's birth, had nausea symptom information at all timepoints across pregnancy, and had measurable levels of at least one maternal urinary EDC biomarker. All women provided written informed consent, and the study was approved by the University of Illinois institutional review board.

Collection of Maternal Sociodemographic, Lifestyle, and Health Information

In early pregnancy [median (25th, 75th percentile): 13.4 (12.4, 14.1) weeks gestation], I-KIDS staff conducted home visits to interview enrolled women about various sociodemographic and lifestyle factors. Women self-reported their race as white, black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or other. Women reported their ethnicity as being Hispanic/Latina or not. We categorized women as being non-Hispanic white or Other (Hispanic/Latina, black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, multiracial, and others). We calculated prepregnancy body mass index (BMI) (kg/m^2) from self-reported prepregnancy weight (kg) and height (m). We determined fetal sex based on sex at birth (male, female). To measure early pregnancy stress levels, women completed the perceived stress scale (PSS), a 10-item questionnaire asking about thoughts and feelings during the last month scored from 0 to 40.[35,36] Scores of 0 to 13 indicate low stress, whereas scores 14 or greater signify moderate or high stress. At their first visit, women completed a semiquantitative food frequency questionnaire (FFQ) adapted from the full-length Block-98 FFQ (NutritionQuest) and validated in pregnant populations.[37–39] We used dietary intakes representing diet patterns from the previous 3 months to calculate an early pregnancy Alternative Healthy Eating Index 2010 (AHEI-2010) average, which is an 11-component diet quality index (totaling 110 total points) based on foods and nutrients known to be predictive of chronic disease risk and mortality in the general population (but also validated in pregnancy[40,41]) with higher scores indicating better overall diet quality.[42,43] Since AHEI-2010 considers moderate alcohol consumption as beneficial to health but clinical guidelines recommend pregnant women abstain from alcohol,[44–46] we removed the alcohol component from the index to create a 10-component diet quality index (maximum: 100 points). We asked women at baseline about fragrant personal care and cleaning product use, and women answered "never or almost never," "sometimes," or "always" to the following: *a*) "How often do you use personal care products that are fragrance-free?" and *b*) "How often do you use fragrance-free cleaning, laundry, and other household products?" From this, we created a composite variable of women who never or almost never used any fragrance-free products and women who used fragrance-free products sometimes or always.

Assessment of Urinary Phthalate/Replacement, Phenol, and Triclocarban Biomarker Concentrations

Because nonpersistent EDCs have relatively short biological half-lives (6–24 h depending on the chemical) and high within-person variability,[47–49] we measured EDC biomarkers in five urine samples across-pregnancy, pooled physically before chemical biomarker measurement. At study clinic/home visits or routine prenatal care clinic visits, women provided at least three and up to five first-morning urine samples at [median (25th, 75th percentile)] 13.4 (12.4, 14.1), 17 (16.4, 17.7), 23.9 (22.9, 24.6), 28.7 (28.1, 29.6), and 34.9 (34.4, 35.6) weeks gestation. Details about urine collection, processing, and storage have been previously detailed.[27] Briefly, women collected first-morning urine into polypropylene urine cups and refrigerated them for up to 24 h. We retrieved the urine samples either from participants' homes during study home visits or from their clinic after a regularly scheduled prenatal care appointment (where the samples remained refrigerated). We transported urine samples back to our laboratory on ice and aliquoted them for long-term storage. To create the pooled sample, we added 900 μL of urine from the first urine sample to a 5-mL cryovial tube. At each visit, we layered fresh urine onto the previous frozen sample for that participant and immediately stored the sample at −80°C. At the end of each pregnancy, we thawed, vortexed, and measured the specific gravity of pooled samples. Each frozen pooled sample represents a single individual's cross-pregnancy exposure.

The frozen pooled urine samples were shipped to the Centers for Disease Control and Prevention (CDC)'s Division of Laboratory Sciences in four batches (batch 1: participants enrolled December 2013–February 2015; batch 2: enrolled February 2015–July 2016;

batch 3: enrolled July 2016–August 2018; batch 4: enrolled September 2018–November 2019). Using previously published isotope-dilution mass spectrometry methods with rigorous quality assurance/quality control protocols and high long-term reproducibility,[50–56] CDC laboratory staff quantified biomarkers for 19 phthalate/replacement metabolites, 11 phenols, and triclocarban.[25] Many women ($n = 156$) did not have measured levels of mono (2-ethyl-5-hydroxyhexyl) terephthalate (MEHHTP), mono(2-ethyl-5-carboxypentyl) terephthalate (MECPTP), and monooxoononyl phthalate (MONP), as these biomarkers were not assessed for batch 1 (participants enrolled December 2013–February 2015).

Self-Reporting of Nausea during Pregnancy

Women self-reported nausea symptoms approximately monthly across pregnancy (13, 17, 23, 28, and 34 median weeks gestation and within 24 h after birth at the hospital). Trained researchers conducted research home visits at median 13 and 34 wk, phone interviews at median 23 and 28 wk, and a separate clinic visit for blood collection and interview at median 17 wk. At the first prenatal visit (median 13 wk gestation), trained researchers asked women if they had experienced nausea since conception (answer: "yes" or "no"). At the next visit, we asked women if they still have nausea (answer: "yes" or "no") and date when it ended if "no." We also asked if they started experiencing any new nausea since the last visit (answers: "yes" or "no") and when it started if "yes." We categorized women as "never having nausea" if they did not report nausea at any point in pregnancy.

Using these self-reported nausea symptoms, we categorized women as having "typical nausea" if they reported having nausea since conception and their symptoms ended by median 17 wk gestation. We categorized women as having "persistent nausea" if they reported having nausea since conception and their symptoms persisted past 17 wk gestation. Lastly, we categorized women as having "irregular symptoms" if they reported nausea symptoms that started and stopped more than once during pregnancy. Thus, women did not subjectively describe their nausea as "typical," "persistent," or "irregular," but rather we generated these categories based on symptoms women reported across pregnancy. We elected to categorize women with intermittent symptoms as a separate group because it is possible that their symptoms differed in severity or physiological underpinnings compared to the other groups. We selected the 17-wk gestation cut-off to delineate persistent from typical nausea as nausea that most women experience commonly resolves between 16 and 18 wk gestation.[7] As most women experience some nausea during pregnancy and some studies suggest that not experiencing any nausea may be associated with adverse fetal outcomes,[57] we used typical nausea as our reference group in all models.

Statistical Analysis

Derivation of analytic sample. The derivation of our analytic sample is detailed in Figure S1. Briefly, of the 660 women who completed the first I-KIDS visit, 563 remained until the birth of their child. Some women were excluded from this analysis, as they did not have sufficient information to create the nausea persistence variable ($n = 64$) or had chemicals measured in a later batch ($n = 32$). Our final analytic sample included 467 women who have at least one measured EDC biomarker and nausea persistence information. We summarized information on sociodemographic, health, and lifestyle factors in the reference population and our analytic sample as frequency (percent) or median (25th, 75th percentile) (Table 1).

Modeling of urinary chemical concentrations. For nonzero biomarker concentrations below the limit of detection (LOD), we used instrument-read values to avoid bias associated with imputing concentrations <LOD.[58] In our statistical analyses, regardless of the number of women with values >LOD we only included chemical biomarkers with concentrations >0 ng/mL in at least 90% of women (Table S1). This resulted in butylparaben, bisphenol F (BPF), and triclocarban being excluded from single-pollutant and mixture analyses. To avoid undefined estimates for ln-transformed zero concentrations [ethylparaben $n = 4$; bisphenol A (BPA) $n = 3$; and the sum of urinary biomarkers of di(isononyl) cyclohexane-1,2-dicarboxylate (ΣDiNCH), bisphenol S (BPS), benzophenone-3 (BP-3), and 2,5-dichlorophenol (2,5-DCP) $n = 1$], we used the formula [ln(chemical concentration +0.0001)] for each chemical value in linear regression and mixture models.

For phthalates/replacements, we approximated women's exposure to phthalate/replacement parent compounds using their urinary metabolite concentrations. Specifically, we calculated parent molar sums (nmol/mL) by summing metabolites from common precursors: mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) for the sum of di-2-ethylhexyl phthalate (DEHP) metabolites (ΣDEHP); monocarboxyoctyl phthalate (MCOP), mono-isononyl phthalate (MiNP), and monooxononyl phthalate

Table 1. Demographics of women in the I-KIDS prospective, pregnancy cohort ($n = 467$).

Characteristic	*n* (%)
Race/Ethnicity[a]	
Non-Hispanic white (Ref)	376 (80.7)
Other[b]	90 (19.3)
Education[a]	
Some college or less (Ref)	85 (18.2)
College graduate or higher	382 (81.8)
Income	
<$60,000	130 (28.1)
$60,000–$99,999	177 (38.2)
>$100,000	156 (33.7)
Alcohol since conception[a]	
None (Ref)	271 (58.2)
Any alcohol consumed	195 (41.8)
Fragrance-free product use[a]	
Sometimes/always (Ref)	291 (62.3)
Never	176 (37.7)
Parity[a]	
No children (Ref)	242 (51.8)
At least one child	225 (48.2)
Fetal sex[a]	
Male (Ref)	224 (48.0)
Female	243 (52.0)
Nausea during pregnancy	
Typical nausea (Ref)	198 (42.4)
Never nausea	43 (9.2)
Persistent nausea	115 (24.6)
Irregular nausea	111 (23.8)
	Median (25th, 75th percentile)
Maternal age (years)[a]	29.9 (27.3, 32.7)
Prepregnancy body mass index (kg/m^2)[a]	24.5 (21.9, 29.2)
Early pregnancy Alternative Healthy Eating Index 2010[a,c]	51.6 (44.2, 59.8)
Early pregnancy perceived stress scale score[a]	10.8 (6.8, 16.1)

Note: EDCs, endocrine-disrupting chemicals; I-KIDS, Illinois Kids Development Study; Ref, reference.
[a]Variables included in adjusted regression models for associations of EDCs with nausea during pregnancy.
[b]Includes ethnically Hispanic/ Latina, black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Multiracial, and others.
[c]Alcohol intake was removed from the index (total score out of 100). Some women are missing data (race/ethnicity: $n = 1$; diet quality index: $n = 19$; perceived stress score: $n = 8$; alcohol since conception: $n = 1$).

(MONP) for the sum of metabolites of di-isononyl phthalate (ΣDiNP); mono-n-butyl phthalate (MBP) and mono-hydroxybutyl phthalate (MHBP) for the sum of di-n-butyl phthalate metabolites (ΣDBP); mono-isobutyl phthalate (MiBP) and mono-hydroxyisobutyl phthalate (MHiBP) for the sum of di-isobutyl phthalate metabolites (ΣDiBP); cyclohexane-1,2-dicarboxylic acid-monohydroxy isononyl ester (MHiNCH) and cyclohexane-1,2-dicarboxylic acid-mono(carboxyoctyl) ester (MCOCH) for the sum of DiNCH metabolites (ΣDiNCH); and mono(2-ethyl-5-hydroxyhexyl) terephthalate (MEHHTP) and mono(2-ethyl-5-carboxypentyl) terephthalate (MECPTP) for the sum of DEHTP metabolites (ΣDEHTP). Specific formulas were previously published[24] and are reported in table footers. Molar concentrations were back-converted to nanograms per milliliter by multiplying ΣDEHP, ΣDiNP, ΣDBP, ΣDiBP, ΣDiNCH, and ΣDEHTP by the molecular weights of MECPP, MCOP, MBP, MiBP, MHiNCH, and MECPTP, respectively.[33,59,60] We estimated exposure to di-isodecyl phthalate (DIDP), di-n-octyl phthalate (DnOP), benzylbutyl phthalate (BBzP), and di-ethyl phthalate (DEP) using nanogram per milliliter concentrations of their urinary metabolites monocarboxynonyl phthalate (MCNP), mono(3-carboxypropyl) phthalate (MCPP), mono-benzyl phthalate (MBzP), and monoethyl phthalate (MEP), respectively. All phthalate/replacement and phenol biomarker concentrations were specific gravity–adjusted to account for urine dilution.[61] Biomarker concentrations (ng/mL) and limits of detection (LODs) are reported in Table S1. To understand how EDC concentrations in I-KIDS compared to a nationally representative sample, we also compared biomarker concentrations of I-KIDS women to those from same-age (18–40 years old) women in NHANES survey cycles 2013–14, 2015–16, and 2017–18.[62]

Covariate selection. Based on prior literature and our data, we generated a directed acyclic graph (DAG) to identify a minimum sufficient adjustment set of covariates (Figure S2).[1,4] We assessed correlations between covariates to test for potential multicollinearity; however, all covariates were only weakly or moderately correlated ($r < 0.4$) (Table S2). All models accounted for maternal age, race/ethnicity, educational attainment, prepregnancy BMI, early pregnancy diet quality (AHEI-2010) (as a potential source of some EDCs), fragrant product use (as a potential source of some EDCs), early pregnancy stress (PSS 10), alcohol use since conception, parity, and fetal sex. Race/ethnicity was considered a proxy for unmeasured structural factors like environmental racism that may confound our associations of interest. Age (years), prepregnancy BMI (kg/m^2), diet quality, and stress were modeled as continuous variables, whereas all others were categorized with the reference group indicated in Table 1. We excluded women who were missing any of these covariates from regression analyses.

Evaluating associations of EDC biomarkers with persistent nausea during pregnancy. To address our primary objective, we evaluated whether EDC biomarkers were associated with persistent nausea compared to typical nausea using covariate-adjusted multinomial logistic regression models, with the covariates detailed above. To improve model fit, we natural log (ln)-transformed all EDC biomarkers. In secondary analyses, we also considered the relationships of EDC biomarkers with atypical nausea patterns [never having nausea (reference) or having irregular nausea]. We also fit multinomial logistic regression models without covariates to assess unadjusted associations of EDC biomarkers with nausea during pregnancy (Table S3).

Evaluating associations of an EDC biomarker mixture with nausea persistence during pregnancy. We utilized two different methods with unique strengths to evaluate covariate-adjusted, joint associations of phthalates/replacements and phenol biomarkers (excluding butylparaben, BPF, and triclocarban biomarkers, as described above) with persistent nausea. Both methods provide inference on the importance of each chemical within the mixture. First, we used quantile-based g-computation (QGComp) with the goal of quantitatively evaluating the risk of persistent nausea using easily interpretable joint effect estimates and confidence intervals (CIs).[31] We used QGComp to estimate the association of the EDC mixture with persistent nausea compared to typical nausea using logistic regression. We generated results without bootstrapping to obtain partial negative and partial positive associations and weights, which indicate relative importance and direction of each coexposure to the joint association. Then, because persistent nausea is not a rare outcome, we fit models with 500 bootstraps to estimate risk ratios with more precise confidence intervals, avoiding potentially overestimating our effect estimates. As we transformed all biomarker concentrations into deciles, the resulting relative risk (RR) and 95% CIs are interpreted as the risk of nausea persistence if all chemicals in the EDC biomarker mixture increased by 10%.

Second, we used Bayesian kernel machine regression (BKMR), with the goal of estimating a nonparametric, high-dimensional exposure–response function to identify nonlinear dose–response relationships and chemical–chemical interactions within the EDC mixture.[32] We ln-transformed, centered, and scaled all coexposures and continuous covariates. We fit hierarchical BKMR models, using the binominal family and 200,000 iterations to determine the joint relationship of EDC biomarker mixture with probit odds of persistent nausea. Hierarchical BKMR allowed us to group the phthalates/replacements and phenols that we included in the mixture as two separate groups. To assess a joint association, we created dose–response curves where we modeled the relationship of the EDC mixture at various quantiles across its distribution relative to the median with persistent nausea. We calculated group and individual posterior inclusion probabilities (PIPs) to identify important EDC classes and biomarkers. Lastly, we interpreted univariable dose–response curves to identify nonlinear relationships and bivariable plots to identify chemical–chemical interactions (i.e., the relationship of one EDC biomarker with persistent nausea differs by another biomarker's level of exposure).

Evaluating differences in associations by fetal sex. As nausea prevalence in pregnancy may differ by fetal sex,[34,63] we investigated if associations of EDCs (individual and joint) with persistent nausea differ between women carrying females and those carrying males. In logistic regression models, we included a multiplicative interaction term to identify differences and reported interaction p-values. To simplify the interpretation of results from interaction models in QGComp and BKMR analyses, we stratified our sample by fetal sex and fit separate models.

Sensitivity analyses. We performed two sensitivity analyses to better understand the relationship between EDC exposure and persistent nausea in pregnancy. First, as we did not identify strong correlations across chemical classes (i.e., chemicals were most strongly correlated within each chemical class), we modeled phthalates/replacements and phenols as separate QGComp mixtures. This approach further delineates the risk of persistent nausea by specific classes of chemicals, which may aid with risk assessment by regulatory bodies. Second, as a large number of participants did not have data on DEHTP metabolites (MEHHTP and MECPTP) and a third metabolite of DiNP (MiNP) due to the CDC measuring these after study onset, we conducted analyses in a smaller subset of women to understand the potential role of these chemicals within the joint EDC mixture.

Reporting of findings and interpreting meaningful results. For single pollutant logistic regression results, odds ratios (ORs) and 95% CIs represent the odds of nausea (never, persistent, or irregular) for a two-fold higher EDC biomarker concentration compared to typical nausea. Our main QGComp results are interpreted as the

risk ratio (RR) and CI associated with a decile higher concentration of all EDC biomarkers simultaneously. For BKMR, we assessed trends visually and reported meaningful PIPs based on the largest PIPs selected in each group. To ensure model assumptions were met, we performed regression diagnostics for single-pollutant analyses and checked for convergence with the Markov chain Monte Carlo procedure in BKMR. Rather than focusing on statistical significance thresholds, we identified potentially meaningful findings by assessing the direction, strength, and precision of the associations, as recommended by the American Statistical Association.[64] As such, we did not adjust for multiple comparisons. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (Table S4). We performed logistic regression analyses in SAS version 9.4 (SAS Institute Inc.) using PROC LOGISTIC. We conducted QGComp and BKMR in R Statistical Software (version 4.2.2; R Development Core Team) using R packages: "qgcomp: Quantile G-Computation"[65] and "bkmr: Bayesian Kernel Machine Regression."[66]

Results

Participant Characteristics and Nausea Prevalence

Most of the 467 women included in this study were non-Hispanic white (81%), college-educated (82%), with a total family income >$60,000 (72%), and did not consume alcohol since conception (58%) (Table 1). Only 9% of women never had nausea during pregnancy, with 42% of women experiencing typical nausea, followed by 25% with persistent nausea, and 24% with irregular nausea. Some characteristics (alcohol use since conception, prepregnancy diet quality index, prepregnancy stress scores, prepregnancy BMI, and fragrance-free product use) differed by the nausea characteristics (Table S5). Specifically, relative to women with typical nausea, women with persistent nausea were less educated, less likely to have consumed alcohol since conception, had lower use of fragrance-free products, had worse diet quality, and had higher stress levels.

Concentrations and Correlations of Maternal Urinary Chemical Biomarkers

Urinary biomarker concentrations are presented in Table S1. Most chemicals had concentrations ≥LOD in the vast majority (>90%) of women, except MiNP, MCOCH, butyl paraben, ethyl paraben, bisphenol F, and triclocarban, which were only detectable (≥LOD) in 42.5%, 50.6%, 42.9%, 54%, 63.6%, and 29.9% of participants, respectively. Some EDC biomarkers were moderately-to-strongly correlated with each other (Figure S3), including methylparaben with propylparaben ($r = 0.7$); 2,4-DCP with 2,5-DCP ($r = 0.7$) and MCPP with ΣDiNP (two metabolite and three metabolite sums) ($r = 0.8$). Additionally, ethylparaben was weakly correlated with methylparaben ($r = 0.4$), and MCNP was weakly correlated with MCPP ($r = 0.3$) (Figure S3). Compared to women in NHANES, I-KIDS participants had similar concentrations of most chemical biomarkers but slightly lower concentrations of MEP, ethylparaben, methylparaben, and propylparaben, and higher levels of ΣDEHTP, BP-3, and triclosan (TCS) (Table S1).

Associations of Individual EDC Biomarkers with Persistent Nausea during Pregnancy

In all women, only ΣDiNCH was associated with persistent nausea during pregnancy (Table 2). Specifically, two-fold higher ΣDiNCH concentration was associated with 18% higher odds of persistent nausea compared to typical nausea (OR = 1.18; 95% CI: 1.01, 1.37). We observed just one notable difference in associations by fetal sex, despite most interaction p values being >0.10. Specifically, in women carrying males, two-fold higher ethylparaben concentration was associated with 12% higher odds of persistent nausea

Table 2. Associations of individual EDCs with persistent nausea during pregnancy by fetal sex in the I-KIDS prospective pregnancy cohort ($n = 295$).

	Persistent nausea compared to typical nausea ($n = 295$)			
Biomarker	All women	Female ($n = 151$)	Male ($n = 144$)	p_{int}
Phthalates/replacements		Odds Ratio (95% confidence interval)		
ΣDEHP	1.17 (0.91, 1.52)	1.37 (0.92, 2.03)	1.08 (0.77, 1.50)	0.36
MCPP	1.19 (0.96, 1.48)	1.17 (0.86, 1.59)	1.23 (0.91, 1.68)	0.80
MCNP	1.00 (0.78, 1.27)	0.99 (0.71, 1.38)	0.99 (0.69, 1.44)	0.98
MBzP	1.02 (0.86, 1.21)	0.94 (0.75, 1.18)	1.14 (0.89, 1.46)	0.26
MEP	1.12 (0.92, 1.35)	1.08 (0.83, 1.41)	1.15 (0.88, 1.50)	0.74
ΣDiNP (two metabolites)	1.06 (0.89, 1.26)	1.04 (0.81, 1.32)	1.10 (0.86, 1.41)	0.73
ΣDiNP (three metabolites)	1.16 (0.92, 1.45)	1.22 (0.90, 1.64)	1.10 (0.75, 1.61)	0.67
ΣDBP	1.22 (0.93, 1.61)	1.31 (0.91, 1.87)	1.12 (0.74, 1.69)	0.57
ΣDiBP	1.03 (0.82, 1.30)	1.25 (0.91, 1.71)	0.81 (0.56, 1.17)	0.08
ΣDiNCH	1.18 (1.01, 1.37)	1.17 (0.95, 1.45)	1.18 (0.94, 1.49)	0.96
ΣDEHTP	0.93 (0.77, 1.12)	0.82 (0.63, 1.07)	1.05 (0.81, 1.36)	0.19
Phenols				
BPA	1.13 (0.94, 1.36)	1.08 (0.88, 1.33)	1.28 (0.89, 1.82)	0.43
BPS	1.06 (0.88, 1.28)	1.09 (0.82, 1.44)	1.08 (0.81, 1.45)	0.98
Methylparaben	1.00 (0.88, 1.14)	0.90 (0.75, 1.08)	1.12 (0.93, 1.36)	0.09
Ethylparaben	1.07 (0.98, 1.16)	1.01 (0.89, 1.14)	1.12 (0.99, 1.26)	0.23
Propylparaben	1.01 (0.91, 1.11)	0.94 (0.82, 1.09)	1.07 (0.93, 1.23)	0.21
BP-3	0.95 (0.86, 1.06)	0.93 (0.80, 1.07)	0.98 (0.82, 1.17)	0.62
TCS	0.93 (0.84, 1.03)	0.89 (0.76, 1.03)	0.98 (0.84, 1.13)	0.36
2,4-DCP	0.92 (0.74, 1.15)	0.87 (0.64, 1.19)	0.98 (0.72, 1.32)	0.60
2,5-DCP	0.97 (0.85, 1.12)	0.96 (0.78, 1.19)	0.98 (0.81, 1.18)	0.92

Note: Odds ratio and 95% confidence intervals are interpreted as odds of persistent nausea (nausea lasting beyond 17 weeks gestation) for each two-fold increase in EDC biomarker compared to reference group (typical nausea; $n = 187$). Logistic regression models accounted for age, race/ethnicity, education, diet quality, fragrant product use, prepregnancy BMI, early pregnancy perceived stress, alcohol since conception, parity, and fetal sex. Models assessing fetal sex included a multiplicative interaction term (p_{int}). EDCs were assessed using a pooled urine sample of up to five first-morning across pregnancy urine samples. Some women are missing covariates ($n = 25$; race/ethnicity: $n = 1$; diet quality index: $n = 19$; perceived stress score: $n = 8$; alcohol since conception: $n = 1$). BP-3, benozophenone-3; BPA, bisphenol A; BPS, bisphenol S; EDCs, endocrine disrupting chemicals; ΣDBP, sum of di-n-butyl phthalate metabolites; ΣDEHP, sum of di-2-ethylhexyl phthalate metabolites; ΣDEHTP, sum of di-2-ethylhexyl terephthalate metabolites; ΣDiNP, sum of di-isononyl phthalate metabolites; ΣDiBP, sum of di-iso-butyl phthalate metabolites; ΣDiNCH, sum of di(isononyl) cyclohexane-1,2-dicarboxylate metabolites; I-KIDS, Illinois Kids Development Study; MBzP, monobenzyl phthalate; MCNP, monocarboxynonyl phthalate; MCPP, mono(3-carboxypropyl)phthalate; MEP, monoethyl phthalate; p_{int}, $p_{interaction}$; TCS, triclosan; 2,4-DCP, 2,4-dichlorophenol; 2,5-DCP, 2,5-dichlorophenol.

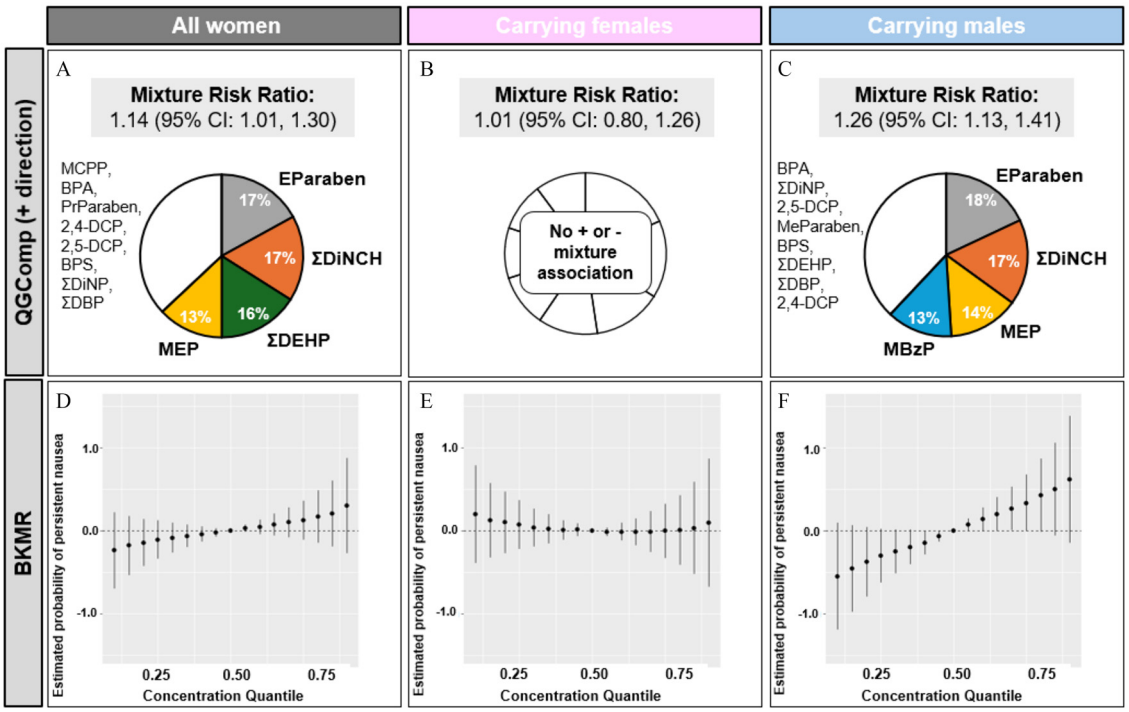

Figure 1. Associations of a nonpersistent EDC mixture with persistent nausea during pregnancy in the I-KIDS prospective pregnancy cohort: QGComp in (A) all women, (B) women carrying females, (C) women carrying males; BKMR in (D) all women, (E) women carrying females, and (F) women carrying males. Risk ratios and 95% confidence intervals of persistent nausea vs. typical nausea were generated from QGComp models fit with 500 bootstraps. Pie charts display percentages of EDC biomarker weights generated from nonbootstrapped QGComp models. Only positive associations are displayed as the overall risk ratios were in the positive directions. Probit BKMR models were fit using 200,000 iterations to generate plots (estimates and 95% credible intervals at various quantiles of exposure relative to the median), which are interpreted as the estimated probability of persistent nausea compared to typical nausea as the EDC biomarker mixture increases. The mixture includes ΣDEHP, ΣDiNP, ΣDBP, ΣDiBP, ΣDiNCH, MCPP, MCNP, MBzP, MEP, BPA, BPS, methylparaben, ethylparaben, propylparaben, BP-3, TCS, 2,4-DCP, and 2,5-DCP. All QGComp and BKMR models accounted for maternal age, race/ethnicity, educational attainment, diet quality, fragrant product use, prepregnancy BMI, early pregnancy stress, alcohol since conception, parity, and fetal sex. Models were stratified by fetal sex to estimate association in women carrying females and males. EDC biomarkers were quantified in a pooled urine sample of up to five first-morning cross-pregnancy urine samples. $n = 295$ (151 carrying a female and 144 carrying a male fetus). Corresponding numeric data can be found in Tables S6 and S8. Note: 2,4-DCP, 2,4-dichlorophenol; 2,5-DCP, 2,5-dichlorophenol; BKMR, Bayesian kernel machine regression; BP-3, benzophenone-3; BPA, bisphenol A, BPS, bisphenol S; CI, confidence interval; DBP, di-n-butyl phthalate; DEHP, di-2-ethylhexyl phthalate; DiBP, di-isobutyl phthalate; DiNCH, di(isononyl) cyclohexane-1,2-dicarboxylate; DiNP, di-isononyl phthalate; EDC, endocrine disrupting chemical; EParaben, ethylparaben; I-KIDS, Illinois Kids Develoment Study; MBzP, monobenzyl phthalate; MCCP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MeParaben, methylparaben; PrParaben, propylparaben; QGComp, quantile-based g-computation; Σ, sum; TCS, triclosan; +, positive; −, negative.

(OR = 1.12 95% CI: 0.99, 1.26) (Table 2). Individual EDCs were not associated with persistent nausea in women carrying females.

Associations of an EDC Biomarker Mixture with Persistent Nausea during Pregnancy

When we evaluated associations jointly as a mixture using QGComp, in all women, a 10% higher EDC biomarker mixture concentration was associated with 14% higher risk of persistent nausea compared to typical nausea (RR = 1.14 95% CI: 1.01, 1.30), with ΣDiNCH (17%), ethylparaben (17%), ΣDEHP (16%), and MEP (13%) contributing most to the positive direction (Figure 1; Table S6). Despite only observing one notable sex-specific association in single-chemical models (i.e., ethylparaben as described above), the joint association appeared to be driven by women carrying males, in whom a 10% higher mixture was associated with 26% higher risk of persistent nausea compared to typical nausea (RR = 1.26; 95% CI: 1.13, 1.41), with ethylparaben (18%), ΣDiNCH (17%), MEP (14%), MBzP (13%), BPA (12%), and DiNP (two metabolites; 12%) contributing the most to the positive direction (Figure 1; Table S6). We did not observe a relationship between the EDC biomarker mixture and persistent nausea in women carrying females (RR = 1.01; 95% CI: 0.80, 1.26) (Figure 1; Table S6).

Using hierarchical BKMR, the relationship in all women trended in the positive direction due to ΣDiNCH (PIP: 0.35), TCS (PIP: 0.20), BPA (PIP: 0.19), MCPP (PIP: 0.18), and ethylparaben (PIP: 0.16) (Figure 1; Tables S7 and S8). Similar to QGComp, we observed differences by fetal sex. In women carrying males, we identified a potentially higher probability of persistent nausea with higher EDC biomarker mixture concentration (Figure 1). Phthalates/replacements (PIP: 0.73) and phenols (PIP: 0.67) were strongly selected in the model, with MEP (PIP: 0.37), ΣDiNCH (PIP: 0.17), BPA (0.20), and methylparaben (PIP: 0.15) being of particular importance (Table S7). In women carrying females, there was no relationship between the EDC biomarker mixture and persistent nausea (Figure 1; Table S8). We did not identify any nonlinearities or chemical–chemical interactions in all women, women carrying males, or women carrying females (Figures S4–S7).

Sensitivity Analyses

First, when we modeled phthalates and phenols as separate mixtures, our findings were generally consistent with our primary results. In all women, a 10% higher phthalate mixture concentration was associated with 12% higher risk of persistent nausea (RR = 1.12; 95% CI: 1.02, 1.24) due to DiNCH (30%) and DEHP (24%) (Table S9). The overall relationship was driven by women

carrying males, in whom each 10% higher phthalate biomarker level was associated with 20% higher risk of persistent nausea (RR = 1.20; 95% CI: 1.05, 1.37) due to MEP (33%) and DiNCH (28%) (Table S9). There was not a meaningful relationship of the phthalate mixture with persistent nausea in women carrying females (RR = 1.07; 95% CI: 0.93, 1.23). Phenols were not associated with higher risk of persistent nausea in all women or in women carrying females (RR = 1.03; 95% CI: 0.92, 1.16; RR = 0.92; 95% CI: 0.78, 1.09, respectively) (Table S10). However, consistent with our primary results, in women carrying males, a 10% higher phenol biomarker level was associated with 14% higher risk of persistent nausea (RR = 1.14; 95% CI: 1.01, 1.30) due to ethylparaben (41%) and BPA (30%) (Table S10). Second, in analyses that included ΣDEHTP and ΣDiNP (three metabolites vs. two metabolites in main analysis) in the mixture, our effect estimates were smaller with less precision (which was expected because of the decreased sample sizes), and there were some differences in biomarker contributions to the effect (Table S11). Specifically, in all women, a 10% higher biomarker mixture concentration was associated with a 10% higher risk of persistent nausea (RR = 1.10; 95% CI: 0.93, 1.29), due to ethylparaben (27%), ΣDiNP (three metabolites; 15%), and BPA (12%). Furthermore, in women carrying males, a 10% higher biomarker mixture concentration was associated with a 23% higher risk of persistent nausea (RR = 1.23; 95% CI: 1.00, 1.51), due to ethylparaben (26%), ΣDiNCH (15%), and ΣDiNP (three metabolites; 14%) (Table S11). Consistent with our main analyses, the EDC biomarker mixture was not associated with persistent nausea in women carrying females. Using BKMR, the relationship in all women remained null, whereas the relationship in women carrying males had similar trending positive estimates as the main analysis but with considerably less precision (Figure S8). Additionally, the PIPs in women carrying males differed from the main analysis, with ethylparaben (PIP: 0.82), ΣDiBP (PIP: 0.40), and MEP (PIP: 0.29) being the most important (Table S12). Consistent with our main analysis, the EDC mixture was not associated with persistent nausea in women carrying females.

Secondary Analysis: associations of EDC Biomarkers and Mixture with Atypical Nausea Patterns in Pregnancy

In all women, EDCs were not associated with never having nausea compared to typical nausea, except potentially at higher levels of exposure. But, in women carrying females, some phthalates (ΣDEHP, ΣDiBP) were associated with higher odds of never having nausea, some phenols (methylparaben, 2,5-DCP) were associated with lower odds of never having nausea, and the EDC mixture was associated with lower odds of never having nausea. In women carrying males, while methylparaben and propylparaben were associated with higher odds of never having nausea, joint associations were inconsistent, with possible higher odds of never developing nausea at higher exposure levels (Tables S13–S16; Figure S9). Furthermore, despite some individual phthalate biomarkers being associated with irregular nausea compared to typical nausea (MEP, ΣDBP in all women; ΣDiBP in women carrying females), there were no observed joint associations, except in women carrying females, where ΣDiBP may be responsible for a weak and imprecise joint association only at higher levels of exposure (Tables S13 and S17–S19; Figure S10).

Discussion

Summary of Major Findings

To our knowledge, ours is the first study to investigate the relationship between EDCs and nausea during pregnancy, an understudied condition that has potential short- and long-term implications for women's health, including mental health during pregnancy and cardiovascular disease postpartum.[67–70] Our most salient findings were in women carrying males, showing that some EDCs, particularly in a mixture, were associated with persistent nausea compared to typical nausea. The primary EDC biomarkers of importance were the phthalate replacement plasticizer DiNCH and ethylparaben, commonly used as an antibacterial in personal care and cleaning products. In contrast, findings related to atypical nausea patterns were less compelling. Our results suggest that EDC exposure in pregnancy could be related to having nausea that persists across pregnancy; however, additional studies are needed to elucidate potential underlying biological pathways, including likely hormone-mediated relationships, as well as to understand the long-term implications for both mother and child.

EDCs and Risk of Persistent Nausea during Pregnancy in All Women and Differences by Fetal Sex

We reported positive relationships of the phthalate replacement, ΣDiNCH, with persistent nausea in all women, and of ethylparaben with persistent nausea in women carrying males. Furthermore, ethylparaben, ΣDiNCH, and MEP were primary drivers of the joint association with persistent nausea in all women and in women carrying males. Interestingly, when we modeled separate phthalate/replacement and phenol mixtures, the primary driver of the mixture association in all women appeared to be phthalates/replacements (due to ΣDiNCH and ΣDEHP) but not phenols. Despite this, these class-specific mixture results confirmed our primary findings that, in women carrying males, both phthalates/replacements (due to ΣDiNCH) and phenols (due to ethylparaben) were associated with risk of persistent nausea. There is some evidence from epidemiologic studies that both DiNCH and ethylparaben are associated with adverse pregnancy and birth outcomes,[27,59,71] as well as changes in women's hormonal, inflammatory, and metabolic biomarker levels.[25,72–75] Specifically, our prior work in I-KIDS showed that ethylparaben, alone and as part of a mixture, was associated with lower TSH concentrations in all women and in women carrying males.[25] However, exact biological mechanisms from experimental studies are unclear. One *in vitro* study reported that DiNCH disrupted steroidogenesis at supraphysiological doses but was not estrogenic or anti-androgenic,[76] whereas another *in vitro* study reported that DiNCH did not impact steroidogenesis but that its metabolites activated estrogen, androgen, and peroxisome proliferator–activated receptor gamma (PPARγ) receptors at high concentrations.[77] Additionally, experimental studies have shown that parabens only weakly bind to estrogen receptors.[78] Thus, it may be that DiNCH and ethylparaben's mechanisms of action are not through sex steroid pathways, which needs to be more extensively investigated. As pregnancy nausea likely has hormonal underpinnings, the relationship of EDCs with nausea in pregnancy due to hormonal disruption is biologically plausible. However, it is unclear which hormones are responsible for nausea, as findings from epidemiologic studies are mixed. Specifically, a study of 129 Scandinavian women with uncomplicated pregnancies identified a positive association of testosterone (at mean 17 and 33 wk) with nausea and vomiting at 33 wk gestation[14]; a study of 262 white women from Boston reported a positive association of estradiol (but not other hormones) with nausea at 16 and 27 wk gestation[15]; and a study of 1,682 pregnant women from the Netherland's Holistic Approach to Pregnancy and the first Postpartum Year (HAPPY) study reported a positive association of hCG (but not thyroid hormones) with first trimester nausea and vomiting.[16] Recently, researchers have reported associations of the placental hormone growth/differentiation factor-15 (GDF15) with HG; however, it is unclear if GDF15 plays a role in less severe forms

of pregnancy nausea, and no studies have explored if EDCs are associated with this placental hormone.[17,79–81]

Our fetal sex-specific findings from mixture models are not surprising, as many pregnancy complications, such as early pregnancy loss, stillbirth, and preeclampsia, differ by fetal sex.[82] Furthermore, previous research has reported sexually dimorphic responses to EDCs in relation to pregnancy sex steroid and thyroid hormones,[24,25] as well as pregnancy outcomes, such as preeclampsia[28] and gestational weight gain.[27] Additionally, some studies suggest that nausea and vomiting in pregnancy (NVP) is a sexually dimorphic condition.[34,63] These findings could be explained by placental differences between male and female fetuses, as placentae are sexed organs with differences in both function and morphology.[83–86] In addition, X chromosome inactivation in female fetuses, Y chromosome presence in male fetuses, and sex steroid hormone (e.g., testosterone) differences in male and female fetuses could explain our findings.[82,87] Our sex-specific findings from joint EDC models strengthen the biological plausibility of the relationship between EDCs and persistent nausea, as we would be unlikely to observe consistently sexually dimorphic findings by chance alone. However, caution is warranted when making broad conclusions about the sex-specific nature of these relationships because sex-specific findings were less apparent in single-pollutant results (with few meaningful interaction p values). Additionally, in single-pollutant models, we observed similar odds ratios between women carrying males and females, and some odds ratios were actually larger in women carrying females.

Prior Studies Evaluating Environmental Exposures and Nausea in Pregnancy

EDCs have been linked to other pregnancy-related adverse health outcomes, including gestational diabetes, gestational hypertension, and inappropriate gestational weight gain.[27,29,88] However, to our knowledge, there are no studies considering the role of EDCs in nausea symptomology during pregnancy, and prior research related to the roles of other environmental exposures in NVP is sparse. Specifically, while one study of 1,458 pregnant Bangladeshi women reported higher drinking water arsenic concentrations were associated with higher odds of self-reported NVP,[19] acute arsenic toxicity is associated with nausea and vomiting in nonpregnant individuals, so this relationships may not be pregnancy-specific but is rather due to arsenic's known toxic properties.[89] Some other studies have reported higher odds of NVP with marijuana use.[90,91] It is possible that these findings are related to cannabinoid hyperemesis syndrome, where heavy users of cannabis experience intense episodes of nausea and vomiting.[92] However, reverse causality is also a likely explanation, as women with NVP may use marijuana to alleviate their symptoms. Based on the paucity of prior literature related to this work, substantially more research is needed on environmental drivers of nausea during pregnancy. Future epidemiologic studies should also continue to explore hormonal predictors of NVP to determine if risk of persistent nausea is due to changes in hormones, especially those known to be disrupted by environmental exposures. While no commonly used experimental models of pregnancy nausea exist, future experimental studies could continue to explore EDC mechanisms of toxicity beyond those that act via hormone receptors.

Strengths and Limitations

Our study has many strengths. First, I-KIDS queried symptoms repeatedly across pregnancy which allowed us to model persistent nausea during pregnancy, rather than severity of symptoms over a shorter duration (e.g., 24 h) as with the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) index or other scales. This method also allowed us to evaluate atypical nausea patterns, such as never having nausea or having intermittent nausea, which may differ from both typical and persistent nausea. Second, we measured EDC biomarkers in a pool of up to five first-morning urine samples collected throughout pregnancy that reflects exposure at any one point during pregnancy and provides a more stable estimate of gestational exposure than a single urine sample.[47,93,94] We also investigated a panel of many nonpersistent EDCs (and replacement chemicals) from multiple chemical classes, and we have reported previously that I-KIDS women have concentrations of these chemicals comparable to reproductive-age women in NHANES.[33] Third, based on what we know about nausea in pregnancy, EDCs' mechanisms of action, and the strength of our reported associations, our hypothesis is biologically plausible. Fourth, we selected covariates using a directed acyclic graph and accounted for many important potential confounders, such as diet quality and fragrant product use. Lastly, we used two different, but complementary and equally robust, machine learning methods—QGComp and BKMR. Despite some added complexity in interpreting results from two mixture methods,[95] we used QGComp for its easily interpretable output, whereas BKMR allowed us to assess nonlinearities and chemical–chemical interactions.

This study also has some limitations. First, I-KIDS did not assess perceived nausea severity, and women with the most severe symptoms may have been too sick to enroll in the study. If women with severe symptoms who did not enroll had lower EDC exposure, then we may have overestimated the relationship of EDCs with persistent nausea. Thus, future studies may be needed to assess the relationship of EDCs with severe nausea. Second, our pooled EDC biomarker assessment strategy resulted in some exposure occurring after our outcome of interest (persistent nausea) and did not allow for us to assess trimester-specific relationships. Third, we are unable to make causal claims, as we cannot rule out unmeasured confounding. Although it is less likely, we also cannot rule out that the relationship between EDCs and persistent nausea was due to reverse causation, whereby having nausea during pregnancy somehow results in higher EDC exposure. However, the literature is unclear on whether pregnancy nausea alters habits due to aversive smells, and there are conflicting reports about which smells are especially offensive. For example, one study reported "cleaning solvents, perfumes, and soaps" trigger nausea symptoms,[96] whereas a different study reported aversive smells are primarily fatty foods with minimal impact of scented personal care or cleaning products.[97] Regardless, it seems unlikely that women avoiding scented/fragranced products would increase their EDC exposure as many prior studies have shown that higher scented/fragranced PCP use is associated with higher exposure to many EDCs, including those investigated in the current study.[98–102] Therefore, future longitudinal exposure assessment or intervention studies are needed to resolve the potential issue of reverse causation. Fourth, the I-KIDS cohort is a relatively homogeneous sample of non-Hispanic white, well-educated, married women, which may limit generalizability. Fifth, some of our analyses may be underpowered, such as those with women never experiencing nausea. Finally, we only focused on a panel of nonpersistent EDCs from daily use products, so additional studies are needed to consider a more comprehensive collection of known EDCs.

Conclusions

In this study, we confirmed our hypothesis that nonpersistent EDCs from both food and personal care product sources are associated with nausea during pregnancy, an understudied pregnancy condition that affects the majority of women during pregnancy and impacts quality of life and long-term health. Specifically, higher levels of ethylparaben, DiNCH, MEP, and MBzP exposure, within the context of a mixture, were associated with greater risk of

persistent nausea in women carrying males. Our research may identify a potentially modifiable contributor to nausea that could be targeted with various interventions. Future research is needed to evaluate the biological underpinnings of our findings that link EDCs with nausea (i.e., disruption of hormones like sex steroids or neurotransmitters like serotonin) and to understand the clinical implications of our findings, such as determining whether behavioral and lifestyle modifications that reduce EDC exposure (e.g., DiNCH from diet or parabens from scented products and cosmetics) can mitigate some nausea symptoms. In addition, the relationship of EDCs with persistent nausea during pregnancy may be a missing link between known associations of these same chemicals with adverse birth outcomes, such as low birth weight.[103–105]

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