Title
Joint impact of phthalate exposure and stressful life events in pregnancy on preterm birth

Journal
Environment International, 133(Pt B)

ISSN
0160-4120

Authors
Ferguson, Kelly K
Rosen, Emma M
Barrett, Emily S
et al.

Publication Date
2019-12-01

DOI
10.1016/j.envint.2019.105254

Peer reviewed

HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Environ Int. 2019 December ; 133(Pt B): 105254. doi:10.1016/j.envint.2019.105254.

Joint impact of phthalate exposure and stressful life events in pregnancy on preterm birth

Kelly K. Ferguson[1], **Emma M. Rosen**[1], **Emily S. Barrett**[2], **Ruby H.N. Nguyen**[3], **Nicole Bush**[4], **Thomas F. McElrath**[5], **Shanna H. Swan**[6], **Sheela Sathyanarayana**[7,8]

[1]Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

[2]Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA

[3]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA

[4]Department of Psychiatry and Pediatrics, University of California at San Francisco, San Francisco, CA, USA

[5]Division of Maternal-Fetal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[6]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[7]Department of Pediatrics, Seattle Children's Research Institute, University of Washington, Seattle, WA, USA

[8]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA

Abstract

Background—Urinary phthalate metabolites and psychosocial stress in pregnancy have each been associated with preterm birth (PTB), but no study has examined the joint impact of these two environmental exposures. We hypothesized that there would be stronger associations between phthalate exposure and PTB in mothers with higher stress in pregnancy compared to mothers with lower stress.

Methods—We addressed this question using data from The Infant Development and the Environment Study (TIDES), a prospective birth cohort conducted at four US sites (N=783). We examined urinary phthalate metabolite concentrations measured in samples collected from up to three trimesters of pregnancy. Mothers reported their exposure to stressful life events (SLE) in each trimester in a questionnaire administered in the third trimester. PTB was defined as delivery before 37 weeks completed gestation (n=71, 9.1%). We examined associations between urinary

Corresponding author: Kelly K. Ferguson, 111 TW Alexander Drive, Research Triangle Park, NC, 27709. Tel: 984-287-3700. kelly.ferguson2@nih.gov.

Conflict of interest statement: The authors declare that they have no actual or potential conflicts of interests.

phthalate metabolite concentrations (individual time points and on average) and PTB using logistic regression models adjusted for maternal race, age, pre-pregnancy body mass index, education, specific gravity, and gestational age at sample collection. In addition, we created models stratified by whether or not mothers were exposed to any or no SLE in pregnancy.

Results—Summed di-2-ethylhexyl phthalate (ΣDEHP) metabolites measured in urine samples from the third trimester, but not the first trimester, were associated with an increased odds ratio (OR) of PTB (OR=1.44, 95% confidence interval [CI]=1.06, 1.95). In models stratified by SLE, associations between third trimester ΣDEHP concentrations and PTB were significant only for women experiencing one or more SLE during pregnancy (OR for ΣDEHP: 2.09, 95% CI: 1.29, 3.37) but not for women with no SLE during pregnancy (OR for ΣDEHP: 1.04, 95% CI: 0.66, 1.63) (p for interaction=0.07).

Conclusions—We observed an association between urinary ΣDEHP levels and PTB that was modified by whether a mother was exposed to one or more psychosocial stressors during pregnancy. Additional research to understand the joint impacts of chemical and non-chemical exposures, with an emphasis on timing of exposure, is needed in order to advance the state of the science on how the environment influences pregnancy.

Keywords

phthalates; preterm birth; gestational age; stress; psychological; pregnancy

Introduction

Phthalates are non-persistent compounds used in personal care products and plastics. Exposure occurs through dermal absorption, ingestion of contaminated foods and beverages, and inhalation and is ubiquitous in pregnant women (Woodruff et al. 2011). Data supporting an association between exposure to phthalates in pregnancy and preterm birth are accumulating, but results are not always consistent (Casas et al. 2015; Ferguson et al. 2014b; Meeker et al. 2009; Shoaff et al. 2016; Watkins et al. 2016; Whyatt et al. 2009). Psychosocial stress in pregnancy has also been associated with preterm birth (Hobel 2004), and has action through certain mechanistic pathways, such as epigenetic changes and alteration of glucocorticoid activity (Kim et al. 2018; Obel et al. 2005), that may overlap with those of phthalates. This raises the possibility of a joint effect. Combined exposure to chemical and non-chemical stressors has been associated with deleterious outcomes of pregnancy and child development in other contexts (Barrett et al. 2016; Chen et al. 2008; Cowell et al. 2015; Vesterinen et al. 2017; y Ortiz et al. 2017). However, to date, the combination of environmental chemical exposures and psychosocial stress in the etiology of preterm birth has not been studied. Examining combined effects of environmental exposures, including both chemical and non-chemical factors, is important because it can highlight individual susceptibility and inform public health prevention strategies.

Within The Infant Development and the Environment Study (TIDES), a large pregnancy cohort study, we examined the joint impact of phthalate and psychosocial stress exposure in pregnancy on preterm birth. We assessed phthalate exposure with urinary metabolites measured at up to three time points per participant in pregnancy and tested for interaction

with psychosocial stress by examining associations among women who self-reported experiencing stressful life events during pregnancy and among those who reported no stressful life events.

Methods

Study population

TIDES recruited women between August 2010 and August 2012 to participate in a prospective cohort study examining the association between maternal urinary phthalate metabolites in pregnancy and infant reproductive development. Women were recruited from the following academic clinics during routine prenatal care: University of California, San Francisco (UCSF); University of Rochester Medical Center (URMC); University of Minnesota (UMN); and University of Washington/Seattle Children's Hospital (UW/SCH). UCSF, UMN, and UW/SCH are located in major urban centers from the Northwestern (UCSF, UW/SCH) and Midwestern (UMN) United States. URMC in Rochester, New York, is located in the Northeastern United States and has a smaller population compared to the other locations and is also the most racially diverse (US Census Bureau 2010). Women were eligible to participate if they were 18 years or older, English speaking (or Spanish at UCSF), had a singleton pregnancy, did not report a condition (medical or otherwise) that might prevent them from continuing participation throughout the study, were <13 weeks pregnant at recruitment, and planned to deliver at a study site. Enrolled women completed a questionnaire and provided a spot urine sample at three routine visits across pregnancy, one per trimester (i.e., T1, 2, and 3) (Swan et al. 2015). Additional information on recruitment procedures, questionnaire completion, and study design has been previously described (Barrett et al. 2014). Prior to participation, all women provided signed informed consent. All study procedures were approved by site-specific IRBs and at the Icahn School of Medicine at Mount Sinai, the TIDES Coordinating Center. For the present analysis, we included women who had at least one urinary measurement of phthalates analyzed during pregnancy as well as information on gestational age at delivery (N=783).

Phthalate metabolite analysis

Women provided urine samples in sterile phthalate-free polypropylene cups specimen cups at each study visit in the first (T1), second (T2) and third (T3) trimesters. Immediately after collection, specific gravity was measured using a hand-held refractometer to assess urine dilution. Additional details on sample collection, processing, and analysis have been previously described (Swan et al. 2015). Urinary phthalate metabolites were measured in spot urine samples in subsets over time. T1 samples were analyzed first by the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC) and the University of Washington (UW), as described in detail elsewhere (Silva et al. 2007; Swan et al. 2015). Briefly, the analytic methods entailed enzymatic deconjugation from glucuronidated forms, solid phase extraction, separation with high performance liquid chromatography, and detection by either isotope-dilution tandem mass spectrometry (CDC) or electrospray ionization-tandem mass spectrometry (UW) (Swan et al. 2015). Analytes measured included the following phthalate metabolites: the di-2-ethyl hexyl phthalate (DEHP) metabolites mono-2-ethylhexyl phthalate (MEHP),

mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP); mono-ethyl phthalate (MEP); mono-benzyl phthalate (MBzP); mono-n-butyl phthalate (MBP); mono-isobutyl phthalate (MiBP); and mono-3-carboxypropyl phthalate (MCPP). Additionally, mono-carboxy-isononyl phthalate (MCNP), mono-carboxy-isooctyl phthalate (MCOP), and the phthalate alternative metabolite cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester (MHINCH) were measured at CDC but not at UW. For all measurements within this set, including those measured both at CDC and UW, values below the limit of detection (LOD) were assigned the value LOD divided by the square root of 2, as has been recommended when the data are not highly skewed (Hornung and Reed 1990).

The second analysis set includes urine from T2 and T3 provided by a subset of mothers of boys (n=169) who were selected randomly from all mothers of boys who had provided urine in each trimester, to examine windows of vulnerability to exposure for the primary endpoints of the study (Martino-Andrade et al. 2016). These were also analyzed at the CDC at the same time as the first set of samples, using the same methods described above. The same phthalate metabolites were included in this analytic set as the first, and values below the LOD were handled in the same manner.

In the third analysis set, the remaining urine samples from T3 were analyzed at the CDC in 2017. Again, the analytic approach was the same as in previous sets. For this set, the CDC provided machine-reported values for phthalate metabolite levels below the LOD, per an update in protocol, and these were kept as reported for analyses.

At each visit, urinary concentrations of DEHP metabolites were converted to nmol/L and summed (hereafter referred to as ΣDEHP) (Wolff et al. 2008). To examine the distributions of metabolites in the sample, all metabolites as well as ΣDEHP were corrected for specific gravity using the following formula: $P_c = P[((1.014 - 1) / Sg - 1)]$ where P_c represents the specific gravity-corrected phthalate metabolite concentrations, P represents the measured phthalate metabolite concentrations, 1.014 is the mean of specific gravity among all TIDES samples analyzed, and Sg is the specific gravity measured in the sample (Boeniger et al. 1993). To create an estimate of phthalate exposure across pregnancy, we calculated subject-specific geometric averages of the specific gravity-corrected metabolites available across pregnancy (hereafter referred to as pregnancy averages). For statistical analyses, all metabolites from individual visits as well as pregnancy averages were natural log-transformed. Phthalate metabolites with <50% detection were not included in primary analyses.

Preterm birth

Gestational age at delivery was assigned based on first available ultrasound (n=386), or, if that was not available, self-reported last menstrual period (n=397). Preterm birth was defined as delivery prior to 37 weeks completed gestation. We additionally examined the association with spontaneous preterm birth, as our previous work demonstrated associations that were greatest in magnitude among individuals with this delivery presentation (Ferguson et al. 2014b). Preterm births were considered spontaneous if delivery was immediately preceded by spontaneous labor or premature rupture of membranes (PROM). Information on PROM

and spontaneous labor was abstracted from medical records by trained medical abstractors at each of the four TIDES sites (Rosen et al. 2019).

Psychosocial stress

On the third trimester questionnaire, women responded to whether or not they had experienced any one of a list of stressful life events (SLE) during each trimester. The questions were adapted from validated questionnaires (Dohrenwend et al. 1978; Holmes and Rahe 1967). The list comprised job loss, serious illness, family death, relationship difficulties with spouse/partner, and legal or financial problems. Women were dichotomized into those reporting any SLE in pregnancy versus those who reported no SLE in pregnancy, as previously published in the TIDES study population by Barrett et al. (2016).

Statistical analysis

All analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC). We examined demographics among study participants and assessed distributions of urinary phthalate metabolites by visit. Adjusted logistic models were fit for both overall preterm birth and spontaneous preterm birth at each visit individually and for pregnancy averages. Covariates were selected based on a DAG generated from a review of relevant literature (Supplemental Figure 1). Our final model included the following variables as potential confounders: maternal age (continuous, years), pre-pregnancy body mass index (BMI) (continuous, kg/m^2), education (3 level, nominal) and maternal race (white, black, other). Income was carefully considered as a confounder as well but was excluded since it had a minimal impact on effect estimates. The same set of covariates were included in models examining phthalate metabolites from individual visits and for pregnancy averages, with two exceptions. For models of phthalate metabolites from individual visits, we modeled uncorrected phthalate metabolite concentrations and adjusted for urinary specific gravity (Barr et al. 2004) as well as gestational age at sample collection, to account for variability that may be attributed to changes in phthalate exposure, excretion, or metabolism over the course of pregnancy (Ferguson et al. 2014a). However, for models of pregnancy averages, we accounted for specific gravity by adjusting metabolite concentrations prior to averaging, as above, and did not account for gestational age at sample collection because adjustment for averages of these variables would not translate mathematically. To test the robustness of our primary results, we additionally examined models 1) including study center as a covariate, and 2) without any covariates. All results are presented as odds ratios (OR) in association with a natural log-unit increase in urinary phthalate metabolite measure.

Missing covariate values were imputed using Markov Chain Monte Carlo multiple imputation in SAS version 9.4 using proc MI. Ten imputations were performed and the following variables were included in the imputation model: race, maternal ethnicity, maternal age, pre-pregnancy BMI, education, income, study center, infant sex, and preterm status. Distributions of imputed covariates were compared to those of observed covariates to ensure reasonable values. All models were run with imputed covariates and were analyzed using proc MIANALYZE to account for the additional variability introduced by imputation.

We examined potential effect modification of the relationship between maternal phthalate concentrations and preterm birth by psychosocial stress, as indicated by SLE (any SLE vs. no SLE) in pregnancy. First, we estimated OR for preterm birth in association with experiencing any SLE (i.e., >0 SLE) in pregnancy. Second, we stratified the sample by any vs. no SLE in pregnancy and examined differences in the associations between urinary phthalate metabolites and preterm birth, adjusting these stratified models for the same covariates included in primary models described above. To test for interaction, we calculated p-values for the interaction terms between urinary phthalate metabolite and the dichotomous psychosocial stress variable.

Results

Our sample included 783 women with at least one urinary phthalate measure and information on gestational age at birth (Figure 1). Participants were primarily in their 30s, of normal BMI (18.5-25 kg/m^2), white, non-smokers, married, had income levels over 65k per year, and had achieved at least some college education (Table 1). Approximately 91% of the mothers in our sample (n=712) delivered at term while 9% (n=71) delivered before 37 completed weeks of gestation. 70.4% of preterm deliveries were spontaneous. Median (range) gestational age in weeks at each study visit was as follows: T1=11.1 (9.43-12.43); T2=19.7 (18.9-21.9); T3=32.1 (30.4-34.6).

Most metabolites of phthalate and phthalate alternatives were above the LOD (Table 2). MHINCH was the only measured metabolite with <50% above LOD and thus was not examined in preterm birth models. Urinary metabolite levels generally increased across pregnancy for MEP, MBP, MBzP, MiBP, and MCNP and decreased across pregnancy for MCPP, MCOP, and MHINCH. Levels of ΣDEHP metabolites were similar in magnitude across study visits.

In adjusted models, we observed associations between T3 urinary phthalate metabolite concentrations and preterm birth, but no associations with concentrations measured at T1 or T2 (Table 3). An ln-unit increase in ΣDEHP levels at T3 were associated with a 44% increased odds of overall preterm birth (OR: 1.44 [95% CI: 1.06, 1.95]). T3 levels of MBP, MiBP, and MCNP were all associated with non-significant increases in odds of overall preterm birth as well (MBP: 1.17 [95% CI: 0.88, 1.55]; MiBP: 1.17 [95% CI: 0.88, 1.55]; MCNP: 1.13 [95% CI: 0.88, 1.45]). There were no statistically significant associations between phthalate metabolite pregnancy averages and overall preterm birth, though averages across pregnancy for MBP and ΣDEHP showed suggestive associations (MBP: 1.26 [95% CI: 0.90, 1.76]; ΣDEHP: 1.33 [95% CI: 0.91, 1.94]). Results from models that included study center as well as crude models were similar (Supplemental Tables 1 and 2, respectively). Results were also similar in models where covariates were not imputed (Supplemental Table 3).

Associations between phthalate concentrations and spontaneous preterm birth were similar in magnitude compared to overall preterm birth but were less precise, likely due fewer cases (n=71 overall preterm births vs. 50 spontaneous preterm births for models of pregnancy averages). T1 levels of MBP were associated with a 45% increased odds of spontaneous

preterm birth (OR: 1.45 [95% CI: 1.01, 2.10]) and MCOP was also associated with elevated odds (OR: 1.48 [95% CI: 1.09, 2.01]). There were no associations between T2 phthalate levels and spontaneous preterm birth. T3 levels of ΣDEHP, MIBP, and MCNP were associated with increased odds of spontaneous preterm birth: (ΣDEHP: 1.47 [95% CI: 1.04, 2.08]; MiBP: 1.22 [95% CI: 0.89, 1.68]; MCNP: 1.24 [95% CI: 0.94, 1.63]). Though there were no metabolites that reached statistical significance using pregnancy averages, MBP, MCNP, and MCOP were associated with elevated odds of spontaneous preterm birth (MBP: 1.47 [95% CI: 0.99, 2.17]; MCOP: 1.21 (95% CI: 0.91, 1.67); MCNP: 1.20 [95% CI: 0.87, 1.65]).

Because we observed the strongest associations between T3 phthalate and preterm birth, we examined effect modification by SLE in pregnancy in T3 models. Among women with T3 phthalate metabolite measurements, a total of 710 women provided information about SLE experienced at any time point during pregnancy: 281 women reported at least one SLE in pregnancy (n=24 preterm) and 429 reported no SLE in pregnancy (n=34 preterm; Figure 1). There were no differences in urinary phthalate metabolite concentrations at T3 between individuals in the two groups (Supplemental Table 4). SLE in pregnancy were also not associated with preterm birth in crude or adjusted models (Supplemental Table 5). In general, OR for the associations between phthalate metabolites and PTB were higher among women who experienced SLE in pregnancy compared to those who did not (Figure 2; Supplemental Table 6). Tests for interaction indicated significant differences for MCNP (p=0.01) and, marginally, for ΣDEHP (p=0.07). For ΣDEHP, women who experienced SLE had an elevated OR of preterm (2.09, 95% CI: 1.29, 3.37) whereas the association was null among women who did not experience SLE (OR: 1.04, 95% CI: 0.66, 1.63). The associations for MCNP were similar, where OR were elevated among women who experienced SLE (1.72, 95% CI: 1.16, 2.56) but null among women who did not (0.76, 95% CI: 0.51, 1.15).

Discussion

A growing body of evidence supports an association between maternal urinary phthalate metabolites in pregnancy and preterm birth (Ferguson et al. 2014a; Ferguson et al. 2014b; Latini et al. 2003; Meeker et al. 2009; Weinberger et al. 2014; Whyatt et al. 2009). Consistent with this literature, in the TIDES population we observed higher odds of preterm birth in association with ΣDEHP concentrations measured in the third trimester of pregnancy. MBP levels averaged over pregnancy were also associated with increased odds of preterm birth, with an effect estimate very similar to what we previously observed in the LIFECODES birth cohort, a study population from Boston (OR=1.26 in TIDES; OR=1.27 in LIFECODES]). Further, in TIDES, we find stronger associations between ΣDEHP and MCNP and preterm birth among women reporting stressful life events.

Findings from studies of phthalates and preterm birth or gestational age at delivery are not completely consistent (Adibi et al. 2009; Casas et al. 2015; Huang et al. 2018; Polanska et al. 2016; Shoaff et al. 2016; Suzuki et al. 2010; Watkins et al. 2016; Wolff et al. 2008). However, some study design and exposure characteristics are similar in those studies that have reported an association. Most notably, very few studies have a sufficient number of

preterm births to have the power to examine these associations. TIDES is one of the largest studies to address this question. Sample sizes for other studies range from 68-404, with between 2-32 cases of preterm birth where reported (Adibi et al. 2009; Casas et al. 2015; Huang et al. 2018; Meeker et al. 2009; Polanska et al. 2016; Shoaff et al. 2016; Suzuki et al. 2010; Watkins et al. 2016; Weinberger et al. 2014; Whyatt et al. 2009; Wolff et al. 2008).

In the LIFECODES birth cohort, utilizing a case-control design with the largest number of preterm births (n=130), the findings were similar to those from the current study in several ways. First, the specific phthalate metabolites associated with preterm birth are consistent between the two studies. In TIDES, the phthalate metabolites with the highest OR for overall preterm birth were ΣDEHP and MBP, which was mirrored in LIFECODES (Ferguson et al. 2014b). Second, focusing on windows of vulnerability to exposure, we show here in TIDES that associations between ΣDEHP and preterm birth were greater in magnitude with metabolites analyzed in the third trimester (OR=1.44) compared to the first trimester (OR=1.06). This was also similar in LIFECODES, although the trend was clearer among spontaneous preterm births (Ferguson et al. 2014a). Late pregnancy exposures to phthalates may be the most relevant for spontaneous preterm birth due to upregulation of inflammatory events that play a role in the initiation of parturition (Ferguson et al. 2014a).

In the present study, as well as in LIFECODES, we examined the association between urinary phthalate metabolites and preterm birth when we restricted to preterm births that had a spontaneous presentation at delivery. Spontaneous preterm birth is more likely to arise through inflammation and oxidative stress in pregnancy (McElrath et al. 2008), which are the mechanisms that we hypothesize mediate the relationship between exposure and preterm birth (Ferguson et al. 2016). Examining spontaneous preterm birth thus allows us to examine cases arising through a similar mechanism, rather than focusing on cutoffs based on gestational age at delivery which, though differentially associated with adverse health events in childhood, are not necessarily homogenous based on the underlying etiology. We did not observe the same increase in OR for the phthalate-preterm association when we reduced our preterm cases to spontaneous preterm births only, as we observed in LIFECODES. In fact, we observed that effect estimates at T1 were stronger among spontaneous preterm births, which is contrary to our expectations and our previous work. However, this may be attributed to the relatively small number of spontaneous preterm births available for the present analysis.

Few studies have examined environmental chemicals and psychosocial stress simultaneously (Lewis et al. 2011), and none has examined interactions of these in the etiology of preterm birth. However, studies of other outcomes support our findings of a joint impact of these exposures. Previously in the TIDES population we observed that the association between urinary phthalate metabolites and anogenital distance in male infants was modified by maternal SLE (Barrett et al. 2016). There is also evidence that prenatal stress modifies the association between other environmental chemical exposures in pregnancy, including heavy metals and air pollutants, and childhood neurodevelopmental as well as respiratory outcomes (Cowell et al. 2015; Cowell and Wright 2017; y Ortiz et al. 2017).

We utilized the sum of the number of stressful life events occurring across the course of pregnancy as an indicator of exposure to psychosocial stressors during gestation. While providing a measure of cumulative exposure, this approach omits information on timing of exposure to stress. We chose to create a summary measure across pregnancy, instead of examining stressful life events by trimester, because: 1) it is likely that a single stressful event (e.g., family death) in one trimester would also cause stress in other trimesters (e.g., family member sickness prior to death or grief subsequent to death); 2) to achieve a larger sample size; and 3) for consistency with our previous work (Barrett et al. 2014). However, additional information on timing of stress exposures in pregnancy could reduce exposure misclassification. Additionally, stressful life events capture only one dimension of stress. Psychosocial stress is a complex and dynamic state that is the consequence of not just stressful life events, but a person's perception of stress, their ability to buffer stress with social support, and the cumulative stress that person experiences across her lifecourse (Bush et al. 2017). This research question should be examined with specific attention to timing of stress exposure and a richer parameterization of stress future work.

We hypothesized that oxidative stress, which we showed as a partial mediator of the phthalate-preterm association in previous work from the LIFECODES study (Ferguson et al. 2016), would be a shared mechanism of action for both phthalate and stress exposures, and would explain the observed interaction. However, in this study population and in a prospective cohort of pregnant women in Puerto Rico, we did not observe any associations between SLE or other stress parameterizations in pregnancy and oxidative stress biomarkers (Eick et al. 2018; Eick et al. [epub ahead of print]). Other possibilities could include epigenetic mechanisms or endocrine disruption. Exposure to phthalates as well as stress in pregnancy have been associated with epigenetic changes in the placenta which could have an impact on timing of delivery (Burris et al. 2016; Cao-Lei et al. 2016; LaRocca et al. 2014; Zhao et al. 2015). Regulation of endocrine function is also key to the maintenance of pregnancy (Wadhwa et al. 2001; Wadhwa et al. 2004). Stress is commonly understood to increase levels of cortisol and consequently corticotropin-releasing hormone, which precipitates parturition (Lockwood 1999). There also evidence that phthalate exposure could cause increases in these hormones (Kim et al. 2018; Wang et al. 2016). In a previous chemical-by-non-chemical exposure study, Wright et al. observed that mercury was associated with changes in cortisol levels in a pregnant population, but only when women were simultaneously exposed to psychosocial stress (Schreier et al. 2015). Of course, the mechanisms do not necessarily need to overlap for an interaction to be real. Multiple hits (e.g., hormonal and inflammatory) could lead to the observed joint impact. The biological consequences of phthalate and stress interactions in pregnancy should be explored in future human studies.

Our study had several limitations. First, despite a large sample size, the number of preterm births was small, especially for examining interaction with SLE. Second, our assessment of psychosocial stress was limited, as mentioned above, by lack of information on timing of stress during pregnancy or information on how the participant perceived the stressful life events encountered. Third, we did not have full measurement of urinary phthalate metabolites in samples collected at T2 (i.e., 2nd trimester). Thus, lack of association during this window should be interpreted with caution. Fourth, we used multiple laboratories to

measure urinary phthalate metabolites, which may have introduced measurement error. Fifth, we had multiple comparisons, which may have resulted in some chance findings. Lastly, because our population was primarily white and well-educated, our findings may not be generalizable to populations that experience higher levels or different types of psychological stressors.

The strengths of our study included our assessment of phthalate exposure at multiple time points during pregnancy, our ability to examine SLE across pregnancy, and our large, prospective study design.

Conclusion

Improving understanding of the environmental contribution to preterm birth has the potential for substantial public health impact. This study supports existing evidence of an association between maternal exposure to phthalates in pregnancy and preterm birth. It also highlights the importance of co-exposures, such as psychosocial stressors occurring during gestation, in modifying this association. Women with greater exposure to stress in pregnancy may be more vulnerable to adverse effects of phthalates than others. Additional research to understand the joint impacts of chemical as well as non-chemical exposures is necessary in order to advance the state of the science on how the environment influences health in pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This research was supported in part by the Intramural Research Program of the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH) (ZIAES103313) and by the following NIEHS, NIH, grants: R01ES016863, R01ES025169, P30ES023515, R01ES016863-02S4, and P30 ES005022. We thank Antonia Calafat (Centers for Disease Control) as well as the laboratory at the University of Washington for urinary phthalate metabolite analyses. Finally, we gratefully acknowledge the study coordinators, Garry Alcedo, Sarah Caveglia, Alana Cordeiro, and Stacey Moe, as well as the study's medical record abstractors: Sabrina Bedell, Ashley Carter, Sarah Caveglia, Andrea Hart, Savannah King, Ellen Laschansky, Ashley Santilli, and Simar Singh.

References

Adibi JJ, Hauser R, Williams PL, Whyatt RM, Calafat AM, Nelson H, et al. 2009 Maternal urinary metabolites of di-(2-ethylhexyl) phthalate in relation to the timing of labor in a us multicenter pregnancy cohort study. American Journal of Epidemiology 169:1015–1024. [PubMed: 19251754]

Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. 2004 Urinary creatinine concentrations in the us population: Implications for urinary biologic monitoring measurements. Environmental health perspectives 113:192–200.

Barrett ES, Sathyanarayana S, Janssen S, Redmon JB, Nguyen RH, Kobrosly R, et al. 2014 Environmental health attitudes and behaviors: Findings from a large pregnancy cohort study. European journal of obstetrics, gynecology, and reproductive biology 176:119–125.

Barrett ES, Parlett LE, Sathyanarayana S, Redmon JB, Nguyen RH, Swan SH. 2016 Prenatal stress as a modifier of associations between phthalate exposure and reproductive development: Results from a multicentre pregnancy cohort study. Paediatric and perinatal epidemiology 30:105–114. [PubMed: 26576028]

Boeniger MF, Lowry LK, Rosenberg J. 1993 Interpretation of urine results used to assess chemical exposure with emphasis on creatinine adjustments: A review. American Industrial Hygiene Association journal 54:615–627. [PubMed: 8237794]

US Census Bureau. 2010 United states quickfacts. Available: https://www.census.gov/quickfacts/fact/table/US/PST045218 [accessed 08/01/19].

Burris HH, Baccarelli AA, Wright RO, Wright RJ. 2016 Epigenetics: Linking social and environmental exposures to preterm birth. Pediatric Research 79:136. [PubMed: 26460521]

Bush NR, Jones-Mason K, Coccia M, Caron Z, Alkon A, Thomas M, et al. 2017 Effects of pre-and postnatal maternal stress on infant temperament and autonomic nervous system reactivity and regulation in a diverse, low-income population. Development and psychopathology 29:1553–1571. [PubMed: 29162167]

Cao-Lei L, Laplante DP, King S. 2016 Prenatal maternal stress and epigenetics: Review of the human research. Current Molecular Biology Reports 2:16–25.

Casas M, Valvi D, Ballesteros-Gomez A, Gascon M, Fernández MF, Garcia-Esteban R, et al. 2015 Exposure to bisphenol a and phthalates during pregnancy and ultrasound measures of fetal growth in the inma-sabadell cohort. Environmental Health Perspectives 124:521–528. [PubMed: 26196298]

Chen E, Schreier HM, Strunk RC, Brauer M. 2008 Chronic traffic-related air pollution and stress interact to predict biologic and clinical outcomes in asthma. Environmental Health Perspectives 116:970–975. [PubMed: 18629323]

Cowell WJ, Bellinger DC, Coull BA, Gennings C, Wright RO, Wright RJ. 2015 Associations between prenatal exposure to black carbon and memory domains in urban children: Modification by sex and prenatal stress. PLoS One 10:e0142492. [PubMed: 26544967]

Cowell WJ, Wright RJ. 2017 Sex-specific effects of combined exposure to chemical and non-chemical stressors on neuroendocrine development: A review of recent findings and putative mechanisms. Current environmental health reports 4:415–425. [PubMed: 29027649]

Dohrenwend BS, Askenasy AR, Krasnoff L, Dohrenwend BP. 1978 Exemplification of a method for scaling life events: The peri life events scale. Journal of health and social behavior:205–229. [PubMed: 681735]

Eick SM, Barrett ES, van ‘t Erve TJ, Nguyen RH, Bush NR, Milne G, et al. 2018 Association between prenatal psychological stress and oxidative stress during pregnancy. Paediatric and perinatal epidemiology.

Eick SM, Meeker JD, Swartzendruber A, Rios-McConnell R, Shen Y, Milne G, et al. [epub ahead of print]. Associations between psychosocial stress and oxidative stress during pregnancy in northern puerto rico. Free Radical Biology and Medicine.

Ferguson KK, McElrath TF, Ko Y-A, Mukherjee B, Meeker JD. 2014a Variability in urinary phthalate metabolite levels across pregnancy and sensitive windows of exposure for the risk of preterm birth. Environment International 70:118–124. [PubMed: 24934852]

Ferguson KK, McElrath TF, Meeker JD. 2014b Environmental phthalate exposure and preterm birth. JAMA pediatrics 168:61–68. [PubMed: 24247736]

Ferguson KK, Chen Y-H, VanderWeele TJ, McElrath TF, Meeker JD, Mukherjee B. 2016 Mediation of the relationship between maternal phthalate exposure and preterm birth by oxidative stress with repeated measurements across pregnancy. Environmental Health Perspectives 125:488–494. [PubMed: 27352406]

Hobel CJ. 2004 Stress and preterm birth. Clinical Obstetrics and Gynecology 47:856–880. [PubMed: 15596939]

Holmes TH, Rahe RH. 1967 The social readjustment rating scale. Journal of psychosomatic research.

Hornung RW, Reed LD. 1990 Estimation of average concentration in the presence of nondetectable values. Applied Occupational and Environmental Hygiene 5:46–51.

Huang L-L, Zhou B, Ai S-H, Yang P, Chen Y-J, Liu C, et al. 2018 Prenatal phthalate exposure, birth outcomes and DNA methylation of alu and line-1 repetitive elements: A pilot study in china. Chemosphere 206:759–765. [PubMed: 29793068]

Kim JH, Lee J, Moon H-B, Park J, Choi K, Kim SK, et al. 2018 Association of phthalate exposures with urinary free cortisol and 8-hydroxy-2′-deoxyguanosine in early childhood. Science of the Total Environment 627:506–513. [PubMed: 29426173]

LaRocca J, Binder AM, McElrath TF, Michels KB. 2014 The impact of first trimester phthalate and phenol exposure on igf2/h19 genomic imprinting and birth outcomes. Environmental research 133:396–406. [PubMed: 24972507]

Latini G, De Felice C, Presta G, Del Vecchio A, Paris I, Ruggieri F, et al. 2003 In utero exposure to di-(2-ethylhexyl) phthalate and duration of human pregnancy. Environmental Health Perspectives 111:1783. [PubMed: 14594632]

Lewis AS, Sax SN, Wason SC, Campleman SL. 2011 Non-chemical stressors and cumulative risk assessment: An overview of current initiatives and potential air pollutant interactions. International Journal of Environmental Research and Public Health 8:2020–2073. [PubMed: 21776216]

Lockwood CJ. 1999 Stress-associated preterm delivery: The role of corticotropin-releasing hormone. American journal of obstetrics and gynecology 180:S264–S266. [PubMed: 9914630]

Martino-Andrade A, Liu F, Sathyanarayana S, Barrett E, Redmon J, Nguyen R, et al. 2016 Timing of prenatal phthalate exposure in relation to genital endpoints in male newborns. Andrology 4:585–593. [PubMed: 27062102]

McElrath TF, Hecht JL, Dammann O, Boggess K, Onderdonk A, Markenson G, et al. 2008 Pregnancy disorders that lead to delivery before the 28th week of gestation: An epidemiologic approach to classification. American journal of epidemiology 168:980–989. [PubMed: 18756014]

Meeker JD, Hu H, Cantonwine DE, Lamadrid-Figueroa H, Calafat AM, Ettinger AS, et al. 2009 Urinary phthalate metabolites in relation to preterm birth in mexico city. Environmental Health Perspectives 117:1587. [PubMed: 20019910]

Obel C, Hedegaard M, Henriksen TB, Secher NJ, Olsen J, Levine S. 2005 Stress and salivary cortisol during pregnancy. Psychoneuroendocrinology 30:647–656. [PubMed: 15854781]

Polanska K, Ligocka D, Sobala W, Hanke W. 2016 Effect of environmental phthalate exposure on pregnancy duration and birth outcomes. International journal of occupational medicine and environmental health.

Rosen EM, van't Erve TJ, Boss J, Sathyanarayana S, Barrett ES, Nguyen RH, et al. 2019 Urinary oxidative stress biomarkers and accelerated time to spontaneous delivery. Free Radical Biology and Medicine 130:419–425. [PubMed: 30445128]

Schreier HM, Hsu H-H, Amarasiriwardena C, Coull BA, Schnaas L, Téllez-Rojo MM, et al. 2015 Mercury and psychosocial stress exposure interact to predict maternal diurnal cortisol during pregnancy. Environmental Health 14:28. [PubMed: 25889585]

Shoaff JR, Romano ME, Yolton K, Lanphear BP, Calafat AM, Braun JM. 2016 Prenatal phthalate exposure and infant size at birth and gestational duration. Environmental Research 150:52–58. [PubMed: 27236572]

Silva MJ, Samandar E, Preau JL Jr., Reidy JA, Needham LL, Calafat AM. 2007 Quantification of 22 phthalate metabolites in human urine. Journal of chromatography B, Analytical technologies in the biomedical and life sciences 860:106–112. [PubMed: 17997365]

Suzuki Y, Niwa M, Yoshinaga J, Mizumoto Y, Serizawa S, Shiraishi H. 2010 Prenatal exposure to phthalate esters and pahs and birth outcomes. Environment International 36:699–704. [PubMed: 20605637]

Swan S, Sathyanarayana S, Barrett E, Janssen S, Liu F, Nguyen R, et al. 2015 First trimester phthalate exposure and anogenital distance in newborns. Human Reproduction 30:963–972. [PubMed: 25697839]

Vesterinen HM, Morello-Frosch R, Sen S, Zeise L, Woodruff TJ. 2017 Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. PLoS One 12:e0176331. [PubMed: 28700705]

Wadhwa PD, Culhane JF, Rauh V, Barve SS. 2001 Stress and preterm birth: Neuroendocrine, immune/inflammatory, and vascular mechanisms. Maternal and child health journal 5:119–125. [PubMed: 11573837]

Wadhwa PD, Garite TJ, Porto M, Glynn L, Chicz-DeMet A, Dunkel-Schetter C, et al. 2004 Placental corticotropin-releasing hormone (crh), spontaneous preterm birth, and fetal growth restriction: A

prospective investigation. American journal of obstetrics and gynecology 191:1063–1069. [PubMed: 15507922]

Wang XK, Agarwal M, Parobchak N, Rosen A, Vetrano AM, Srinivasan A, et al. 2016 Mono-(2-ethylhexyl) phthalate promotes pro-labor gene expression in the human placenta. PloS one 11:e0147013. [PubMed: 26751383]

Watkins DJ, Milewski S, Domino SE, Meeker JD, Padmanabhan V. 2016 Maternal phthalate exposure during early pregnancy and at delivery in relation to gestational age and size at birth: A preliminary analysis. Reproductive toxicology 65:59–66. [PubMed: 27352641]

Weinberger B, Vetrano AM, Archer FE, Marcella SW, Buckley B, Wartenberg D, et al. 2014 Effects of maternal exposure to phthalates and bisphenol a during pregnancy on gestational age. Journal of Maternal-Fetal Neonatal Medicine 27:323–327. [PubMed: 23795657]

Whyatt RM, Adibi JJ, Calafat AM, Camann DE, Rauh V, Bhat HK, et al. 2009 Prenatal di (2-ethylhexyl) phthalate exposure and length of gestation among an inner-city cohort. Pediatrics 124:e1213–e1220. [PubMed: 19948620]

Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, et al. 2008 Prenatal phenol and phthalate exposures and birth outcomes. Environ Health Perspect 116:1092–1097. [PubMed: 18709157]

Woodruff TJ, Zota AR, Schwartz JM. 2011 Environmental chemicals in pregnant women in the united states: Nhanes 2003–2004. Environmental Health Perspectives 119:878–885. [PubMed: 21233055]

y Ortiz MT, Téllez-Rojo MM, Trejo-Valdivia B, Schnaas L, Osorio-Valencia E, Coull B, et al. 2017 Maternal stress modifies the effect of exposure to lead during pregnancy and 24-month old children's neurodevelopment. Environment International 98:191–197. [PubMed: 27865525]

Zhao Y, Shi Hj, Xie Cm, Chen J, Laue H, Zhang Yh. 2015 Prenatal phthalate exposure, infant growth, and global DNA methylation of human placenta. Environmental and molecular mutagenesis 56:286–292. [PubMed: 25327576]

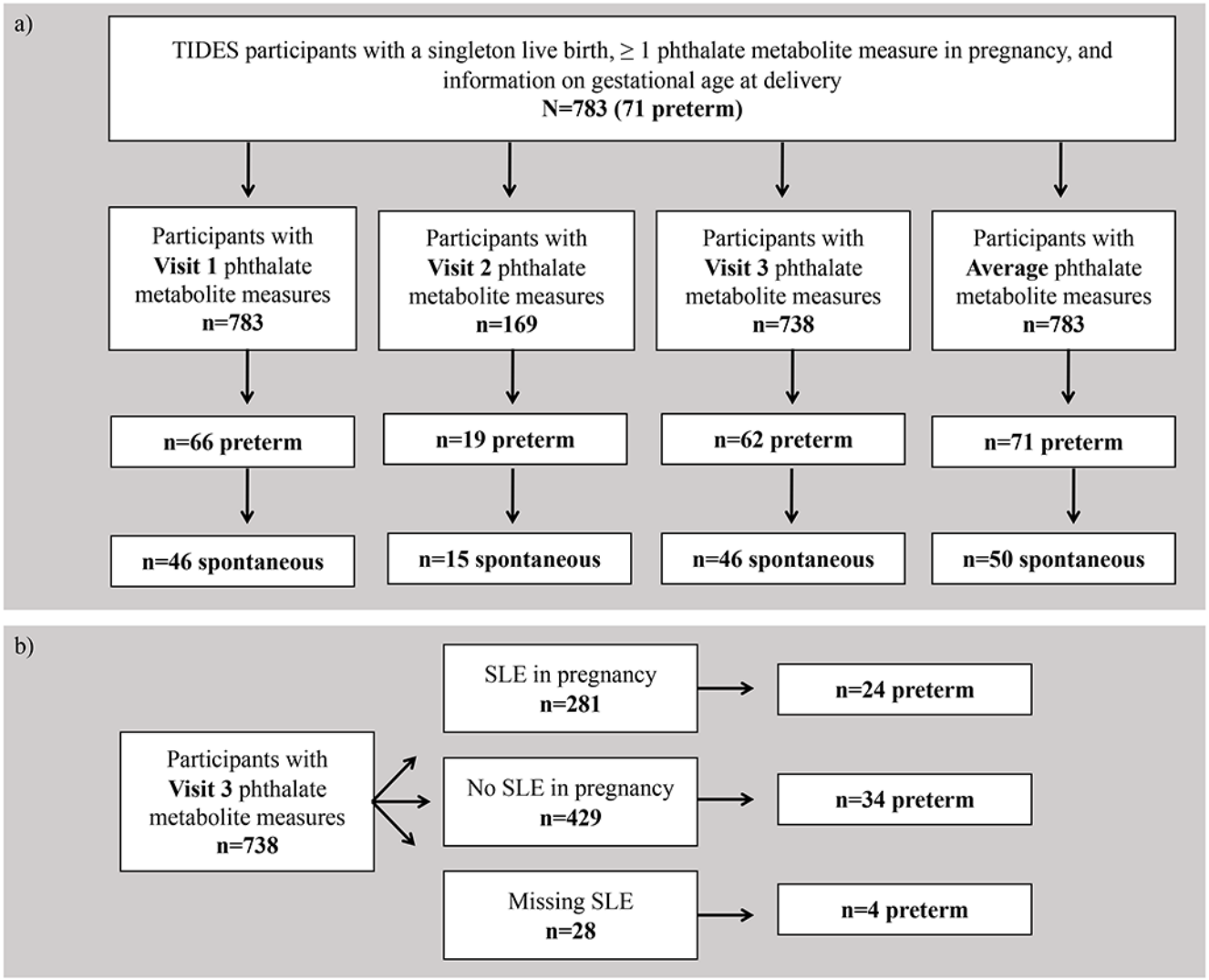

Figure 1.

TIDES participants included in the analysis of a) phthalate exposure in pregnancy and preterm and spontaneous preterm birth; and b) the joint effect of phthalate and stressful life event exposures in pregnancy and preterm birth.

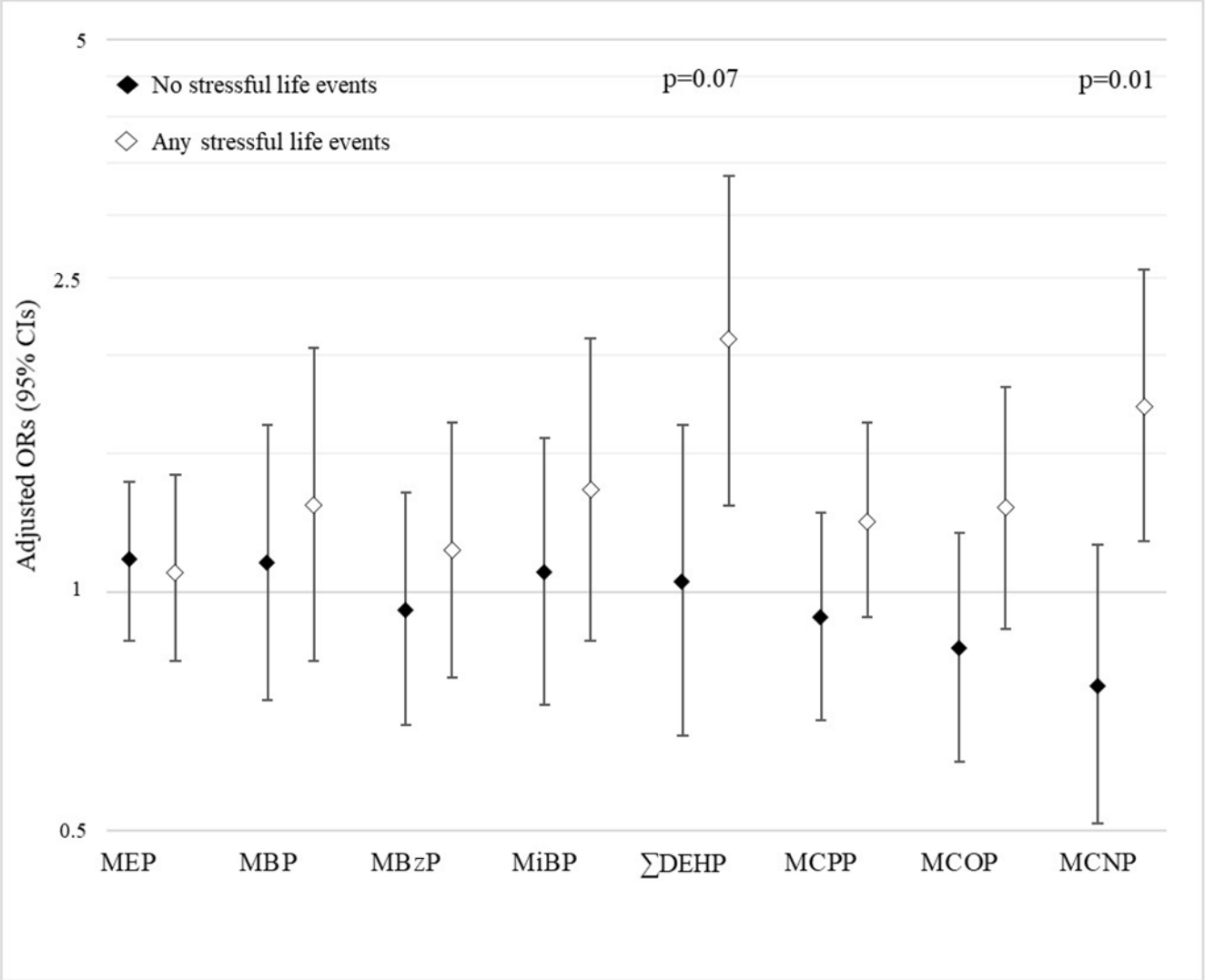

Figure 2.

Adjusted[a] odds ratios (95% confidence interval) for overall preterm birth with an ln-unit increase in T3 urinary phthalate metabolites in models stratified by maternal experience of stressful life events during pregnancy (none vs. any).

[a]Models adjusted for race (white, black, other), maternal age (continuous), pre-pregnancy BMI (continuous), education (nominal), specific gravity, and gestational age at sample collection. No stressful life events: n=34 preterm, 395 term. Any stressful life events: n=24 preterm, 257 term. Note: Results include imputed data.

Table 1.

Characteristics of the study population (n=783): N (%).

		Overall	Preterm	Term
Maternal age (n_{miss}=99)	<25 years	94 (13.7)	10 (17.5)	84 (13.4)
	25-29 years	148 (21.6)	14 (24.6)	134 (21.4)
	30-34 years	241 (35.2)	17 (29.8)	224 (35.7)
	≥35 years	201 (29.4)	16 (28.1)	185 (29.5)
Pre-pregnancy BMI (n_{miss}=11)	<18.5 kg/m^2	16 (2.07)	0 (0)	16 (2.28)
	18.5 – 24.99 kg/m^2	435 (56.3)	31 (44.9)	404 (57.5)
	25 – 29.99 kg/m^2	169 (21.9)	18 (26.1)	151 (21.5)
	≥30 kg/m^2	152 (19.7)	20 (29.0)	132 (18.8)
Race (n_{miss}=2)	White	534 (68.4)	49 (69.0)	485 (68.3)
	Black	102 (13.1)	12 (16.9)	90 (12.7)
	Other	145 (18.6)	10 (14.1)	135 (19.0)
Hispanic/Latino (n_{miss}=11)	Yes	68 (8.81)	6 (8.70)	62 (8.82)
	No	704 (91.2)	63 (91.3)	641 (91.2)
Smoking at 3rd trimester (n_{miss}=69)	None	678 (95.0)	62 (96.9)	616 (94.8)
	Any	36 (5.04)	2 (3.13)	34 (5.23)
Alcohol at 3rd trimester (n_{miss}=72)	None	650 (91.4)	60 (93.8)	590 (91.2)
	Any	61 (8.58)	4 (6.25)	57 (8.81)
Marital status (n_{miss}=4)	Married/living as married	647 (83.1)	56 (80.0)	591 (83.4)
	Single	132 (16.9)	14 (20.0)	118 (16.6)
Education (n_{miss}=9)	High school or less	109 (14.1)	13 (18.6)	96 (13.6)
	Any college/tech school	336 (43.4)	37 (52.9)	299 (42.5)
	Any graduate work	329 (42.5)	20 (28.6)	309 (43.9)
Income (n_{miss}=29)	<25k	182 (24.1)	24 (34.8)	158 (23.1)
	25-65k	155 (20.6)	11 (15.9)	144 (21.0)
	>65k	417 (55.3)	34 (49.3)	383 (55.9)
Infant sex	Male	384 (49.0)	35 (49.3)	349 (49.0)
	Female	399 (51.0)	36 (50.7)	363 (51.0)
Study center	UCSF	187 (23.9)	14 (19.7)	173 (24.3)
	UMN	210 (26.8)	21 (29.6)	189 (26.5)
	URMC	223 (28.5)	25 (35.2)	198 (27.8)
	UW	163 (20.8)	11 (15.5)	152 (21.4)

Abbreviations: BMI, body mass index; UCSF, University of California San Francisco; UMN, University of Minnesota; URMC, University of Rochester Medical College; UW, University of Washington.

Table 2.

Percentiles of urinary sg-corrected phthalate metabolites by study visit: μg/L.

	T1			T2			T3		
	N	**% <LOD**	**50th (25th, 75th)**	**N**	**% <LOD**	**50th (25th, 75th)**	**N**	**% <LOD**	**50th (25th, 75th)**
MEP	754	0.9	31.3 (13.5, 81.9)	169	0.6	33.7 (14.5, 79.5)	738	1.2	36.2 (14.2, 107)
MBP	754	7.6	8.44 (4.83, 14.0)	169	5.9	7.98 (3.54, 14.9)	738	2.3	10.8 (5.32, 17.4)
MBzP	754	13	4.00 (2.05, 8.56)	169	4.7	3.29 (1.81, 8.34)	738	4.7	4.82 (2.22, 11.5)
MiBP	754	3.1	5.11 (2.90, 9.01)	169	1.8	5.40 (3.14, 9.71)	738	3.7	7.14 (4.14, 12.4)
ΣDEHP[a]	754	NA	0.09 (0.05, 0.14)	169	NA	0.08 (0.05, 0.14)	738	NA	0.09 (0.06, 0.14)
MCPP	754	25	2.05 (1.03, 4.83)	169	8.9	1.74 (0.97, 3.87)	738	11.8	1.89 (0.97, 4.59)
MCOP	464	0	15.2 (8.16, 44.2)	169	0	14.7 (6.99, 30.8)	738	0	13.5 (6.79, 35.3)
MCNP	464	4.1	2.18 (1.45, 4.38)	169	5.3	2.03 (1.36, 4.08)	738	1.8	2.41 (1.45, 4.35)
MHINCH	464	89	0.37 (0.23, 0.68)	169	92	0.37 (0.23, 0.68)	738	85	0.31 (0.18, 0.55)

[a]Summed metabolites of di-2-ethylhexyl phthalate presented in nmol/L.

Table 3.

Adjusted[a] odds ratios (95% confidence intervals) for overall preterm and spontaneous preterm birth with an ln-unit increase in sg-corrected urinary phthalate metabolites.

Preterm birth	**T1**	**T2**	**T3**	**Pregnancy average**
N (term, preterm)	**687, 66**	**150, 19**	**676, 62**	**712, 71**
MEP	1.07 (0.89, 1.29)	1.10 (0.61, 1.37)	1.08 (0.91, 1.28)	1.11 (0.90, 1.37)
MBP	1.19 (0.87, 1.62)	0.93 (0.54, 1.59)	1.17 (0.88, 1.55)	1.26 (0.90, 1.76)
MBzP	0.95 (0.73, 1.22)	0.78 (0.47, 1.30)	1.06 (0.84, 1.34)	1.01 (0.78, 1.32)
MiBP	0.90 (0.65, 1.24)	1.05 (0.56, 1.98)	1.17 (0.88, 1.55)	1.04 (0.74, 1.44)
ΣDEHP	1.06 (0.78, 1.43)	0.93 (0.51, 1.71)	1.44 (1.06, 1.95)	1.33 (0.91, 1.94)
MCPP	1.00 (0.82, 1.21)	0.79 (0.51, 1.23)	1.10 (0.90, 1.33)	1.04 (0.82, 1.33)
MCOP[b]	1.19 (0.91, 1.55)	1.06 (0.70, 1.62)	1.07 (0.85, 1.34)	1.06 (0.84, 1.35)
MCNP[b]	1.06 (0.77, 1.46)	1.19 (0.75, 1.90)	1.13 (0.88, 1.45)	1.02 (0.76, 1.37)
Spontaneous preterm birth				
N (term, spontaneous preterm)	**687, 46**	**150, 15**	**676, 46**	**712, 50**
MEP	1.12 (0.90, 1.39)	0.85 (0.54, 1.35)	1.08 (0.89, 1.30)	1.13 (0.89, 1.44)
MBP	1.45 (1.01, 2.10)	0.87 (0.48, 1.58)	1.14 (0.82, 1.60)	1.47 (0.99, 2.17)
MBzP	1.01 (0.74, 1.37)	0.86 (0.49, 1.49)	1.08 (0.83, 1.42)	1.05 (0.77, 1.43)
MiBP	0.95 (0.66, 1.38)	1.06 (0.52, 2.15)	1.22 (0.89, 1.68)	1.18 (0.80, 1.73)
ΣDEHP	0.99 (0.69, 1.43)	0.96 (0.51, 1.84)	1.47 (1.04, 2.08)	1.33 (0.85, 2.08)
MCPP	1.10 (0.88, 1.39)	0.75 (0.46, 1.23)	1.11 (0.89, 1.38)	1.15 (0.87, 1.51)
MCOP[b]	1.48 (1.09, 2.01)	1.13 (0.72, 1.77)	1.10 (0.86, 1.42)	1.21 (0.92, 1.58)
MCNP[b]	1.21 (0.84, 1.72)	1.24 (0.74, 2.07)	1.24 (0.94, 1.63)	1.20 (0.87, 1.65)

[a]T1-3 adjusted for race (white, black, other), maternal age (continuous), pre-pregnancy BMI (continuous), education (nominal), specific gravity, and gestational age at sample collection. Pregnancy average models adjusted for race, maternal age, pre-pregnancy BMI only.

[b]Sample sizes for MCOP and MCNP at T1: n=424 term; n=39 preterm; n=28 spontaneous preterm. Sample sizes for MCOP and MCNP averages: n=705 term; n=67 preterm; n=48 spontaneous preterm. Note: Results include imputed data.