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Urinary concentrations of phenols in association with biomarkers of oxidative stress in pregnancy: Assessment of effects independent of phthalates

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Abstract

Background: Maternal exposure to environmental phenols is common in pregnancy and has been linked to preterm birth, preeclampsia, and reduced fetal growth. One potential mechanism may be through increased maternal oxidative stress.

Objective: We examined the associations between a panel of 10 urinary phenols, including dich loro phenols, benzophenone-3, parabens, triclosan and triclocarban, and bisphenol-S, and two urinary oxidative stress biomarkers, 8-hydroxydeoxyguanosine (8-OHdG) and 8-isoprostane. All exposure and outcome biomarkers were measured at 4 time points in pregnancy.

Methods: We used repeated measures models to examine the association between repeated exposure and outcome biomarkers. Additionally, we used adaptive elastic net (AENET) to identify non-null associations accounting for the correlation structure of exposures, both for phenols and urinary phthalate metabolites that were previously associated with the oxidative stress biomarkers in our study population.

Results: In adjusted repeated measures models, we observed that dichlorophenols, benzophenone-3, triclosan, and some parabens were associated with increases in both oxidative

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Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.104903.

stress biomarkers. The greatest effect estimates were observed for 2,5-dichlorophenol; an interquartile range (IQR) increase in this compound was associated with a 15.2% (95% confidence interval [CI] = 11.0, 19.6) increase in 8-OHdG and a 16.7% (95% CI = 9.66, 24.2) increase in 8-isoprostane. Bisphenol-S detection was associated with a clear increase in 8-isoprostane (18.5%, 95% CI = 7.68, 30.5) but a more modest increase in 8-OHdG (6.18%, 95% CI = −0.27, 13.1). However, AENET models did not consistently select any of the phenols as predictors of 8-OHdG or 8-isoprostane when phthalate metabolites were included in the model.

Conclusion: Overall, urinary phenols were associated with increases in biomarkers of oxidative stress in pregnancy but either to a lesser extent, or due to correlation with, urinary phthalate metabolites.

Keywords

Oxidative stress; Phenols; Parabens; Phthalates; Pregnancy; Mixtures

1. Introduction

Phenols are a class of chemicals that are produced naturally by plants and microorganisms but are also industrially synthesized and found in many commonly used consumer goods. Industrially synthesized phenols include, but are not limited to: 1) dichlorophenols, which are primarily used in pesticides; 2) bisphenols, which are used in plastics as well as tin can linings and thermal receipt papers; 3) parabens, which are used as anti-microbials in various personal care products; and also 4) triclosan which is used in hand soaps and oral care products. The prevalence of exposure to these compounds in the general US population is high (Centers for Disease Control and Prevention, 2009). Previous studies suggest that maternal exposure to some phenols in pregnancy is associated with adverse birth outcomes, including reduced fetal growth (Philippat et al., 2014; Philippat et al., 2011; Wolff et al., 2008). However, the mechanism involved remains in question. Some of these chemicals have suspected endocrine disrupting activity, but the evidence in human populations is sparse (Darbre and Harvey, 2008; Kim and Choi, 2014; Witorsch and Thomas, 2010). An alternative and plausible pathway may be through generation of either systemic or utero-placental specific oxidative stress.

Excessive production of reactive oxygen species (ROS) within the human body can cause damage to lipids, DNA, and proteins (Dalle-Donne et al., 2006). Too much damage can result in tissue injury or other downstream consequences that could contribute to adverse pregnancy outcomes, such as preterm birth and preeclampsia (Hubel, 1999; Menon, 2014). Elevated levels of lipid damage markers, such as 8-iso-prostaglandin $F_{2\alpha}$ (8-isoprostane) and DNA damage markers, such as 8-hydroxydeoxyguanosine (8-OHdG) have been associated with both adverse pregnancy and childhood health outcomes in human studies (Ferguson et al., 2017; Peter Stein et al., 2008).

Environmental phenols may increase ROS generation, leading to elevated levels of these downstream markers, through several mechanisms. For example, 2,4-dichlorophenol may reduce antioxidant enzyme activity (Zhang et al., 2004). While a number of studies have examined the relationship between bisphenols and triclosan and oxidative stress, few

have examined other environmental phenols or have investigated this question in pregnant populations (Asimakopoulos et al., 2016; Wang et al., 2019; Yang et al., 2009; Watkins et al., 2015; Iyer et al., 2018; Kim and Hong, 2017).

Our previous preliminary analysis of pregnant women in Puerto Rico ($N = 52$) demonstrated that some phenols, particularly butyl paraben, were associated with increases in oxidative stress biomarkers including 8-OHdG and 8-isoprostane (Watkins et al., 2015). In the present study, we sought to replicate these findings in a larger pregnant population in which we measured urinary phenols as well as oxidative stress biomarkers at 4 time points during pregnancy. Furthermore, because urinary phthalate metabolites and bisphenol-A (BPA) have been previously associated with these oxidative stress biomarkers in our study population (Ferguson et al., 2014a; Ferguson et al., 2016) and have some shared exposure sources with the phenols measured in the present analysis, we sought to determine which individual chemicals among the correlated mixture were the strongest contributors to associations with each oxidative stress biomarker. To do so, we used a regularized multivariate regression method that can handle correlated exposure data, namely, the adaptive elastic net (AENET) (Zou and Zhang, 2009).

2. Methods

2.1. Study population

Pregnant women were recruited from 2006 to 2008 as part of LIF-ECODES, a large prospective birth cohort study conducted at Brigham and Women's Hospital in Boston, MA. Women were followed throughout the duration of pregnancy and provided urine samples from up to four study visits (median 10, 18, 26, 35 weeks of gestation). Demographic and behavioral characteristics were collected by questionnaire at the first study visit. This included information on maternal age, race/ethnicity, education level, health insurance provider, prepregnancy body mass index (BMI), tobacco and alcohol use in pregnancy, and information on personal and family medical history.

From the women who delivered during this time frame, we selected participants for a nested case-control study of preterm birth (Ferguson et al., 2014b). This included nearly all (130) women who delivered preterm (< 37 weeks of gestation) as well as 352 random (i.e., unmatched) participants who delivered after 37 weeks (n = 482 subjects total). Women from this subset were similar in demographic characteristics to women from the rest of the cohort recruited during this time period (Cantonwine et al., 2016). For examples, the mean age in the weighted subset was 32.7 years whereas in the overall cohort the mean age was 32.1 years, and the percent white, black, and other race/ethnicity was 59%, 16%, and 25% in our weighted subset as compared to 61%, 14%, and 25% in the overall cohort. Of the women in this subset, 481 had urine samples available from one or more visits for the analysis of urinary phenol concentrations.

2.2. Urinary biomarkers

All available urine samples ($n = 1651$) were assayed for concentrations of ten phenols and two oxidative biomarkers. Oxidative stress measurements were performed using enzyme

immunoassay (EIA) by Cayman Chemical (Ann Arbor, MI) with methods described in detail elsewhere (Ferguson et al., 2014a). Briefly, samples were pre-processed for the measurement of total 8-isoprostane levels by hydrolysis with affinity purification. Eluted sample for 8-isoprostane and unprocessed urine for 8-OHdG were diluted for EIA.

Urinary phenol concentrations were measured in previously unthawed urine samples in order to minimize potential contamination. Analysis was performed by NSF International (Ann Arbor, MI) using isotope dilution-liquid chromatography-tandem mass spectrometry with methods, also described in detail previously (Ferguson et al., 2018). Briefly, samples underwent deconjugation from glucuronidated species and online solid phase extraction prior to mass spectrometer analysis, similar to the approach utilized by the Centers for Disease Control and Prevention (National Center for Health Statistics (NCHS), n.d.). Analysis was performed using a Thermo Scientific (Waltham, MA, USA) Quantiva triple quadrupole mass spectrometer in negative ionization mode. Replicates of spiked samples were analyzed for quality control and demonstrated good intra- and inter-day accuracy and precision (Ferguson et al., 2018). The quantified phenols included: 2,4-dichlorophenol (2,4-DCP); 2,5-dichlorophenol (2,5-DCP); benzophe-none-3; butyl paraben; ethyl paraben; methyl paraben; propyl paraben; triclosan; bisphenol-S (BPS); and triclocarban. Concentrations below the limit of detection (LOD) were imputed using machine-read values where available and otherwise were replaced by the LOD divided by the square root of 2.

For the AENET analyses, we used measures of urinary phthalate metabolites and BPA analyzed by the same laboratory and at the same study visits with methods described in detail elsewhere (Ferguson et al., 2014a). Phthalate metabolites examined in the present analysis included: the molar sum of di-2-ethylhexyl phthalate metabolites (ΣDEHP); mono-benzyl phthalate (MBzP); mono-n-butyl phthalate (MBP); mono-iso-butyl phthalate (MiBP); mono-ethyl phthalate (MEP); and mono-3-carboxypropyl phthalate (MCPP).

Urinary specific gravity, an indicator of urine dilution, was measured using a digital handheld refractometer (ATAGO Company Ltd., Tokyo, Japan). To present distributions of urinary phenols and to examine correlations between phenols and phthalate metabolites, we corrected concentrations for specific gravity (Ferguson et al., 2018). For statistical models, uncorrected concentrations were used and specific gravity was included as a covariate (Barr et al., 2004).

2.3. Statistical analysis

All statistical analyses were performed in RStudio version 1.1.423. Unless specified, all analyses were performed with inverse probability weighting so that associations would be generalizable to the overall cohort and not overly represent associations observed among women who had a preterm birth.

We utilized linear mixed effect (LME) models to examine the association between repeated measures of continuous phenol and oxidative stress biomarker concentrations. All models included a random intercept for participant ID to account for correlation in measures taken at multiple time points during pregnancy. For phenols that were detected in a low proportion

of samples (> 50% below LOD), we modeled each time point as a binary variable (detect vs. non-detect) in LME models. Covariates included in adjusted models were those associated with exposure or outcome biomarkers that impacted effect estimates by > 10%. Final models were adjusted for: urinary specific gravity (continuous); gestational age at sample collection (continuous); maternal age (continuous); race (categorical; white, black, other); education level (categorical; High school or less, some college, college graduate, above); pre-pregnancy BMI (continuous); and smoking during pregnancy (yes, no).

In sensitivity analyses, we tested the robustness of our results by examining the associations among control individuals only (delivery > 37 weeks of gestation) without weights. We also tested the impact of the urine dilution adjustment approach by examining models of specific gravity-corrected phenols, without including specific gravity as a covariate. To investigate effect modification by maternal race/ethnicity as well as gestational age at sample collection, we calculated interaction terms using the method described by Buckley et al., where interaction terms between race/ethnicity (or visit) and exposure biomarker as well as each covariate were included in LME models (Buckley et al., 2017).

2.4. Adaptive elastic net (AENET)

Because exposure to phenols and phthalates exists naturally as a mixture, we used AENET to identify non-null associations with oxidative stress biomarkers from among this correlated set. AENET analyses included the urinary phthalate metabolites ΣDEHP, MBZP, MBP, MiBP, MEP, MCPP and BP A, in addition to the eight phenols that were detected in over 50% of all samples measured. To examine correlation between urinary phenols and phthalate metabolites, we calculated Spearman correlation coefficients between all specific gravity-corrected biomarkers. To determine which compounds within the mixture were contributing most to the associations with the oxidative stress biomarkers, we applied AENET (Zou and Zhang, 2009) using the *gcdnet* package in R (Yang et al., 2017). Because AENET cannot handle repeated measures in its current design, we modeled associations for each study visit (1–4) separately. Furthermore, because AENET cannot handle survey weights, and because we observed that associations were similar in cases of preterm birth compared to controls, we restricted this analysis to controls only.

We constructed the adaptive weights for the AENET using the coefficient estimates obtained from elastic net. We let the parameter for the ℓ_2 penalty (λ_2) take values from 0 to 2, in increments of 0.1. For each fixed λ_2, the function automatically computes the solutions for a fine grid of λ_1's, the ℓ_2 regularization parameter, assuming a least square loss. We selected the combination of λ_1 and λ_2 that yielded the smallest 10-fold cross-validated mean square error and used their corresponding coefficient estimates as adaptive weights. We obtained standard errors and *p*-values for the AENET coefficients by following Zou and Zhang (2009).

3. Results

The majority of women in the study population were white, privately insured, held a college degree, had a pre-pregnancy BMI under 25kg/m^2, did not smoke or drink during pregnancy, and were parous (Table 1). LODs and distributions of urinary oxidative stress and phenol

biomarkers are shown in Table 2. Both oxidative stress markers were highly detected in the study population, and most phenols were detected in over 75% of all samples measured. BPS and triclocarban detection was low (79% and 93% below the LOD, respectively). Thus, for these exposures, we created categorical variables at each study visit to indicate whether or not the compound was detected in the sample, and this binary variable was used for LME models. Urinary oxidative stress biomarker concentrations were associated with socioeconomic status (SES) in this study population, as we have presented elsewhere (Ferguson et al., 2014a). Particularly, 8-isoprostane levels were higher among women who were black and who had lower education levels, public health insurance providers, higher BMI, and who smoked during pregnancy. Patterns were similar but less pronounced for 8-OHdG. Among exposure biomarkers, urinary dichlorophenols showed a similar pattern with higher concentrations observed among lower SES groups, but patterns for other environmental phenols were less consistent (Ferguson et al., 2018).

Adjusted results from LME models demonstrated that dichlorophenols, benzophenone-3, triclosan, and some of the parabens were associated with increases in both 8-OHdG and 8-isoprostane (Table 3). Among the parabens, methyl and propyl parabens were associated with increases in both oxidative stress biomarkers with effect estimates that were similar in magnitude; however, butyl and ethyl parabens were only associated increases in 8-isoprostane (% change with interquartile range [IQR] increase for butyl paraben = 9.92, 95% confidence interval [CI] = 1.80, 18.7; % change for ethyl paraben = 12.8, 95% CI = 5.01, 21.1). BPS detection was also associated with an increase in 8-isoprostane (% change with detection of BPS = 18.5, 95% CI = 7.68, 30.5) but only modestly associated with 8-OHdG. Triclocarban detection, albeit low, was not associated with either marker.

Adjusted results were robust to sensitivity analyses where we examined models adjusting for specific gravity and gestational age at sample collection, but not other covariates (Supplemental Table 1), and where we examined associations without inverse probability weights among controls only (delivery ≥ 37 weeks of gestation; Supplemental Table 2). In models of specific gravity-corrected phenols, results were also, for the most part, similar (Supplemental Table 3). However, effect estimates were generally smaller. We also noted that associations between BP3 and parabens and 8-isoprostane were null in these models, while they were positive and statistically significant in models where specific gravity was included as a covariate.

Associations did not differ significantly by timing of sample collection (p for interactions > 0.05; data not shown). Most associations also did not differ significantly by race/ethnicity. However, for 2,5-dichlorophenol, the associations with both 8-OHdG (p for interaction = 0.05) and 8-isoprostane (p for interaction = 0.01) were greater in magnitude among white and other race/ethnicity mothers compared to black mothers (Supplemental Table 4). For 8-OHdG, an IQR increase in 2,5-dichlorophenol was associated with a 17.2% increase (95% CI = 10.6, 24.2) among whites and a 14.0% increase (95% CI = 7.58, 20.8) among mothers of other race/ethnicity, but only a 5.65% increase (95% CI = −3.15, 15.3) among blacks. For 8-isoprostane, an IQR increase in 2,5-dichlorophenol was associated with a similar percent increase in whites (26.2%) and mothers of other race/ethnicity (14.0%), but again only a small and non-significant increase in levels among blacks (1.28%, 95% CI = −9.82, 13.7).

3.1. Adaptive elastic net

Among continuous exposures, specific gravity-corrected urinary phenols and phthalate metabolites had low to moderate correlations with one another and correlations were generally stronger within class (Table 4). For example, parabens were moderately to highly correlated (Spearman $R = 0.33–0.82$), and dichlorophenols were highly correlated with one another (Spearman $R = 0.59$). The exception to this was that low molecular weight phthalates, including MBzP, MBP, MiBP, and MEP, were moderately correlated with the dichlorophenols (Spearman $R = 0.18–0.33$).

AENET results differed considerably by visit, but generally showed the most consistent associations between phthalate metabolites and oxidative stress biomarkers. For 8-OHdG (Table 5), the most consistent exposure biomarkers that were selected for inclusion in the models were MBP and MiBP, which were associated with statistically significant increases in 8-OHdG at each study visit (7–21% change with IQR increase). Dichlorophenols were also included in models for two out of the four visits with significant or near-significant associations (7–11% change with IQR increase). For 8-isoprostane (Table 6), again, the most consistent markers selected and statistically significant were MBP and MiBP. ΣDEHP metabolites, MBzP, and MCPP were also selected for 3 out of 4 visits but the associations were not consistently significant. None of the phenols were consistently selected and significant across the study visits for models of 8-isoprostane.

4. Discussion

In pregnant women from the Boston area, we observed that elevated urinary concentrations of phenols—particularly dichlorophenols, ben-zophenone-3, triclosan, and some parabens—were associated with increases in the urinary oxidative stress biomarkers 8-OHdG and 8-isoprostane. Further, detection of the BPA replacement BPS was associated with increases in both markers as well. However, when we utilized AENET to identify the most important predictors among the correlated set of exposures, including both phenols and urinary phthalate metabolites, the phenols did not appear to be important predictors in the model.

Data on phenol exposure and oxidative stress in human populations, outside of the literature on BPA, is sparse. The only other study to examine dichlorophenols in relation to oxidative stress biomarkers was our preliminary analysis of pregnant women in Puerto Rico, where no associations with 8-OHdG or 8-isoprostane were observed (Watkins et al., 2015). Our findings showed increases in both biomarkers in association with 2,4- and 2,5-dichlorophenol concentrations, which could be attributable to larger sample size for testing this association in our study or to other population differences. Our results are consistent with a laboratory study of freshwater fish which demonstrated impaired antioxidant activity with 2,4-dichlrophenol treatment (Zhang et al., 2004).

Benzophenone-3 was also examined in the Puerto Rico study, and was associated with positive but non-significant increases in both 8-OHdG and 8-isoprostane. Another study by Kim et al. observed no association between benzophenone-3 and malondialdehyde, which is, like 8-isoprostane, a biomarker of lipid peroxidation (Kim et al., 2016). However, it

should be noted that malondialdehyde is subject to a number of limitations as a biomarker of oxidative stress, particularly because it is not very specific (Meagher and FitzGerald, 2000).

Urinary paraben concentrations in our study population were associated with increases in 8-OHdG (methyl and propyl paraben) and 8-isoprostane (all parabens). There is some evidence for paraben associations with elevated oxidative stress biomarkers from previous studies of pregnant women (Watkins et al., 2015; Kang et al., 2013), although results are not always consistent across the parabens measured.

In vitro evidence shows that triclosan has the capacity to generate excessive ROS production in human hepatocytes, as indicated by elevated levels of 8-OHdG (Ma et al., 2013). However, a study across populations from 9 countries indicated that triclocarban, but not triclosan, was correlated with urinary 8-OHdG concentrations (Iyer et al., 2018). In the pilot study in Puerto Rico, Watkins et al. also did not detect an association between triclosan and oxidative stress biomarkers (Watkins et al., 2015). The present analysis detected associations between triclosan and both 8-OHdG and 8-isoprostane, although they were small in magnitude. The power of our repeated measures analyses in such a large study population may have allowed us to detect differences that previous studies with cross-sectional assessments or smaller sample sizes could not. Although we did not observe an association between detection of triclocarban and oxidative stress biomarkers this may have been due to very low detection rate in our population (7%) and this relationship should be examined among populations where higher levels of exposure exist, such as in the full study in Puerto Rico where levels were much higher than the US general population (Ashrap et al., 2018).

Emerging data suggest that bisphenol-A replacements, including bisphenol-S, could have toxicity that is equivalent or even greater than bisphenol-A (Rochester and Bolden, 2015). In vitro data show that bi-sphenol-S has the capacity to increase ROS production and cause lipid peroxidation in human erythrocytes, although perhaps not to the same extent as bisphenol-A (Maćczak et al., 2017). In our analysis bisphenol-S detection was associated with small but significant increases in both oxidative stress biomarkers. This is consistent with most, though not all, published human data (Asimakopoulos et al., 2016; Wang et al., 2019; Kataria et al., 2017; Zhang et al., 2016). We did not compare the bi-sphenol-S and A associations in our AENET analysis because of the low detection of bisphenol-S, but, as with triclocarban, this should be explored in more detail in populations with higher exposures to both compounds.

When we applied AENET to identify important predictors of the urinary oxidative stress markers among urinary phthalate metabolites and phenols, we observed few consistent associations for any of the phenols measured. Notably, AENET is limited by the inability to allow for repeated measures, so the power that we leveraged in the primary analysis was lost in this mixtures approach. Because we did not detect differences in associations by study visit for phenols in the present analysis or for phthalates in our previous work (Ferguson et al., 2014a), we expect that the variability in effect estimates by visit is attributable to the instability of the exposure biomarkers. Nevertheless, we observed that urinary phthalate metabolites, particularly MBP and MiBP, were consistently selected over phenols in AENET

analyses stratified by study visit. This pattern is consistent with the magnitude of effect sizes we see when comparing the results from these two chemical classes. We previously observed 18–30% increases in 8-OHdG and 42–56% increases in 8-isoprostane in association with an IQR increase in MBP or MiBP (Ferguson et al., 2014a), which were much greater in magnitude compared to what we observed for phenols (highest percent change = 15–16%). Additionally, although it is difficult to compare the results of toxicology studies since some of these compounds have been studied much more than others, the existing data seem to robustly support associations between phthalate treatment and ROS production (Seo et al., 2004; Xu et al., 2013; Zhou et al., 2011), whereas findings from studies on phenols are less conclusive. Thus, while the direct associations observed between phenols and oxidative stress markers exist, they may be less physiologically important when considering joint exposure to phthalates.

The results from the AENET analysis highlight the value of variable selection techniques in studies of correlated exposure biomarkers. We observed that dichlorophenol biomarkers in particular were correlated with the urinary phthalate metabolites MBzP, MBP, and MiBP, which may be attributable to shared exposure sources including pharmaceuticals, cleaning products, and deodorizers (Hauser et al., 2004; Lee et al., 2018; Ye et al., 2014). Among the phthalate metabolites measured, these compounds showed the strongest associations with urinary oxidative stress biomarkers in our previous work (Ferguson et al., 2014a). Thus, associations between some phenols and urinary oxidative stress markers from single-pollutant models may have been attributable to the correlations between these compounds. While this has been suspected for some time, and has driven interest in improving methods for disentangling the effects of single compounds within a mixture, the present analysis highlights how important this is in epidemiologic research. Future biomarker work in populations where correlated compounds are measured, investigators should consider application of models like AENET to verify that any observed associations are not due to co-pollutant confounding.

8-OHdG and 8-isoprostane are both produced as a consequence of excess ROS in a system (Il'yasova et al., 2012). However, they are markers of very different mechanisms (oxidative DNA damage and lipid peroxidation, respectively), and are consequently weakly correlated in this and other study populations (Peter Stein et al., 2008). We observed some, but not complete, consistency between phenols and these two markers. For example, butyl and ethyl parabens were associated with increases in 8-isoprostane but only modest and non-significant increases in 8-OHdG. These differences could reflect underlying toxicological mechanisms of action from each compound and the fact that 8-OHdG and 8-isoprostane are not solely a reflection of ROS production. For example, 8-isoprostane may also be generated by upregulation of certain enzymatic pathways, and 8-OHdG levels in urine may be related to DNA excision repair processes (van't Erve et al., 2015; Kondo et al., 2000). If phenols are influencing one but not both of these pathways, we would expect differences in associations with each oxidative stress biomarker. Alternatively, differences in contaminant associations with 8-OHdG and 8-isoprostane could reflect the ability of the markers to accurately capture ROS damage. Much additional work is necessary to understand the exact pathways by which these chemicals are acting to induce the associations observed with circulating oxidative stress biomarkers.

An important observation in our analysis was that the associations between BP3 and parabens and oxidative stress biomarkers were different based on the method used for urine dilution adjustment. In models where specific gravity was included as a covariate, as is recommended by Barr et al. (2004), associations were significant and positive, although modest in magnitude. In models of specific gravity-corrected exposures and outcomes, the associations were null. This instability in results could reflect residual measurement error bias in our results. Future studies of these research questions should carefully test the sensitivity of results to urine dilution adjustment approaches, and ideally should consider measuring exposure and outcome biomarkers in separate samples (e.g., in samples collected on proximate days).

Our study was limited by lack of information on diet, which may be an unmeasured confounder in our analysis. Other unmeasured environmental chemical exposures may also confound these associations, although phthalates appear to be the class of chemicals most highly correlated with phenols in pregnancy (Tamayo-Uria et al., 2019). Additionally, although we used inverse probability weightings to generalize our findings to the base Brigham and Women's Hospital population, this study recruits from a tertiary care center where pregnancies may be more likely to be associated with additional co-morbidities; thus, findings may lack generalizability. Finally, oxidative stress biomarkers were assessed using enzyme immunoassay, which may be less precise than mass spectrometry. These limitations are countered by a number of strengths, including repeated measures of exposure and outcome at four time points during gestation and the availability of multiple exposure biomarkers that allowed for making inferences about the effects of phenols when exposure occurs in a relevant mixture.

In conclusion, we observed associations between urinary phenols and oxidative stress biomarkers. With the application of AENET analysis, the effects of phenols were minimal compared to those observed among phthalates, particularly the metabolites of the low molecular weight di-*n*-butyl and di-isobutyl phthalates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ROS	reactive oxygen species
8-OHdG	8-hydroxydeoxyguanosine
BPA	bisphenol-A
AENET	adaptive elastic net

2,4-DCP	2,4-dichlorphenol
2,5-DCP	2,5-dichlorophenol
BPS	bisphenol-S
LOD	limit of detection
BMI	body mass index
IQR	interquartile range
CI	confidence interval
ΣDEHP	molar sum of di-2-ethylhexyl phthalate metabolites
MBzP	mono-benzyl phthalate
MBP	mono-*n*-butyl phthalate
MiBP	mono-iso-butyl phthalate
MEP	mono-ethyl phthalate
MCPP	mono-3-carboxypropyl phthalate

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Table 1

Demographic characteristics of the study population ($N = 481$).

		N	Weighted %
Age	< 25 years	54	12
	25– < 30 years	95	20
	30– < 35 years	189	39
	35– < 40 years	116	24
	≥ 40 years	27	5
Race/ethnicity	White	282	59
	Black	77	16
	Other	122	25
Pre-pregnancy BMI (nmiss = 11)	< 25 kg/m^2	263	57
	25– < 30 kg/m^2	119	25
	≥ 30 kg/m^2	88	18
Health insurance (nmiss = 12)	Private	378	80
	Public	91	20
Education (nmiss = 11)	High school	68	14
	Technical school	77	16
	Junior/some college	138	29
	College graduate +	187	41
Tobacco use	No	453	95
	Yes	28	5
Alcohol use (nmiss =10)	No	448	95
	Yes	19	5

Abbreviations: BMI, body mass index.

Table 2

Weighted distributions of specific gravity corrected urinary phenol and oxidative stress biomarker concentrations in urine samples collected from up to four visits during pregnancy (N = 481 participants, *N* = 1675 samples).

			Percentiles			
	LOD	**% < LOD**	**25th**	**50th**	**75th**	**95th**
Phenols						
2,4-DCP (ng/mL)	0.2	18.5	0.41	0.69	1.46	8.19
2,5-DCP (ng/mL)	0.2	3.75	1.40	3.22	11.6	201
BP3 (ng/mL)	0.4	0.30	11.5	42.3	250	2914
Butyl PB (ng/mL)	0.2	31.6	0.23	0.84	6.00	33.9
Ethyl PB (ng/mL)	1.0	40.5	0.87	2.13	14.2	106
Methyl PB (ng/mL)	1.0	0.12	68.4	185	436	1350
Propyl PB (ng/mL)	0.2	1.03	12.6	45.1	123	440
Triclosan (ng/mL)	2.0	20.5	3.52	10.6	59.5	469
BPS (ng/mL)	0.4	79.4	< LOD	< LOD	0.70	2.08
Triclocarban (ng/mL)	2.0	92.7	< LOD	< LOD	3.02	10.6
Oxidative stress biomarkers						
8-OHdG (ng/mL)	0.01	0.00	62.3	121	209	417
8-isoprostane (pg/mL)	3.9	4.00	91.6	191	358	738

Abbreviations: LOD, limit of detection; DCP, dichlorophenols; BP3, benzophe-none-3; BPS, bisphenol-S; PB, paraben; 8-OHdG, 8-hydroxydeoxyguanosine.

Table 3

Adjusted[a] percent change (95% confidence interval) in urinary oxidative stress biomarker in association with an interquartile range difference in urinary phenol concentration[b].

	8-OHdG		8-isoprostane	
	% Change (95% CI)	P	% Change (95% CI)	P
2,4-DCP	9.16 (5.95, 12.5)	< 0.01	8.47 (3.46, 13.7)	< 0.01
2,5-DCP	15.2 (11.0, 19.6)	< 0.01	16.7 (9.66, 24.2)	< 0.01
BP3	10.0 (5.46, 14.8)	< 0.01	9.00 (1.39, 17.2)	0.02
Butyl PB	3.32 (−1.21, 8.04)	0.17	9.92 (1.80, 18.7)	0.02
Ethyl PB	4.28 (−0.19, 8.95)	0.07	12.8 (5.01, 21.1)	< 0.01
Methyl PB	9.30 (5.40, 13.3)	< 0.01	9.50 (3.32, 16.1)	< 0.01
Propyl PB	7.32 (3.55, 11.2)	< 0.01	7.32 (1.27, 13.7)	0.01
Triclosan	6.12 (2.08, 10.3)	< 0.01	7.02 (0.14, 14.4)	0.05
BPS[b]	6.18 (−0.27, 13.1)	0.06	18.5 (7.68, 30.5)	< 0.01
Triclocarban[b]	3.05 (−6.76, 13.9)	0.56	3.87 (−11.7, 22.2)	0.65

Abbreviations: DCP, dichlorophenols; BP3, benzophenone-3; BPS, bisphenol-S; PB, paraben; 8-OHdG, 8-hydroxydeoxyguanosine. Results from weighted linear mixed effects models including a random intercept for ID. $N = 464$ participants, 1555 samples.

[a]Models adjusted for urinary specific gravity, gestational age at sample collection, maternal age, Race/Ethnicity, education level, pre-pregnancy body mass index, and smoking during pregnancy.

[b]Bisphenol-S and triclocarban modeled as above vs. below the limit of detection.

Table 4

Spearman correlation coefficients between urinary specific gravity-corrected phenol and phthalate metabolite concentrations.

	2,5-DCP	BP3	BPB	EPB	MPB	PPB	TCS	BPA	ΣDEHP	MBzP	MBP	MiBP	MEP	MCPP
2,4-DCP	**0.59**	**−0.08**	−0.02	0.04	0.14	0.12	0.31	0.19	0.01	0.19	0.24	0.24	0.18	0.05
2,5-DCP		**−0.16**	**−0.14**	**−0.10**	0.13	0.09	−0.03	0.22	0.02	0.26	0.31	0.33	0.21	0.06
BP3			**0.24**	**0.24**	**0.12**	**0.13**	**0.11**	**−0.08**	0.05	**−0.11**	−0.03	**−0.08**	**−0.07**	0.06
BPB				**0.56**	**0.33**	**0.35**	**0.13**	**−0.06**	0.02	**−0.10**	−0.04	**−0.05**	**0.10**	0.02
EPB					**0.36**	**0.37**	**0.07**	**−0.05**	−0.02	**−0.10**	**−0.06**	**−0.09**	**0.09**	0.00
MPB						**0.82**	**0.13**	**0.09**	−0.02	**0.07**	**0.09**	**0.09**	**0.33**	0.02
PPB							**0.09**	0.04	−0.03	0.03	**0.05**	**0.05**	**0.30**	0.00
TCS								−0.01	−0.03	0.02	0.02	0.04	**0.11**	−0.01
BPA									**0.17**	**0.28**	**0.28**	**0.24**	**0.14**	**0.20**
ΣDEHP										**0.12**	**0.17**	**0.16**	0.03	**0.45**
MBzP											**0.57**	**0.44**	**0.17**	**0.22**
MBP												**0.61**	**0.28**	**0.31**
MiBP													**0.27**	**0.22**
MEP														**0.09**

Abbreviations: DCP, dichlorophenols; BP3, benzophenone-3; BPB, butyl paraben; EPB, ethyl paraben; MPB, methyl paraben; PPB, propyl paraben; BPA, bisphenol-A; EDEHP, summed di-2-ethylhexyl phthalate metabolites; MBzP, mono-benzyl phthalate; MBP, mono-*n*-butyl phthalate; MiBP, mono-isobutyl phthalate; MEP, monoethyl phthalate; MCPP, mono-3-carboxypropyl phthalate. Bolding denotes statistical significance ($p < 0.05$).

Table 5

Adaptive elastic net results: Adjusted[a] percent change (95% confidence interval) in 8-OHdG in association with an interquartile range difference in urinary phenol or phthalate metabolite concentration.

	Visit 1		Visit 2		Visit 3		Visit 4	
	% Δ (95% CI)	p	% Δ (95% CI)	p	% Δ (95% CI)	p	% Δ (95% CI)	p
2,4-DCP			7.84 (2.18, 13.8)	< 0.01			7.40 (−0.11, 15.5)	0.05
2,5-DCP					11.3 (3.91, 19.3)	< 0.01	8.49 (−0.35, 18.1)	0.06
BP3			7.38 (−0.59, 16.0)	0.07	7.56 (−1.10, 17.0)	0.09		
Butyl PB							−6.91 (−14.7, 1.58)	0.11
Ethyl PB					−8.07 (−16.0, 0.64)	0.07		
Methyl PB							7.61 (0.47, 15.3)	0.04
Propyl PB	6.37 (−2.19, 15.7)	0.15			4.53 (−2.36, 11.9)	0.20		
Triclosan								
BPA			3.78 (−2.87, 10.9)	0.27	6.57 (−0.21, 13.8)	0.06		
ΣDEHP	4.89 (−3.26, 13.7)	0.25						
MBzP			7.74 (0.70, 15.3)	0.03			8.98 (2.20, 16.2)	< 0.01
MBP	18.1 (10.7, 25.9)	< 0.01	7.64 (1.20, 14.5)	0.02	10.3 (3.76, 17.2)	< 0.01	8.41 (0.33, 17.1)	0.04
MiBP	20.5 (12.9, 28.7)	< 0.01	8.11 (2.01, 14.6)	< 0.01	7.11 (0.37, 14.3)	0.04	14.6 (7.54, 22.1)	< 0.01
MEP							−3.56 (−9.84, 3.16)	0.29
MCPP	6.48 (0.17, 13.2)	0.04						

[a]Models adjusted for urinary specific gravity, gestational age at sample collection, maternal age, Race/Ethnicity, education level, pre-pregnancy body mass index, and smoking during pregnancy. Models include controls only. Blank cells indicate that the exposure was not selected by adaptive elastic net for inclusion in the model. Abbreviations: DCP, dichlorophenols; BP3, benzophenone-3; PB, paraben; BPA, bisphenol-A; ΣDEHP, summed di-2-ethylhexyl phthalate metabolites; MBzP, mono-benzyl phthalate; MBP, mono-*n*-butyl phthalate; MiBP, mono-isobutyl phthalate; MEP, mono-ethyl phthalate; MCPP, mono-3-carboxypropyl phthalate; 8-OHdG, 8-hydroxydeoxyguanosine.

Table 6

Adaptive elastic net results: Adjusted[a] percent change (95% confidence interval) in 8-isoprostane in association with an interquartile range difference in urinary phenol or phthalate metabolite concentration.

	Visit 1		Visit 2		Visit 3		Visit 4	
	% Δ (95% CI)	p	% Δ (95% CI)	p	% Δ (95% CI)	p	% Δ (95% CI)	p
2,4-DCP	13.6 (0.66, 28.1)	0.04						
2,5-DCP			16.5 (2.28, 32.6)	0.02	11.7 (−2.93, 28.6)	0.12		
BP3			13.3 (−4.44, 34.4)	0.15			−16.1 (−27.2, −3.31)	0.02
Butyl PB								
Ethyl PB								
Methyl PB								
Propyl PB								
Triclosan								
BPA			11.8 (−1.79, 27.3)	0.09				
ΣDEHP	11.0 (−2.89, 26.8)	0.13	14.1 (−1.94, 32.8)	0.09	16.2 (−0.69, 35.9)	0.06	10.5 (−3.57, 26.7)	0.15
MBzP	15.7 (3.19, 29.8)	0.01			9.01 (−6.26, 26.8)	0.26	8.10 (−4.73, 22.7)	0.23
MBP			12.8 (1.51, 25.3)	0.03	10.8 (−2.19, 25.5)	0.11	18.4 (3.02, 36.1)	0.02
MiBP			12.3 (0.83, 25.0)	0.04	8.34 (−4.70, 23.2)	0.22	15.7 (2.72, 30.3)	0.02
MEP	21.0 (4.93, 39.5)	< 0.01	10.4 (−5.11, 28.5)	0.20				
MCPP	12.9 (2.12, 24.8)	0.02	6.25 (−4.87, 18.7)	0.28			7.30 (−4.79, 20.9)	0.25

[a]Models adjusted for urinary specific gravity, gestational age at sample collection, maternal age, Race/Ethnicity, education level, pre-pregnancy body mass index, and smoking during pregnancy. Models include controls only. Blank cells indicate that the exposure was not selected by adaptive elastic net for inclusion in the model. Abbreviations: DCP, dichlorophenols; BP3, benzophenone-3; PB, paraben; BPA, bisphenol-A; ΣDEHP, summed di-2-ethylhexyl phthalate metabolites; MBzP, mono-benzyl phthalate; MBP, mono-*n*-butyl phthalate; MiBP, mono-isobutyl phthalate; MEP, mono-ethyl phthalate; MCPP, mono-3-carboxypropyl phthalate.