Science of the Total Environment 833 (2022) 155191

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Pregnancy urinary concentrations of bisphenol A, parabens and other phenols in relation to serum levels of lipid biomarkers: Results from the EARTH study

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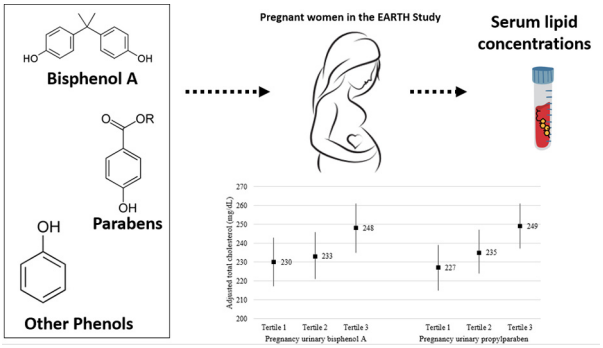
HIGHLIGHTS

- Phenols can interfere with the endocrine system.
- Urinary bisphenol A and propylparaben were associated with higher levels of serum total, non-HDL and LDL cholesterol.
- No associations were found for urinary bisphenol S, benzophenone-3, triclosan, methyl, butyl and ethylparaben with lipid biomarkers.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Adrian Covaci

Keywords:
Phenols
Bisphenol A
Parabens
Lipids
Pregnancy

ABSTRACT

The epidemiologic literature on associations between urinary phenol concentrations and lipid profiles during pregnancy is limited. We examined whether urinary concentrations of phenol and phenol replacement biomarkers were associated with serum lipid levels among pregnant women. This cross-sectional study included 175 women attending the Massachusetts General Hospital Fertility Center who enrolled in the Environment and Reproductive Health (EARTH) Study between 2005 and 2017 and had data available on urinary phenol biomarkers and serum lipids during pregnancy. We used linear regression models to assess the relationship between groups of urinary phenol and phenol replacement biomarkers and serum lipid levels [total cholesterol, high density lipoprotein (HDL), non-HDL, low-density lipoprotein (LDL) cholesterol, and triglycerides], while adjusting for age at sample collection, pre-pregnancy BMI, education, race, infertility diagnosis, cycle type, number of fetuses, trimester and specific gravity. In adjusted models, pregnant women with urinary propylparaben concentrations in the highest tertile had 10% [22 (95% CI =

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http://dx.doi.org/10.1016/j.scitotenv.2022.155191
Received 20 January 2022; Received in revised form 6 April 2022; Accepted 7 April 2022
Available online 12 April 2022

5, 40) mg/dL], 12% [19 (95% CI = 2, 36) mg/dL] and 16% [19 (95% CI = 3, 35) mg/dL] higher mean total, non-HDL and LDL cholesterol, respectively, compared to women with concentrations in the lowest tertile. Similar elevations were observed for urinary bisphenol A concentrations. Urinary bisphenol S, benzophenone-3, triclosan, methylparaben, ethylparaben, and butylparaben were unrelated to serum lipids. Among pregnant women, urinary concentrations of bisphenol A and propylparaben were associated with higher serum levels of total, non-HDL and LDL cholesterol.

1. Introduction

Endocrine-disrupting chemicals are exogenous chemicals, or mixtures of chemicals, that may interfere with any aspect of hormone action (Gore et al., 2015). Specifically, phenols, such as bisphenols, benzophenones, triclosan and parabens, are widely used in food packaging materials, personal care products, and numerous other consumer products (Ghayda et al., 2019; Minguez-Alarcon et al., 2015; Minguez-Alarcon et al., 2016a; Minguez-Alarcon et al., 2017; Minguez-Alarcon et al., 2019). Environmental exposure to these phenols occurs mainly through dermal absorption or ingestion; urine is the optimal matrix for quantifying phenols concentrations because of their short half-lives (<24 h), as well as for being a non-invasive and convenient medium for biological monitoring (Calafat et al., 2015). Bisphenols, benzophenones, triclosan, and parabens are among the most investigated phenols given their endocrine activity and widespread population exposure (CDC, 2022). As metabolic disruptors, higher exposure to these phenolic compounds is linked to obesity and associated with adverse metabolic health outcomes, such as type 2 diabetes and cardiovascular disease (CVD) (Heindel and Blumberg, 2019). Also, some phenols such as bisphenol A and parabens may interfere with the hormonal regulation of energy balance (Heindel et al., 2015; Heindel and Blumberg, 2019).

Dyslipidemia, characterized by high circulating levels of triglycerides, total cholesterol and low-density lipoprotein (LDL) as well as lower circulating levels of high-density lipoprotein (HDL) cholesterol, is a well-known CVD risk factor (Virani et al., 2021), and CVD is the leading cause of mortality in women (CDC, 2020). It has been estimated that between 2014 and 2017, 16% of pregnant women in the USA died because of cardiovascular conditions. Thus, identifying lifestyle factors, such as phenol exposures, that can predict CVD and its related diseases during pregnancy, is of public health interest. To our knowledge, only one epidemiological study has investigated urinary phenols, specifically bisphenol A, and circulating lipid biomarkers during pregnancy (Vuong et al., 2021). Authors reported no associations between urinary bisphenol A concentrations and circulating levels of total lipids, cholesterol, or triglycerides at 16 weeks of gestation in a cross-sectional study of nearly 400 pregnant women in Cincinnati, OH.

Given the scarce data, we investigated the associations of pregnancy urinary concentrations of several phenols and phenol replacements with lipid profiles among women who attended a fertility center and got pregnant using fertility treatments as well as naturally without medical treatments. Because of the metabolic disrupting effect of most phenols and their replacements, we hypothesized that, compared to other pregnant women, women with higher pregnancy urinary phenol concentrations would have higher serum triglycerides, total, non-HDL and LDL cholesterol, as well as lower HDL levels.

2. Methods

2.1. Study population

This study included women enrolled between 2005 and 2017 in the Environment and Reproductive Health (EARTH) Study, a prospective cohort established to assess environmental and dietary determinants of fertility at the Massachusetts General Hospital (MGH) Fertility Center (Minguez-Alarcon et al., 2016b). Women between 18 and 45 years old were eligible to participate and among those contacted by the research staff, approximately 60% enrolled. This analysis includes 175 women with data on both urinary concentrations of phenol biomarkers and serum lipid biomarker levels during pregnancy. Women provided one urine and one blood sample on the same day, with 61 (35%) women having samples collected during the first trimester, 47 (27%) women during the second trimester and 67 (38%) women during the third trimester. Median (IQR) gestational age (weeks) for samples collected in the first, second and third trimester was 8 (7, 9), 23 (20, 26) and 34 (33, 36), respectively. Participants' date of birth was collected at entry, and weight and height were measured by trained study staff. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared at enrollment. At the same entry visit, research staff administered sociodemographic, lifestyle, and medical history questionnaires to participants. Study participants also completed a comprehensive questionnaire on family, medical, reproductive and occupational history, consumer products use, smoking history, and physical activity. Infertility diagnosis was assigned by physicians using the Society of Assisted Reproductive Technology definitions (SART). Pregnancy covariates were abstracted from electronic medical records. The study was approved by the Human Subject Committees of the Harvard T.H. Chan School of Public Health, MGH, and the Centers for Disease Control and Prevention (CDC). Participants signed an informed consent after the study procedures were explained by trained research study staff and all the participant's questions were answered.

2.2. Exposure assessment

During pregnancy, women provided urine samples at the clinic and specific gravity (SG) of the urine was determined at room temperature using a handheld refractometer (National Instrument Company, Inc., Baltimore, MD, USA) calibrated with deionized water before each measurement. Because of the potential for bias, we used the unadjusted urinary phenol concentrations and included SG as a covariate in the statistical models (Barr et al., 2005; Schisterman et al., 2005). The urine was stored at −80 °C and samples were shipped on dry ice overnight to the CDC for analysis. As previously described (Zhou et al., 2014), we used online solid-phase extraction coupled with isotope dilution-high-performance liquid chromatography-tandem mass spectrometry to quantify the urinary concentrations of seven phenol biomarkers (bisphenol A, benzophenone-3, triclosan, methylparaben, propylparaben, butylparaben and ethylparaben) and two bisphenol replacements (bisphenol S and bisphenol F). Sample sizes for certain phenols such as bisphenol S, benzophenone-3, triclosan and ethylparaben are smaller compared to other phenols because we started measuring these biomarkers later in the study. Analyses were not conducted for bisphenol F because of the small sample size ($N = 19$). Limits of detection (LOD) ranged from 0.1 to 2.3 μg/L, depending on the biomarker (Table 2). All concentrations below the LOD were assigned a value equal to the LOD divided by the square root of 2. Along with study samples, each analytical run includes a set of calibrators, reagent blanks, and high- and low-concentration quality control (QC) materials. Concentrations of the QCs are evaluated using standard statistical probability rules (Caudill et al., 2008). If the QC samples fail the statistical evaluation, all of the study samples in the run are re-extracted. CDC analytical methods are public (CDC, 2021) and have been used since the early 2000s for the analyses of tens of thousands of biological specimens, including those collected as part of CDC's ongoing national survey, the National Health and Nutrition Examination Survey (NHANES). NHANES data have provided the most comprehensive assessment of Americans' exposure to phenols, among other chemicals, for decades (CDC, 2022). The CDC laboratory is certified by the Health Care Financing Administration to comply with the

requirements set forth in the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). Therefore, all analytical measurements follow CLIA quality control/quality assurance guidelines, including analysis of samples whose concentrations are unknown to the laboratorians (blinded samples) two times per year; the analytical results are evaluated by an external QA officer (i.e., not a member of the laboratory performing the analyses) who determines whether the results are within previously established confidence limits. Furthermore, two times per year, the CDC laboratory also analyzes proficiency testing urine materials fortified with select phenols as part of the German External QUality Assessment Scheme (G-EQUAS, https://app.g-equas.de/web/) and the External Quality Assessment Scheme for Organic Substances in Urine (OSEQAS, https://www.inspq.qc.ca/en/ctq/eqas) administered by the Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg and the Centre de toxicologie du Québec, Canada, respectively. CDC biomonitoring results have consistently passed these quality assurance evaluations, thus demonstrating proficient laboratory performance.

2.3. Outcome assessment

After blood samples were clotted, tubes were centrifuged at 3000 RPM for 20 min. The resulted serum samples were then spun, aliquoted, frozen and stored at −80 °C until transfer to the Clinical and Epidemiologic (CER) Laboratory at the Boston Children's Hospital (Boston, MA). In one randomly selected serum sample per female participant who also provided a urine sample the same day for phenol quantification, we simultaneously measured three different lipid biomarkers, including triglycerides, total cholesterol and HDL cholesterol levels (mg/dL), with a the Roche Cobas 6000 system using reagents and calibrators from Roche Diagnostics (Indianapolis, IN). These assays are approved by the Food and Drug Administration for clinical use. The CERLab is certified by the Centers for Disease Control and Prevention/National Heart, Lung, and Blood Institute Lipid Standardization Program. Triglycerides were measured enzymatically with correction for endogenous glycerol (Stinshoff et al., 1977). In a preliminary reaction, the endogenous glycerol was phosphorylated in the presence of glycerol kinase and ATP. The formed glycerol-3-phosphate was oxidized to generate H2O2, which reacted with 4-chlorophenol to produce an oxidative product. Then in the actual assay reaction, triglycerides were hydrolyzed by lipase mixture to generate glycerol and fatty acids. Similarly to the preliminary reaction, glycerol was phosphorylated by the action of glycerol kinase and the generated glycerol-3-phosphate is oxidized to produce H2O2. The latter product reacted with a dye to generate a colored product. Cholesterol was measured enzymatically (Allain et al., 1974). The method combined the specificity of the enzymatic reaction with peroxidase/phenol-4-aminophenazone indicator reaction. Cholesterol esters were hydrolyzed by cholesterol esterase to produce free cholesterol. In the presence of oxygen and cholesterol oxidase, cholesterol was oxidized to cholest-4-en-3-one and H2O2. The latter product then reacted with a dye to generate a quinoneimine dye. The intensity of the generated color was measured at 505 nm and was directly proportional to the concentration of cholesterol in the measured sample. The concentration of HDL-C was determined using a direct enzymatic colorimetric assay. In this assay, soluble complexes of non-HDL lipoproteins [low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and chylomicrons] and sulfated alpha-cyclodextrin-Mg++ were formed. The cholesterol component of HDL was then determined using polyethylene glycol (PEG)-modified cholesterol oxidase and esterase, which possess very limited reactivity with the complexed apolipoprotein B-containing lipoproteins (Sugiuchi et al., 1995). This assay has been shown to meet the rigid requirements established by the Lipid Standardization Program (Rifai et al., 1998). We calculated non-HDL as the difference between total cholesterol and HDL cholesterol. We estimated LDL cholesterol following the Friedewald formula: LDL cholesterol = (total cholesterol)-(HDL cholesterol)-(triglycerides/5) (Roberts, 1988). Triglycerides were determined with an intra- and inter- day-to-day reproducibility of 1.8% and 1.7%, respectively. The coefficients of variation (CVs) for total cholesterol concentrations were 1.7% and 1.6%. HDL-C are determined with a day-to-day reproducibility of 3.3% and 1.7%.

2.4. Statistical analysis

We presented demographic and reproductive characteristics and serum lipid biomarker levels as median ± interquartile ranges (IQRs) for continuous variables and counts (percentages) for categorical ones. We also reported distribution of urinary concentrations of phenol and phenol replacement biomarkers using percentiles and means ± standard deviations (SDs). We categorized the urinary phenol biomarker concentrations in tertiles, and we used them as categorical exposure variables with the lowest group considered as the reference group. Urinary bisphenol S, butylparaben and ethylparaben concentrations were divided in two groups (detectable vs. non-detectable) because of the lower detection frequency compared to the other examined phenol biomarkers. We did not log transform the serum lipid biomarker levels because they appeared approximately normally distributed. We used Spearman correlation coefficients (except for phenol biomarkers with relatively low detection frequency) to assess correlations between the measured urinary biomarker concentrations. We applied linear regression models to evaluate the relationship between urinary phenol and phenol replacement biomarkers, as categorical variables, and serum levels of lipid biomarkers. To allow for better interpretation of the results, we presented population marginal means (Searle et al., 1980), adjusting for all the covariates in the model (at the mean level for continuous variables and for categorical variables at a value weighted according to their frequencies).

Confounding was assessed using both prior knowledge regarding biological relevance and descriptive statistics from our study population. The variables considered as potential confounders included factors previously demonstrated to be related to exposure to phenols, and factors associated with both urinary biomarkers and serum lipid levels (Rooney and Domar, 2014; Sharma et al., 2013). We adjusted models for age at sample collection (years), pre-pregnancy BMI (kg/m^2), race (white vs. other), education (graduate degree vs. other), infertility diagnosis (female factor vs. other), cycle type [without medical treatment vs. in vitro fertilization (IVF)/ intrauterine insemination (IUI)], number of babies (singleton vs. twins/triplets), trimester (first vs. second vs. third) and specific gravity. We then conducted stratification by trimester among those phenols that showed associations with serum lipids during pregnancy in our primary analyses, given the rapid metabolic changes that occur during pregnancy resulting in serum lipid differences across trimesters. Statistical analyses were performed with SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

Women had a median (IQR) age of 35 (32, 38) years and BMI of 22.3 (21.3, 25.9) kg/m^2 at sample collection during pregnancy, when they provided the urine and serum samples included in this study (Table 1). The majority of the study participants were white (88%), highly educated (60% had a graduate degree) and only 29% had ever smoked. Most women became pregnant using fertility treatments (83% IUI + IVF) and 82% had singleton pregnancies. Median (IQR) triglycerides, total, HDL and LDL cholesterol (all in mg/dL) were 181 (111, 251), 229 (189, 280), 68.0 (58.0, 79.0) and 120 (92.0, 158), respectively (Table 1). Compared to excluded women, included participants were more likely to undergo IVF fertility treatments and have a female factor infertility diagnosis (data not shown).

Detection frequencies for urinary bisphenol S (60%), butylparaben (58%) and ethylparaben (57%) were not as high as for the other phenols examined (>80%) (Table 2). Median (IQR) bisphenol A and propylparaben (both in μg/L) were 1.00 (0.41, 1.80) and 23.2 (3.70, 105), respectively. Compared to preconception among women from the same EARTH study cohort who did and did not become pregnant, median pregnancy urinary biomarker concentrations (all in μg/L) were lower for bisphenol A (1.00 vs 1.47) (Minguez-Alarcon et al., 2015), benzophenone-3 (92.0 vs. 147)

Table 1
Demographic and reproductive characteristics and serum lipid levels [median (IQR) or N (%)] among 175 pregnant women in the Environment and Reproductive Health (EARTH) Study (2005–2017).

Demographics	
Age, years	35.0 (32.0, 38.0)
Race, N (%)	
White	154 (88)
Black	5 (2)
Asian	8 (5)
Other	8 (5)
Body Mass Index, kg/m^2	22.3 (21.2, 25.7)
Ever smoked, N (%)	50 (29)
Physical activity, hrs/week	5.50 (2.70, 10.0)
Graduate degree, N (%)	105 (60)
Reproductive characteristics	
Primary Infertility diagnosis, N (%)	
Male factor	58 (33)
Female factor	59 (33)
Unexplained	58 (33)
Cycle type resulting in pregnancy, N (%)	
Without medical treatment	29 (17)
IUI	45 (26)
IVF	101 (57)
Number of babies, N (%)	
Singleton (1)	144 (82)
Twins (2)	28 (16)
Triplet (3)	3 (2)
Trimester of sample collection, N (%)	
1st	61 (35)
2nd	47 (27)
3rd	67 (38)
Pregnancy serum lipids, mg/dL	
Total cholesterol	229 (189, 280)
HDL cholesterol	68.0 (58.0, 79.0)
Non-HDL cholesterol	161 (120, 206)
LDL cholesterol	120 (92.0, 158)
Triglycerides	181 (111, 251)

Abbreviations: High density lipoprotein (HDL), intrauterine insemination (IUI), in vitro fertilization (IVF), low-density lipoprotein (LDL).

(Minguez-Alarcon et al., 2019) and triclosan (5.80 vs. 6.04) (Minguez-Alarcon et al., 2017). Similarly, urinary concentrations (all in μg/L) of methylparaben (73.9 vs. 163), propylparaben (23.2 vs. 31.4) and butylparaben (0.30 vs. 1.18) were lower in pregnancy samples compared to preconception ones among women in the EARTH Study regardless of pregnancy status (Minguez-Alarcon et al., 2016a). Compared to female participants in the National Health and Nutrition Examination Survey (CDC, 2022), women in this study had lower urinary concentrations of most of the examined phenols, except benzophenone-3 and propylparaben that had higher concentration. Urinary concentrations of benzophenone-3, methyl and propylparaben were highly correlated with each other (Spearman $r > 0.73$) (Supplemental Table 1). Urinary concentrations of other phenol biomarkers were weakly correlated with each other (Spearman $r < 0.18$).

In models adjusted for age at sample collection, pre-pregnancy BMI, education, race, infertility diagnosis, cycle type, number of fetuses, trimester and specific gravity, we observed that pregnancy urinary concentrations of bisphenol A and propylparaben were associated with higher mean levels of some serum lipid levels (Table 3). Specifically, pregnant women with urinary propylparaben concentrations in the highest tertile had 10% [22 (95% CI = 5, 40) mg/dL], 12% [19 (95% CI = 2, 36) mg/dL] and 16% [19 (95% CI = 3, 35) mg/dL] higher serum total, non-HDL and LDL cholesterol, respectively, compared to women with concentrations in the lowest tertile. Also, women with urinary bisphenol A concentrations in the highest tertile had 9% [18 (95% CI = 3, 39) mg/dL], 13% [19 (95% CI = 0, 40) mg/dL] and 15% [17 (95% CI = -1, 36) mg/dL] higher serum total, non-HDL and LDL cholesterol, respectively, compared to women with concentrations in the lowest tertile. No other associations were found for the examined lipid biomarkers by tertiles of urinary bisphenol S, benzophenone-3, triclosan, methyl, butyl and ethylparaben during pregnancy (Table 3).

Since serum lipid concentrations increased across trimesters, we then performed trimester-specific analyses of urinary propylparaben and bisphenol A with total, non-HDL and LDL cholesterol (Supplemental Table 2). Overall, we observed that associations for propylparaben with the these serum lipids remained during the first trimester (median 8 weeks of gestational age), but were not found in the third (median 34 weeks of gestational age). Contrary, associations for bisphenol A with these lipids remained in trimester 3 and were not observed in trimester 1.

4. Discussion

We investigated the associations of urinary phenol and phenol replacement concentrations with serum lipid biomarker levels during pregnancy in a cross-sectional analysis including 175 subfertile women. We showed positive associations between serum total, non-HDL and LDL cholesterol levels with urinary concentrations of propylparaben and bisphenol A. In the trimester-specific analyses, these associations remained in samples collected during the first trimester for propylparaben, whereas they did in third trimester samples for bisphenol A. Urinary concentrations of other phenols were unrelated to lipid profiles among these women. These results suggest that pregnancy exposures to bisphenol A and propylparaben are associated with circulating lipids levels. This study population is of importance given previous epidemiologic literature showing higher risk of CVD among subfertile women (Cassar et al., 2016; Daan et al., 2014; Escobar-Morreale et al., 2011; Kurabayashi et al., 2016; Liu et al., 2015; Mahalingaiah et al., 2017; Parikh et al., 2012; Rubin et al., 2017; Solomon et al., 2001; Solomon et al., 2002; Tobias et al., 2015; Wang et al., 2011). Assessing exposures to prevalent endocrine disrupting chemicals as it relates to lipid metabolism in this subfertile population can provide key information that could aid in recommendations for improving their cardiometabolic health. Special attention should also be given to the observed results as lipids during pregnancy have been related to fetus and newborn development (Grimes and Wild, 2000).

Pregnancy is an understudied potentially sensitive period of susceptibility to chemical exposures for the health of women and their offspring, since

Table 2
Distribution of urinary phenol and phenol replacement biomarker concentrations (μg/L) among pregnant women in the Environment and Reproductive Health (EARTH) Study (2005–2017).

	N	Detection frequency %	Maximum LOD (μg/L)	Geometric mean (SE)	Mean (SD)	10th	25th	50th	75th	95th
Bisphenol A	175	87	0.4	0.96 (0.08)	1.68 (2.27)	<LOD	0.41	1.00	1.80	5.90
Bisphenol S	83	60	0.1	0.21 (0.03)	0.48 (1.10)	<LOD	<LOD	0.20	0.50	1.60
Benzophenone-3	133	100	0.4	116 (17.9)	685 (2269)	<LOD	33.7	92.0	418	4011
Triclosan	133	80	2.3	10.1 (1.83)	101 (261)	<LOD	<LOD	5.80	42.7	720
Methylparaben	175	99	1.0	92.1 (12.2)	331 (638)	9.30	25.7	73.9	370	1490
Propylparaben	175	98	0.2	17.3 (2.8)	86.6 (209)	0.70	3.70	23.2	105	361
Butylparaben	175	58	0.2	0.51 (0.08)	3.98 (12.1)	<LOD	<LOD	0.30	2.60	20.4
Ethylparaben	83	57	1.0	3.17 (0.6)	19.0 (45.0)	<LOD	<LOD	1.40	12.6	110

Limit of detection (LOD); Standard error (SE); Standard deviation (SD). Note: urinary concentrations are presented as unadjusted for urine dilution.

Table 3
Adjusted[a] serum levels of lipid biomarkers by groups of urinary phenols and phenol replacement biomarker concentrations among 175 pregnant women in Environment and Reproductive Health (EARTH) Study.

	Total cholesterol, mg/dL	HDL cholesterol, mg/dL	Non-HDL cholesterol, mg/dL	LDL cholesterol, mg/dL	Triglycerides, mg/dL
Bisphenol A					
Tertile 1	230 (217, 243)	70.6 (66.4, 74.8)	159 (146, 172)	122 (111, 134)	184 (164, 205)
Tertile 2	233 (221, 246)	69.5 (65.6, 73.4)	164 (152, 176)	123 (112, 134)	206 (187, 225)
Tertile 3	248 (235, 261)‡	68.7 (65.6, 72.9)	179 (166, 192)*	140 (128, 151)‡	198 (178, 219)
Bisphenol S					
Non-detectable	215 (205, 226)	67.3 (63.9, 70.8)	148 (138, 158)	165 (148, 183)	115 (106, 124)
Detectable	219 (206, 232)	68.3 (63.9, 72.8)	151 (138, 163)	178 (155, 200)	115 (104, 127)
Benzophenone-3					
Tertile 1	234 (220, 248)	67.9 (63.6, 72.3)	166 (153, 179)	125 (113, 136)	207 (184, 230)
Tertile 2	228 (214, 241)	70.9 (66.7, 75.1)	157 (144, 169)	119 (107, 130)	190 (167, 212)
Tertile 3	237 (224, 251)	72.0 (67.6, 76.3)	166 (153, 179)	128 (116, 139)	188 (165, 211)
Triclosan					
Tertile 1	225 (212, 238)	69.3 (65.1, 73.5)	156 (143, 168)	116 (105, 128)	196 (174, 218)
Tertile 2	243 (230, 256)*	72.9 (68.7, 77.2)	170 (157, 183)	133 (121, 145)*	184 (162, 207)
Tertile 3	231 (218, 245)	68.6 (64.2, 72.9)	163 (149, 176)	122 (110, 134)	203 (180, 226)
Methylparaben					
Tertile 1	233 (221, 246)	68.4 (64.5, 72.3)	165 (153, 177)	125 (114, 136)	201 (182, 220)
Tertile 2	238 (226, 250)	69.7 (65.9, 73.4)	168 (156, 180)	127 (117, 138)	202 (183, 220)
Tertile 3	240 (228, 252)	70.8 (67.0, 74.6)	169 (157, 181)	132 (121, 143)	185 (167, 204)
Propylparaben					
Tertile 1	227 (215, 239)	68.6 (64.9, 72.4)	158 (147, 170)	119 (108, 129)	198 (179, 216)
Tertile 2	235 (224, 247)	68.2 (64.5, 71.9)	167 (156, 178)	128 (118, 138)	196 (178, 214)
Tertile 3	249 (237, 261)*	72.1 (68.2, 76.0)	177 (164, 189)*	138 (127, 149)*	194 (175, 213)
Butylparaben					
Non-detectable	235 (226, 244)	68.8 (66.0, 71.6)	167 (158, 175)	126 (118, 135)	201 (188, 215)
Detectable	239 (229, 249)	70.7 (67.5, 74.0)	168 (158, 178)	131 (121, 140)	189 (172, 204)
Ethylparaben					
Non-detectable	220 (210,230)	66.1 (62.8, 69.5)	154 (145, 163)	118 (109, 127)	179 (139, 179)
Detectable	213 (201, 225)	69.8 (65.9, 73.7)	143 (132, 154)	111 (101,122)	159 (162, 196)

[a] Data are presented as predicted marginal means (95% CI) unless otherwise noted, adjusted for age at pregnancy, pre-pregnancy BMI, education, race, infertility diagnosis, cycle type, number of babies, trimester and specific gravity.

* *p*-Value < 0.05 when compared that tertile or group with the lowest group.

‡ p-Value < 0.10 when compared that group with the lowest group.

it is characterized by marked cellular proliferation and development as well as metabolic changes and epigenetic programming. Based on the National Academy of Sciences's recommendations, there is a critical need to investigate exposures that occur during different periods in life to improve approaches for risk assessment of endocrine disrupting chemicals in the U.S. population (National Research Council Committee on Improving Risk Analysis Approaches Used by the 2009). To our knowledge, only one previous study has assessed the relationship of urinary phenols with serum lipid levels during pregnancy (Vuong et al., 2021). Specifically, authors evaluated pregnancy urinary concentrations of bisphenol A and circulating levels of total lipids, cholesterol and triglycerides at 16 weeks of gestation in a cross-sectional study of 388 women participating in the Health Outcomes and Measures of the Environment (HOME) Study. In agreement with our results, authors found no associations between bisphenol A and serum triglycerides. However, and contrary to our results, urinary bisphenol A was also unrelated to total cholesterol. Women participating in both the HOME and EARTH studies were mostly white, highly educated and in their thirties. By contrast, median (IQR) urinary bisphenol A concentration in the HOME study samples collected between 2003 and 2006 was 2.00 (0.90, 3.50) μg/L, whereas in our study it was 1.00 (0.41, 1.80) μg/L in samples collected between 2005 and 2017. Lower bisphenol A in our study may be explained by collected urines in recent years given that bisphenol A has been replaced by other bisphenols over time. The differences in bisphenol A and total cholesterol results between both studies may also be explained by differences in total cholesterol between both studies [mean (SD) for HOME = 199 (37.6) mg/dL vs. EARTH = 237 (65.2) mg/dL]. Also, our associations between urinary bisphenol A and total cholesterol was mainly found in the second (median 23 weeks) and third (median 34 weeks) trimesters, whereas lipids in the HOME study were measured at 16 weeks. Recently, positive associations between urinary concentrations of triclosan, methylparaben and propylparaben, and plasma levels of oxylipins related to the lipoxygenase pathway with arachidonic acid precursor were observed among 90 pregnant women participating in the LIFECODES Study (Welch et al., 2021). Welch et al. also demonstrated positive associations between a phenol mixture and plasma oxylipins related to the lipoxygenase pathway with linoleic acid and arachidonic acid precursor. Further studies can help corroborate the observed findings. Special attention should be made to include other groups of women belonging to minority groups and/or with lower socioeconomic status to increase generalizability of study findings.

Among pregnant women from the same study cohort, we previously reported positive associations of pregnancy urinary bisphenol A (Chiu et al., 2017) and propylparaben (Bellavia et al., 2019) with glucose levels, another key component of cardiovascular health (Lloyd-Jones et al., 2010). In addition, we previously found that pregnancy urinary propylparaben concentrations were related to higher gestational weight gain among this study population (Tyagi et al., 2020). Inflammatory biomarkers are also cardiovascular risk factors (Lloyd-Jones et al., 2010) and bisphenol A exposure has been linked to these in other cohorts of pregnant women. Specifically, associations of bisphenol A with interleukin-6 (Ferguson et al., 2016; Watkins et al., 2015) and monocyte chemoattractant protein 1 (Kelley et al., 2019) have been documented. Furthermore, pregnancy propylparaben has been inversely associated with circulating C-reactive protein levels (Watkins et al., 2015). Given the widespread population exposure to phenols (especially bisphenol A and parabens), their associations with key cardiovascular components and the pregnancy-related mortality rates by CVD in the United States, reducing pregnant women's exposure to these chemicals used in everyday consumer products may have positive effects on health.

In vitro experimental models have demonstrated that both bisphenol A and parabens, including propylparaben, can activate peroxisome proliferator-activated receptor (PPAR)-γ inducing adipocyte differentiation

(Pereira-Fernandes et al., 2013). PPAR-γ is also involved in lipid and glucose metabolism regulation and inflammation (Behr et al., 2020; Berger and Moller, 2002; Mirza et al., 2019). Consequently, metabolic perturbations by exposure to BPA or chemical mixtures including BPA have been shown in rodent studies, such as increased liver fat (Rönn et al., 2013), serum levels of triglyceride and cholesterol (Moghaddam et al., 2015) and modifications in lipid homeostasis (Labaronne et al., 2017). Exposure to parabens can also induce changes in gene expression related to adipocyte differentiation and lipogenesis in adipose tissue in female mice (Hu et al., 2016). Furthermore, animal studies have shown that exposure to both gestational BPA (Miyawaki et al., 2007; Tonini et al., 2021) and parabens (Leppert et al., 2020) can adversely impact metabolic endpoints, including cholesterol metabolism, in the offspring.

Limitations of this study include limited generalizability of these results to pregnant women in the general population because this study includes subfertile women attending a hospital-based fertility center. However, this study population is of public health importance as women with impaired fertility are at higher risk of cardiovascular disease than other women (Cassar et al., 2016; Daan et al., 2014; Escobar-Morreale et al., 2011; Kurabayashi et al., 2016; Liu et al., 2015; Mahalingaiah et al., 2017; Parikh et al., 2012; Rubin et al., 2017; Solomon et al., 2001; Solomon et al., 2002; Tobias et al., 2015; Wang et al., 2011). Second, the cross-sectional nature of this analysis does not allow us to establish causality. Third, we cannot confirm that all the serum samples were fasting and this may affect our results. Fourth, as in any observational study, residual confounding by other exposures, lifestyle and reproductive factors is still possible. Despite these limitations, this study has several strengths. First, we are one of the first studies to evaluate several phenolic compounds and their replacements as they relate to lipid biomarkers. Second, we evaluated this research question in a well-established cohort of subfertile women at high risk of cardiovascular disease (Mahalingaiah et al., 2017). Third, we were able to adjust for important confounders, including pre-pregnancy BMI, infertility status, and cycle type—factors that could be affected by both the phenol concentrations and lipid outcomes in pregnancy.

In summary, we observed higher serum total, non-HDL and LDL cholesterol levels with higher urinary concentrations of propylparaben (especially in the first trimester) and bisphenol A (especially in the third trimester) in pregnant women. Urinary concentrations of other phenols were unrelated to lipid profiles among these women. These results suggest that pregnancy exposure to bisphenol A and propylparaben are associated with circulating lipids levels, if confirmed in other study populations, add to the existing epidemiologic literature on pregnancy health.

CRediT authorship contribution statement

Dr. Mínguez-Alarcón had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mínguez-Alarcón, Williams, Hauser and Chavarro. Acquisition of data: Souter and Ford. Urine sample analyses: Calafat. Analysis of data: Mínguez-Alarcón. Interpretation of data: All authors. Drafting of the manuscript: Mínguez-Alarcón and Frueh. Critical revision of the manuscript for important intellectual content: All authors.

Competing financial interest

None of the authors has any conflicts of interest to declare.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade name is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the U.S. Department of Health and Human Services.

Acknowledgments and grant information

The project was funded by grants R01ES022955 and R01ES009718, P30ES000002, and R01ES024381 from the National Institute of Environmental Health Sciences (NIEHS). The authors gratefully acknowledge all members of the EARTH study team, specifically the Harvard T. H. Chan School of Public Health research staff Myra Keller, Ramace Dadd and Alex Azevedo, physicians and staff at Massachusetts General Hospital Fertility Center as well as CERLab and CDC personnel. A special thank you to all of the study participants.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.155191.

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