Environment International 151 (2021) 106440

Contents lists available at ScienceDirect

Environment International

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

Parental preconception exposure to phenol and phthalate mixtures and the risk of preterm birth

Yu Zhang [a,e], Vicente Mustieles [b,c,d], Paige L. Williams [e,f], Blair J. Wylie [g], Irene Souter [h,i], Antonia M. Calafat [j], Melina Demokritou [a], Alexandria Lee [e], Stylianos Vagios [h,i], Russ Hauser [a,e], Carmen Messerlian [a,e,h,i,*]

[a] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[b] University of Granada, Center for Biomedical Research (CIBM), Spain
[c] Instituto de Investigación Biosanitaria Ibs GRANADA, Spain
[d] Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), 18100, Spain
[e] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[f] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[g] Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA, USA
[h] Massachusetts General Hospital Fertility Center, Harvard Medical School, Boston, MA, USA
[i] Vincent Center for Reproductive Biology, Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA, USA
[j] National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA, USA

ARTICLE INFO

Handling Editor: Lesa Aylward

Keywords:
DEHP
BPA
Preterm
Singleton
Subfertile
Couple

ABSTRACT

Background: Parental preconception exposure to select phenols and phthalates was previously associated with increased risk of preterm birth in single chemical analyses. However, the joint effect of phenol and phthalate mixtures on preterm birth is unknown.

Methods: We included 384 female and 211 male (203 couples) participants seeking infertility treatment in the Environment and Reproductive Health (EARTH) Study who gave birth to 384 singleton infants between 2005 and 2018. Mean preconception urinary concentrations of bisphenol A (BPA), parabens, and eleven phthalate biomarkers, including di(2-ethylhexyl) phthalate (DEHP) metabolites, were examined. We used principal component analysis (PCA) with log-Poisson regression and Probit Bayesian Kernel Machine Regression (BKMR) with hierarchical variable selection to examine maternal and paternal phenol and phthalate mixtures in relation to preterm birth. Couple-based BKMR model was fit to assess couples' joint mixtures in relation to preterm birth.

Results: PCA identified the same four factors for maternal and paternal preconception mixtures. Each unit increase in PCA scores of maternal (adjusted Risk Ratio (aRR): 1.36, 95%CI: 1.00, 1.84) and paternal (aRR: 1.47, 95%CI: 0.90, 2.42) preconception DEHP-BPA factor was positively associated with preterm birth. Maternal and paternal BKMR models consistently presented the DEHP-BPA factor with the highest group Posterior Inclusion Probability (PIP). BKMR models further showed that maternal preconception BPA and mono(2-ethyl-5-hydroxyhexyl) phthalate, and paternal preconception mono(2-ethylhexyl) phthalate were positively associated with preterm birth when the remaining mixture components were held at their median concentrations. Couple-based BKMR models showed a similar relative contribution of paternal (PIP: 61%) and maternal (PIP: 77%) preconception mixtures on preterm birth. We found a positive joint effect on preterm birth across increasing quantiles of couples' total mixture concentrations.

Conclusion: In this prospective cohort of subfertile couples, maternal BPA and DEHP, and paternal DEHP exposure before conception were positively associated with preterm birth. Both parental windows jointly contributed to the outcome. These results suggest that preterm birth may be a couple-based pregnancy outcome.

* Corresponding author at: Harvard T.H. Chan School of Public Health, 665 Huntington Avenue, Building 1, 1310C, Boston, MA 02115, USA.
E-mail address: cmesser@hsph.harvard.edu (C. Messerlian).

https://doi.org/10.1016/j.envint.2021.106440
Received 10 November 2020; Received in revised form 22 January 2021; Accepted 1 February 2021
Available online 25 February 2021

1. Introduction

Preterm birth, defined as birth before 37 completed weeks of gestation, is an important predictor of child health and development (Luu et al., 2017; Luyckx, 2017; Moster et al., 2008; Klebanoff and Keim, 2011). Although some risk factors have been identified, such as maternal age, race, socio-economic status, intrauterine infection, and multiple gestations, the underlying causes remain largely unknown (World Health Organization, 2019; Goldenberg et al., 2008; Romero et al., 2014). Despite efforts to reduce known risk factors, a sustained reduction in the rate of preterm birth in the United States has yet to be achieved (Etzel, 2020). Growing evidence has linked environmental exposures, including non-persistent chemicals, to preterm birth (Porpora et al., 2019; Ferguson and Chin, 2017; Birks et al., 2016; Bengtsson et al., 2017; Govarts et al., 2018; Chin et al., 2019; Kamai et al., 2019; Hao et al., 2016).

Endocrine disrupting chemicals (EDCs) are exogenous chemicals that can interfere with any aspect of hormone action (Zoeller et al., 2012). Phthalates and phenols are among the most studied EDCs due to concerns of their reproductive and developmental toxicity (Mustieles et al., 2015; Giulivo et al., 2016; Aker et al., 2019; Ghazipura et al., 2017; Peretz et al., 2014; De Felice et al., 2015; Carvaillo et al., 2019; Johnson et al., 2016; Jamal et al., 2019; Nowak et al., 2018; European Chemicals Agency, 2016; Benjamin et al., 2017). Humans are widely exposed to phthalates and phenols from use of plastics, food packaging materials, personal care products, and numerous other everyday consumer products (Mustieles et al., 2015; Freire et al., 2019; Liao and Kannan, 2014; Weatherly and Gosse, 2017; Karpuzoglu et al., 2013; Centers for Disease Control and Prevention, 2017; Calafat et al., 2008; Xu et al., 2020).

Exposures to some phthalates and phenols in the prenatal period are associated with poor pregnancy outcomes, including preterm birth (Porpora et al., 2019; Ferguson and Chin, 2017; Birks et al., 2016; Bengtsson et al., 2017; Govarts et al., 2018; Chin et al., 2019; Kamai et al., 2019). Our previous work identified preconception as a susceptible period for the potential impact of phenols and phthalates on adverse birth outcomes (Mustieles et al., 2018; Messerlian et al., 2018; Mustieles et al., 2020; Zhang et al., 2020; Messerlian et al., 2017). Environmentally-driven epigenetic mechanisms in gametes during the pre- and *peri*-conception period likely contribute to the etiopathology of adverse pregnancy outcomes, and are considered a plausible mode of action for environmental chemicals (Braun et al., 2017; Menon et al., 2012; Parets et al., 2015; Lin et al., 2016; Luderer et al., 2019).

One of the current challenges in the field of toxicology and environmental epidemiology is the study of chemical mixtures in human populations (Kortenkamp and Faust, 2018). Thus, an increasing number of studies is exploring the effects of chemical mixtures on diverse health outcomes (Ouidir et al., 2020; Mustieles et al., 2017; Chiu et al., 2018; Hou et al., 2020), highlighting the need to implement multipollutant models in environmental epidemiology (Lazarevic et al., 2019; Taylor et al., 2016; Mínguez-Alarcón et al., 2019). Given that mixtures of environmental chemicals may interact with each other leading to additive, synergistic and/or antagonistic effects, the traditional one-chemical-at-a-time strategy may not represent real-world exposure scenarios in which humans are exposed to many chemical families (Birnbaum, 2012; Drakvik et al., 2020; Zhou et al., 2019; Carlin et al., 2013; Braun et al., 2014). Select phthalates and phenols share common exposure sources including diet (e.g., packaged food), cosmetics and other consumer products, potentially resulting in substantial co-exposure to both families of compounds in human populations (Martínez et al., 2018; Kim et al., 2017; Philippat et al., 2015; Borman et al., 2016), and possibly leading to mixture interactions as supported by toxicological data (Suteau et al., 2020; Manikkam et al., 2013; Kortenkamp, 2007).

Using single chemical analyses, we previously reported that maternal and paternal preconception exposure to some phthalates and phenols were associated with an elevated risk of preterm birth (Mustieles et al., 2020; Zhang et al., 2020). Given their simultaneous co-occurrence in real-life scenarios (Kapraun et al., 2017); the present study aimed to examine whether maternal and paternal preconception urinary concentrations of complex mixtures of phenols and phthalate metabolites interact to influence the risk of singleton preterm birth among couples attending a fertility clinic.

2. Materials and methods

2.1. Study cohort

In this present analysis, we used data from the Environment and Reproductive Health (EARTH) Study. The EARTH Study is a prospective preconception cohort of couples who were recruited from the Massachusetts General Hospital (MGH) Fertility Center starting in 2005 up until 2019. The EARTH Study investigates male and female environmental and nutritional factors and their relationship with fertility, pregnancy, and birth outcomes (Messerlian et al., 2018). Details of the study can be found elsewhere (Messerlian et al., 2018). In brief, men (18–55 years) and women (18–46 years) were eligible to participate either independently or as a couple. As couples undergo fertility care, they are followed at each cycle of attempted conception while under treatment observation. During this time, the EARTH Study follows and collects data on health and lifestyle information. Participants also provide urine and blood samples during follow-up.

The present study included 384 mothers and 211 fathers (203 couples) who gave birth to a singleton between 2005 and 2018 for whom we quantified phenol and phthalate biomarkers in at least one urine sample collected before conception of the index pregnancy. Trained study staff explained the study details and answered any questions before obtaining participant's signed informed consents. The study was approved by the Institutional Review Boards of MGH, Harvard T.H. Chan School of Public Health, and the Centers for Disease Control and Prevention (CDC).

2.2. Exposure assessment

Exposure assessment was based on spot urine samples provided by women first at study entry and then from up to two additional spot urine samples obtained during each fertility treatment cycle, corresponding with the early follicular phase. Together, these samples represented the preconception period and included all urine samples collected at baseline entry and at each cycle of attempted pregnancy, up to and including, the cycle of conception of the index birth. Correspondingly, men provided a spot urine sample at study entry and then an additional spot urine sample at every cycle at time of the fertility procedure.

Polypropylene specimen cups were used to collect urine samples. The urinary specific gravity (SG) was measured by a handheld refractometer (National Instrument Company, Inc., Baltimore, MD, USA). Samples were then divided into aliquots, and frozen for long-term storage at −80 °C. Samples were shipped to the CDC (Atlanta, GA, USA) on dry ice overnight for quantification of urinary phenol and phthalate metabolite concentrations using solid phase extraction coupled online with high performance liquid chromatography-isotope dilution tandem mass spectrometry (Zhou et al., 2014). Urinary concentrations were measured for four phenols, including bisphenol A (BPA), methylparaben, propylparaben, butylparaben, and eleven phthalate metabolites, including monoethyl phthalate (MEP); mono-n-butyl phthalate (MBP); mono-isobutyl phthalate (MiBP); monobenzyl phthalate (MBzP); mono(3-carboxypropyl) phthalate (MCPP); monocarboxyisooctyl phthalate (MCOP); monocarboxyisononyl phthalate (MCNP); and four di(2-ethylhexyl) phthalate (DEHP) metabolites [mono (2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)]. The limits of detection (LOD) ranged from 0.1 to 1.2 ng/ml. Concentrations below the

LOD were assigned the LOD divided by the square root of two (Hornung and Reed, 1990).

2.3. Outcome assessment

We abstracted gestational age (days) from delivery records. In order to validate the delivery records estimates, we used guidelines for dating births following medically assisted reproduction from the American College of Obstetricians and Gynecologists (ACOG) (ACOG, 2014). For pregnancies conceived using in-vitro fertilization (IVF), gestational age was estimated as (outcome date – embryo transfer date + 14 days + cycle day of transfer) (ACOG, 2014). For pregnancies using other forms of medically assisted reproduction or that were naturally conceived, gestational age was estimated as (birth date – cycle start date or last menstrual period date). All live births ending before 37 completed weeks' gestation (<259 days) were considered preterm.

2.4. Covariates

Paternal and maternal age, education, race, and smoking status were self-reported via questionnaire at study entry. Height and weight of participants were measured at baseline by study staff. Body Mass Index (BMI) was calculated as kg/m^2. The treating infertility physician diagnosed the underlying cause of infertility using the Society for Assisted Reproductive Technology (SART) definitions (Practice Committee of the American Society, 2015a, 2015b). Data from electronic medical records were abstracted for mode of conception of the index birth and was dichotomized as any assisted reproductive technology (ART) procedures (i.e., all IVF protocols) versus non-ART protocols (i.e., all intrauterine inseminations, ovarian stimulation, or natural/non-medically assisted conceptions).

2.5. Statistical analysis

Each biomarker concentration was multiplied by [(SGp-1)/(SGi-1)] in order to account for urinary dilution, where SGi is the SG of the participant's sample and SGp is the mean SG for all male (mean = 1.016) or all female (mean = 1.015) participants included in the study (Pearson et al., 2009). Because the SG-adjusted biomarker concentrations were skewed, we natural log-transformed values to standardize the distribution and reduce the influence of extreme values. Given the short half-lives of phenols and phthalates, we averaged the natural log-transformed biomarker concentrations of multiple urine samples collected from study entry up to and including the sample from the cycle of conception of the index pregnancy per participant to estimate mean exposure in the preconception window. This strategy allows an improved exposure characterization, lowering the probability of attenuation bias, that is, the tendency towards null findings (Vernet et al., 2019).

We calculated descriptive statistics for biomarker concentrations and the percentage of values above the LOD. We also calculated Spearman correlation coefficients between biomarkers for maternal and paternal preconception windows respectively, as well as for biomarkers within couples. We examined the clinical and demographic characteristics of study participants and their singletons, and reported them as mean (±SD) or number (%).

We first used principal component analysis (PCA) with varimax rotation to classify phenol and phthalate biomarkers into uncorrelated components based on their correlations. This method reduces the number of components while retaining information from the original variables. Factors with eigenvalues greater than one were identified as principal components (O'Rourke and Hatcher, 2013). We then fit modified Poisson regression models (Zou, 2004) for the principal component scores and the binary preterm birth outcome to estimate risk ratio (RR) and 95% confidence interval (95% CI) per unit increase in the factor scores adjusting for the other factor scores. To make the results more intuitive and allow for nonlinearity, we fit Poisson regression across quartiles of PCA-derived factor scores. We conducted PCA and fit Poisson regression models separately for both maternal and paternal preconception biomarkers.

We then employed Bayesian Kernel Machine Regression (BKMR) with a probit kernel exposure–response function to separately examine maternal and paternal preconception phenol and phthalate mixtures in relation to preterm birth. We used BKMR to flexibly model the joint mixture effect, accounting for correlations and interactions between mixture components (Bobb et al., 2015). BKMR further allows the visualization of the exposure–response association for each biomarker within the mixture as well as the cumulative effects of the total mixture. We used BKMR with a hierarchical variable selection based on components obtained from PCA results (i.e., we grouped biomarkers according to the components identified by PCA). We calculated the group posterior inclusion probability (groupPIP) and conditional posterior inclusion probability (condPIP), with the former representing the probability of including a particular biomarker group within the model and the latter representing the probability that a biomarker is included within its principal component.

Results from BKMR are presented as 1) univariate exposure–response association of each individual biomarker concentration in relation to preterm birth estimate when holding the remaining biomarkers in the mixture at their median concentrations; 2) potential interactions within mixtures by estimating the change in preterm birth estimate comparing each individual biomarker concentration at 25th to 75th percentiles, when setting the remaining biomarkers at their 25th, 50th or 75th percentile levels; 3) the cumulative effect of the total mixture on preterm birth adjusting for covariates. The cumulative effect of the total mixture was displayed as the change in preterm birth estimate comparing all biomarkers at their median concentrations (reference) to the concentrations at each 5th percentile, from the 25th up to the 75th percentile.

We selected *a priori* covariates as potential confounders based on substantive knowledge using a directed acyclic graph (DAG). Maternal age and BMI (continuous), education (<college, college, graduate degree), smoking status (never smoked versus ever (former or current)), race (Caucasian, Black/African American, Asian, Other) and ART versus non-ART mode of conception, were included in all models. We included the corresponding paternal covariates in addition to maternal ones in models examining the paternal exposure windows (Bellavia et al., 2020). Statistical analyses were conducted with SAS (version 9.4; SAS Institute Inc., Cary, USA) and R package bkmr (Bobb, 2017). The interpretation of our results considered patterns of associations in light of previous epidemiologic findings rather than relying solely on p-values and their significance (Farland et al., 2016).

2.6. Sensitivity analysis

To examine the association of couples' exposure to mixtures of phenols and phthalates in relation to the risk of preterm birth, BKMR models were also fit to the 203 couples in the cohort. We separated mixtures into maternal and paternal preconception groups and used hierarchical variable selection to compare the parent-of-origin contribution to the study outcome (Valeri et al., 2017). We also restricted the maternal preconception analyses to 203 mothers who participated in the study with their partner in order to obtain more comparable results with the couple-based model.

3. Results

3.1. Study cohort

The study cohort comprised 384 mothers and 211 fathers (203 couples) with a mean age of 34.6 and 35.8 years and a mean BMI of 24.0 and 27.9 kg/m^2, respectively, at study entry (Table 1). Among the 384 singleton infants, mean (SD) gestational age was 39.3 (1.7) weeks and

Table 1
Parental characteristics from 384 mothers and 211 fathers participating in the Environment and Reproductive Health (EARTH) Study, 2005–2018.

Parental Characteristic	Maternal N = 384	Paternal N = 211
Age (years)		
Mean (SD)	34.6 (4.0)	35.8 (4.6)
Age > 35, n (%)	157 (41)	114 (54)
Race, n (%)		
White	323 (84)	186 (88)
Black	10 (3)	4 (2)
Asian	35 (9)	14 (7)
Other	16 (4)	7 (3)
Body Mass Index (BMI, Kg/m^2)		
Mean (SD)	24.0 (4.1)	27.9 (6.3)
BMI > 25, n (%)	120 (31)	144 (68)
Education, n (%)		
<College	50 (13)	71 (34)
College Graduate	121 (32)	58 (28)
Graduate Degree	213 (55)	78 (38)
Smoking Status, n (%)		
Never	289 (75)	145 (69)
Ever (former or current)	95 (25)	66 (31)
Infertility Diagnosis, n (%)		
Male Factor	90 (23)	64 (30)
Female Factor	122 (32)	61 (29)
Unexplained	172 (45)	85 (41)
Primiparous, n (%)	320 (83)	–

8% (n = 30) of infants were born preterm (Table 2). Background characteristics of mothers who enrolled as a couple (n = 203) compared with those who enrolled without a partner (n = 181) are presented in Table S1. Mothers who enrolled with their male partner were more likely to have a male factor infertility diagnosis at baseline (28% vs. 18%). They also had slightly higher geometric mean BPA and the sum of DEHP metabolite concentrations compared with those who enrolled without their male partner (BPA: 1.12 ng/mL vs. 1.06 ng/mL; sum of DEHP metabolites: 40.83 ng/mL vs. 37.78 ng/mL).

3.2. Urinary biomarker concentrations

We included a total of 1600 maternal and 557 paternal urine samples collected from study entry to the conception of the index pregnancy. Women provided on average 4.2 (median: 3; IQR: 2–5) and men on average of 2.6 (median: 2; IQR: 2–3) urine samples. The median time lag between urine sample collection and the conception date of the index pregnancy was 88 days for both maternal and paternal samples. The distribution of biomarkers and detection frequencies are presented in Table S2. Butylparaben had the lowest urinary detection frequency (62.8% for maternal preconception and 32.1% for paternal preconception). The remaining biomarkers had detection frequencies greater than or equal to 70%. Spearman correlation coefficient matrices are shown in Figs. S1–S3 for maternal and paternal preconception, and couples' biomarker concentrations, respectively. Spearman correlation coefficients ranged from −0.15 (MEHP and MCOP) to 0.98 (MEOHP and MEHHP) for the maternal preconception window (Fig. S1), −0.06 (MEHP and MCOP) to 0.98 (MEOHP and MEHHP) for paternal preconception window (Fig. S2), and −0.32 (maternal MEHHP and paternal MCOP) to 0.60 (maternal MECPP and paternal MECPP) for couples' biomarker concentrations (Fig. S3).

Table 2
Birth characteristics of 384 singletons from the Environment and Reproductive Health (EARTH) Study, 2005–2018.

Infant Characteristics	Births	
	2005–2018	
	N = 384[a]	N = 203[b]
Male, n (%)	195 (51)	100 (49)
Birth weight (grams)		
Mean (SD)	3357 (536)	3353 (497)
min–max	1310–4790	1850–4790
Low birth weight		
<2500 g, n (%)	18 (5)	6 (3)
Gestational age (weeks)		
Mean (SD)	39.3 (1.7)	39.3 (1.5)
min–max	29–42	33–42
Preterm birth		
<37 weeks, n (%)	30 (8)	14 (7)
Mode of conception, n (%)		
ART[c]	223 (58)	126 (62)
Non-ART[d]	161 (42)	77 (38)

[a] Singletons from total study population.
[b] Singletons whose parents joined as a couple in the study.
[c] Assisted Reproductive Technology (ART): fresh or frozen in-vitro fertilization protocols, including intracytoplasmic sperm injection.
[d] Non-ART: intrauterine insemination with or without ovulation induction/stimulation; ovulation induction/stimulation with timed intercourse, or non-medically assisted/naturally conceived.

3.3. Maternal preconception mixtures

The maternal preconception PCA identified four principal factors (Table S3). Factor 1 was termed the DEHP-BPA factor, accounting for 33.2% of the total mixture variance, and showed high loading scores for MEOHP, MEHHP, MECPP, MEHP (metabolites of DEHP) and BPA. Factor 2 was termed the paraben factor, accounted for 16.1% of the total variance, and showed high loading scores for methylparaben, propylparaben, butylparaben (the three paraben biomarkers) and MEP. Factor 3 was termed the high molecular weight phthalate (HMWP) factor, accounted for 13.4% of the total variance, and showed high loading scores for MCOP, MCPP and MCNP. Factor 4 accounted for 10.2% of the total variance, and showed high loading scores for MiBP, MBP and MBzP. For simplicity, we termed factor 4 as low molecular weight phthalate (LMWP) factor although MBzP is a high molecular weight phthalate metabolite.

Covariate-adjusted modified Poisson regression models showed that each 1-unit increase in the maternal preconception DEHP-BPA factor score was positively associated with risk of preterm birth (RR 1.36; 95% CI: 1.00, 1.84), while no association was found for the other three factors (Table 3). Quartile analyses showed an elevated risk of preterm birth comparing the fourth quartile to the first quartile of maternal DEHP-BPA factor score, adjusting for covariates (RR 2.82; 95% CI: 0.97, 8.24) (Table S4).

Table 3
Adjusted risk ratio (95% CI) of preterm birth per 1-unit increase in PCA-derived factor scores from 384 mothers and 211 fathers in the Environment and Reproductive Health (EARTH) Study, 2005–2018.

PCA-derived factors	Maternal		Paternal	
	Risk Ratio (95% CI)[a]	P values	Risk Ratio (95% CI)[b]	P values
DEHP-BPA factor	1.36 (1.00, 1.84)	0.05	1.47 (0.90, 2.42)	0.13
Paraben factor	0.93 (0.65, 1.32)	0.68	1.43 (0.86, 2.38)	0.17
High molecular weight phthalate factor	0.88 (0.61, 1.26)	0.49	0.67 (0.38, 1.17)	0.16
Low molecular weight phthalate factor	0.96 (0.65, 1.41)	0.82	0.89 (0.51, 1.52)	0.66

Note: PCA, Principal component analysis; di-(2-ethylhexyl) phthalate (DEHP). All four PCA-derived factors were mutually adjusted for in the maternal/paternal models.
[a] Adjusted for age (continuous), BMI (continuous), ART (yes/no), smoking (ever/never), education (categorical), race (categorical).
[b] Adjusted for maternal and paternal age (continuous), maternal and paternal BMI (continuous), maternal and paternal smoking (ever/never), maternal education (categorical), maternal race (categorical), ART (yes/no).

Probit BKMR models for the maternal preconception biomarkers showed that the DEHP-BPA factor had the highest group posterior inclusion probability (p = 0.65). Within the DEHP-BPA factor group, BPA produced the highest inclusion probability (p = 0.73) (Table S5). The univariate exposure–response analysis found maternal preconception BPA concentration was positively associated with preterm birth estimate, when the remaining biomarkers were held at their median concentrations (Fig. 1). No other discernible patterns were found for the other biomarkers examined (Fig. 1). In examining the figures for potential interactions, we found no apparent differences in the associations between individual biomarkers at the 25th versus 75th percentiles and preterm birth estimates, comparing the results when concentrations of the remaining maternal biomarkers were set at their 25th, 50th, and 75th percentile concentrations (Fig. S4). Furthermore, we did not identify a clear trend of the cumulative effect of the total maternal preconception mixture on preterm birth estimate (Fig. S5).

3.4. Paternal preconception mixtures

The paternal preconception PCA identified the same four factors as the maternal preconception analysis, but with notable differences in the percent of total mixture variance explained by each factor (Table S6). The DEHP-BPA factor still accounted for the highest of the total variance (33.5%) with the HMWP, LMWP and paraben factors accounting for 15.4%, 13.9%, and 10.0% of the total variance, respectively. Poisson regression models showed that each 1-unit increase in the paternal preconception DEHP-BPA factor score was positively associated with preterm birth in the unadjusted model (RR 1.51; 95%CI: 0.98, 2.34), with modest attenuation after covariate adjustment (RR 1.47; 95%CI: 0.90, 2.42) (Table 3). A quartile-based analysis was not possible for paternal preconception DEHP-BPA factor scores as there were no preterm births within the first quartile (Table S4). We furthermore found a suggestive positive association between the paternal paraben factor and preterm birth (RR 1.43; 95%CI: 0.86, 2.38), but no obvious pattern was found between quartiles of paternal paraben factor scores and preterm birth risk (Table S7). Paternal preconception HMWP factor showed a potential negative association with preterm birth although the confidence interval was relatively wide (RR 0.67; 95% CI: 0.38, 1.17) (Table 3). No association was observed for paternal preconception LMWP factor and preterm birth (Table 3).

Similar to the maternal group, paternal preconception probit BKMR models found that the DEHP-BPA factor also had the highest group inclusion probability (p = 0.67). However, for the paternal window, MEHP showed the highest inclusion probability within the DEHP-BPA factor (p = 0.48) (Table S8). We observed a non-linear positive trend between paternal preconception MEHP concentrations and preterm birth estimate, when all other paternal biomarkers were held at their median concentrations (Fig. 2). Negative trends were observed between paternal preconception MiBP and MCPP concentrations and preterm birth estimates, when all other paternal biomarkers were held at their median concentrations (Fig. 2). No apparent interactions were found for any paternal individual biomarker with the remaining paternal

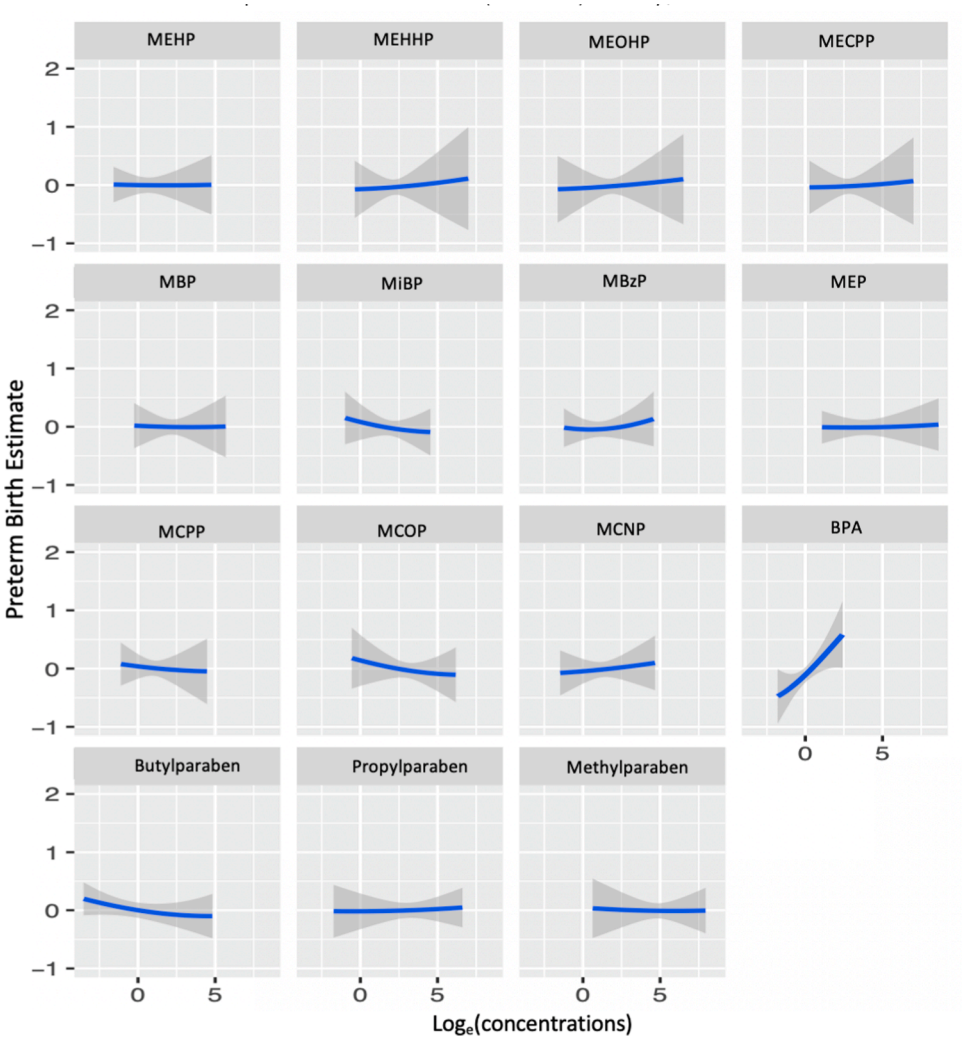

Fig. 1. Univariate dose–response association (estimates and credible intervals) of **maternal preconception** phenol and phthalate metabolite concentrations on preterm birth estimate, holding all other biomarkers at their median concentrations among 384 mothers in the Environment and Reproductive Health (EARTH) Study, 2005–2018. Note: Bisphenol A (BPA); methylparaben; propylparaben; butylparaben; monoethyl phthalate (MEP); mono-n-butyl phthalate (MBP); mono-isobutyl phthalate (MiBP); monobenzyl phthalate (MBzP); mono (2-ethylhexyl) phthalate (MEHP); mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); mono(2-ethyl-5-oxohexyl) phthalate (MEOHP); mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); mono(3-carboxypropyl) phthalate (MCPP); monocarboxyisooctyl phthalate (MCOP); monocarboxyisononyl phthalate (MCNP); models were adjusted for maternal age (continuous), BMI (continuous), ART (yes/no), smoking (ever/never), education (categorical), race (categorical).

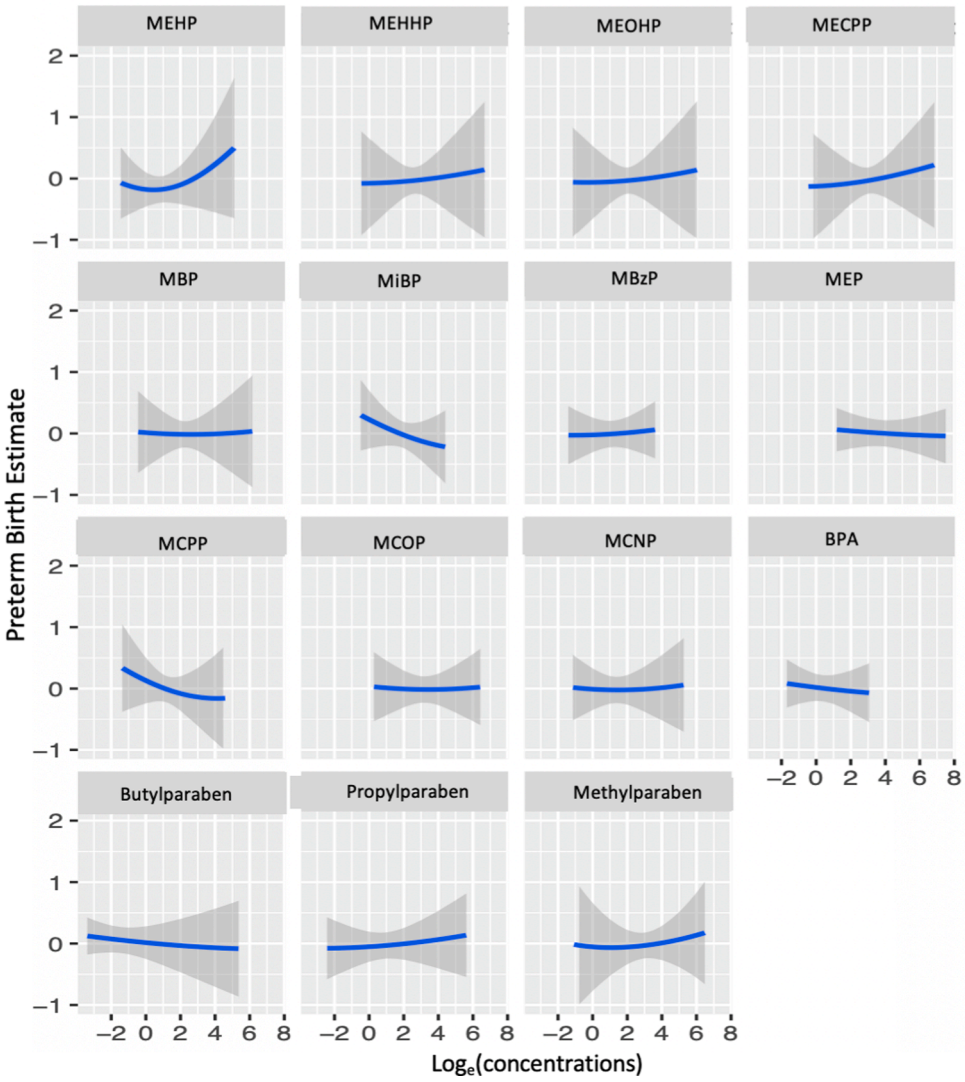

Fig. 2. Univariate dose–response association (estimates and credible intervals) of **paternal preconception** phenol and phthalate metabolite concentrations on preterm birth estimate, holding all other biomarkers at their median concentrations among 211 fathers in the Environment and Reproductive Health (EARTH) Study, 2005–2018. Note: Bisphenol A (BPA); methylparaben; propylparaben; butylparaben; monoethyl phthalate (MEP); mono-n-butyl phthalate (MBP); mono-isobutyl phthalate (MiBP); monobenzyl phthalate (MBzP); mono (2-ethylhexyl) phthalate (MEHP); mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); mono(2-ethyl-5-oxohexyl) phthalate (MEOHP); mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); mono(3-carboxypropyl) phthalate (MCPP); monocarboxyisooctyl phthalate (MCOP); monocarboxyisononyl phthalate (MCNP); models were adjusted for maternal and paternal age (continuous), maternal and paternal BMI (continuous), maternal and paternal smoking (ever/never), maternal education (categorical), maternal race (categorical), ART (yes/no).

biomarkers on preterm birth estimates (Fig. S6). Lastly, there was no detectable trend in the cumulative effect of the total paternal preconception mixtures on preterm birth estimate (Fig. 4).

3.5. Couples' preconception mixtures

In the probit BKMR model of couples (n = 203), the inclusion probability of maternal (p = 0.77) and paternal preconception mixtures (p = 0.61) were similar, suggesting a comparable contribution of exposure from each parent to the outcome (Table S9). Within the paternal preconception mixture, MEHP (p = 0.21) and MCPP (p = 0.20) had the highest inclusion probabilities, while MEHHP (p = 0.36) had the highest inclusion probability within the maternal preconception mixture (Table S9). We found a positive trend between maternal preconception MEHHP and preterm birth estimates when holding the remaining maternal **and** paternal biomarkers at their median concentrations (Fig. 3). We observed a non-linear positive trend between paternal preconception MEHP concentrations and preterm birth estimate, when all the remaining paternal **and** maternal biomarkers were held at their median concentrations (Fig. 3). No interactions were visible between couples' individual biomarker and the other biomarker concentrations on preterm birth estimate (Fig. S7). We did, however, find a positive trend of the cumulative effect of couples' total phenol and phthalate mixture on preterm birth estimate (Fig. 4).

In maternal models restricted to the 203 mothers who enrolled with their male partners, we found an increased risk of preterm birth in relation to the DEHP-BPA factor (RR 1.80; 95% CI: 1.12, 2.88, per 1-unit increase in factor score) after adjusting for covariates (Table S10). In BKMR models, the DEHP-BPA factor had the highest group posterior inclusion probability (p = 0.86), but MEHHP and MEOHP – and not BPA – accounted for the highest conditional posterior inclusion probability within the DEHP-BPA group (p = 0.37) (Table S11). BKMR showed a positive trend between MEHHP and preterm birth estimate when the remaining maternal preconception biomarkers were held at their median concentrations among this restricted sample of women (Fig. S8). No trend was observed between maternal preconception BPA and preterm birth estimate in the restricted model (Fig. S8). Additionally, we found a significant positive cumulative effect of maternal preconception total mixtures assessed through quantiles on preterm birth estimate (Fig. 4).

4. Discussion

Our findings showed that mixtures containing DEHP metabolites and BPA as the main components were associated with an increased risk of preterm birth in both maternal and paternal preconception windows based on PCA results. We furthermore found a suggestive but less robust association between the paternal paraben factor and preterm birth. BKMR models provided complementary information on these

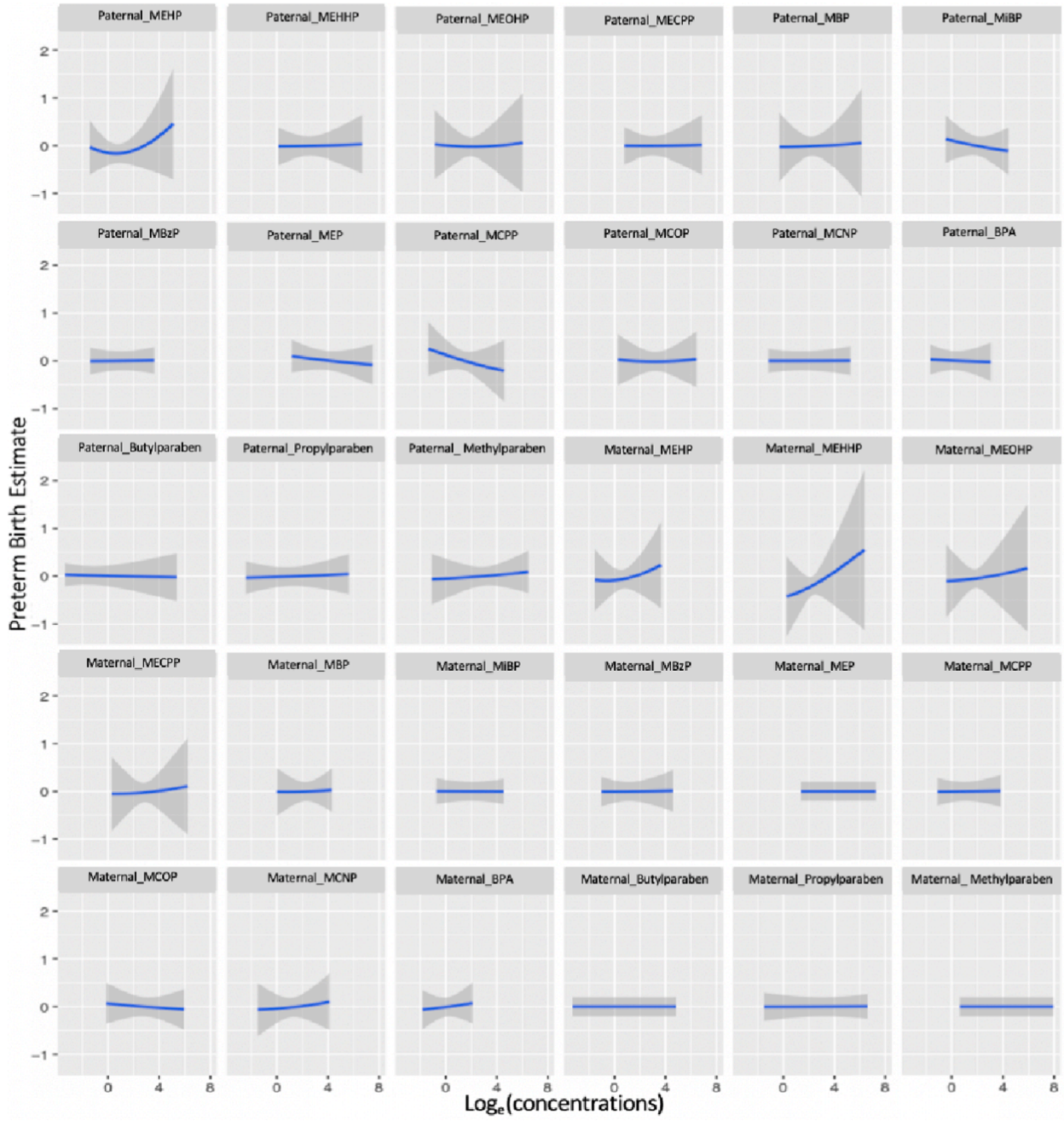

Fig. 3. Univariate dose–response association (estimates and credible intervals) of **couples' preconception** phenols and phthalates metabolite concentrations on preterm birth estimate, holding all other biomarkers at their median concentrations among 203 couples in the Environment and Reproductive Health (EARTH) Study, 2005–2018. Note: Bisphenol A (BPA); methylparaben; propylparaben; butylparaben; monoethyl phthalate (MEP); mono-n-butyl phthalate (MBP); mono-isobutyl phthalate (MiBP); monobenzyl phthalate (MBzP); mono(2-ethylhexyl) phthalate (MEHP); mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); mono(2-ethyl-5-oxohexyl) phthalate (MEOHP); mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); mono(3-carboxypropyl) phthalate (MCPP); monocarboxyisooctyl phthalate (MCOP); monocarboxyisononyl phthalate (MCNP);models were adjusted for maternal age (continuous), BMI (continuous), ART (yes/no), smoking (ever/never), education (categorical), race (categorical).

associations in the context of mixtures. In the maternal preconception mixture analysis, BPA and MEHHP were identified as the strongest contributors to the risk of preterm birth when the remaining biomarkers were held at their median concentrations. In the paternal mixture analysis, MEHP was identified as the strongest contributor to preterm birth risk, showing a non-linear positive trend when all other paternal biomarkers were held at their median concentrations. No interactions within the total mixture in either maternal or paternal preconception windows were found. In sensitivity analyses restricted to couples, hierarchical variable selection coupled to BKMR models showed a similar relative contribution of paternal and maternal preconception biomarkers on the risk of preterm birth. A positive dose–response cumulative effect was observed between couple's preconception exposure to mixtures and preterm birth risk estimates.

In the absence of other preconception cohorts with which to compare our results, the epidemiologic interpretation of the present mixture findings is based on preterm birth results from this same cohort examining maternal and paternal preconception exposure to phenols and phthalates using conventional single-pollutant analyses (Mustieles et al., 2020; Zhang et al., 2020). We previously observed that maternal

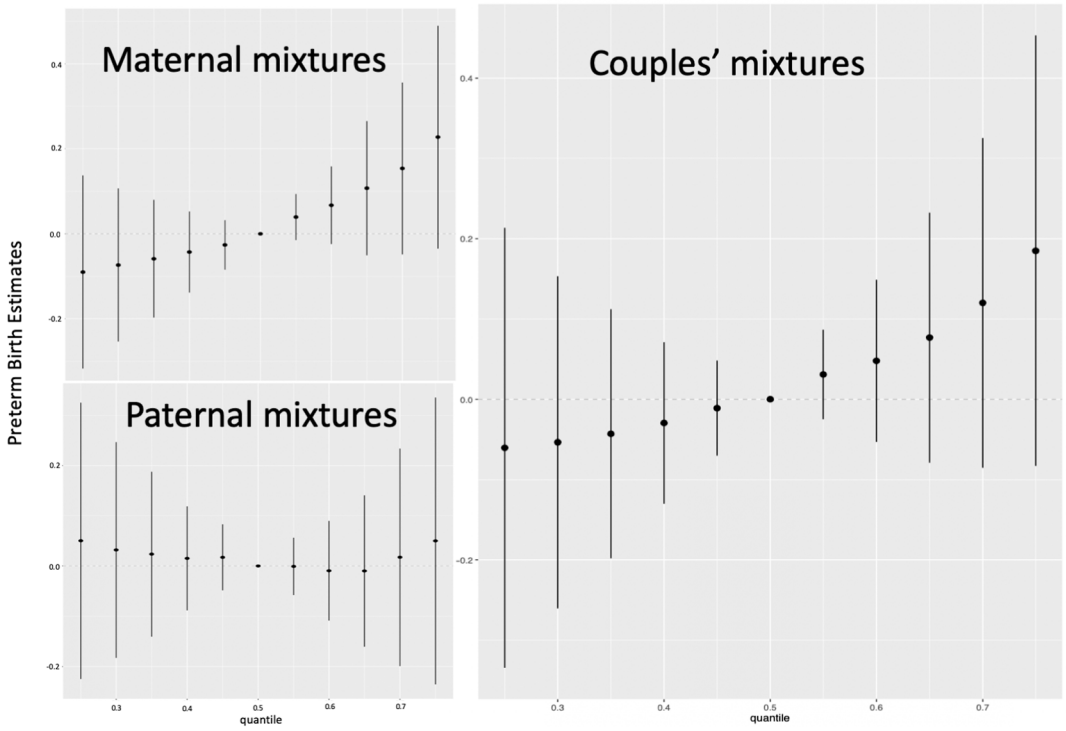

Fig. 4. Cumulative effect (estimates and credible intervals) across per 5th quantile above and below medians of maternal, paternal and couples' total preconception mixture on preterm birth estimate in the Environment and Reproductive Health (EARTH) Study, 2005–2018. Note: Maternal model was restricted to women who participated as couples (n = 203), paternal model included all fathers (n = 211, i.e. 203 who participated as couples and 8 who participated independently), couples model included the 203 couples; reference group is the median concentration of the respective mixture; models for maternal and couples' mixtures were adjusted for maternal age (continuous), BMI (continuous), ART (yes/no), smoking (ever/never), education (categorical), race (categorical); models for paternal mixtures were adjusted for maternal and paternal age (continuous), maternal and paternal BMI (continuous), maternal and paternal smoking (ever/never), maternal education (categorical), maternal race (categorical), ART (yes/no).

preconception exposure to BPA was associated with preterm birth, while paternal paraben exposure also pointed to an increased risk (Mustieles et al., 2020). Regarding phthalates, single chemical analyses showed that both maternal and paternal preconception concentrations of DEHP metabolites were associated with increased risk of preterm birth. However, maternal DEHP exposure appeared to account for the association found among fathers' exposure (Zhang et al., 2020). In single-pollutant analysis, we observed imprecise negative associations for two paternal preconception high molecular weight phthalates (MCPP and MCOP) and preterm birth (Zhang et al., 2020). However, no biologically plausible evidence exists to support this apparent protective finding. Given the imprecise estimate and limited plausible biological evidence, unmeasured confounding by lifestyles might be responsible for the observed seemingly protective association between paternal preconception HMWP factor and preterm birth, which limited further investigation.

In the maternal preconception BKMR model including the total cohort (i.e. 384 mothers), we found that BPA was positively associated with preterm birth (when holding all other biomarkers at their median concentrations), while there was no clear association between the total maternal mixture and preterm birth. However, among the 203 mothers who enrolled with their male partner, BKMR models showed MEHHP as the strongest contributor to preterm birth. Here, we found a positive association between the total maternal preconception mixture and preterm birth risk estimates. It is worth noting that the PCA results were largely consistent in both analyses, pointing to the DEHP-BPA factor as the main component associated with preterm birth. Women who enrolled as couples had slightly higher DEHP metabolites and BPA concentrations than those who did not, and their male partners showed a higher proportion of male infertility diagnosis. Any inconsistencies between the two models might suggest different chemical interplays (i.e. different cumulative effects) when DEHP metabolites and BPA were present at different concentrations, and/or different interplays between the effect of chemicals on progenitors based on slight variations in the proportion of parent-of-origin infertility diagnosis. Nevertheless, both BPA and MEHHP were identified as the chemicals of greatest concern among the phenols and phthalates examined in the maternal preconception window.

Together with the results obtained in single-chemical analyses for phenol (Mustieles et al., 2020) and phthalate (Zhang et al., 2020) biomarkers, the current PCA and BKMR results support the following: 1) maternal preconception exposure to both BPA and DEHP appears to be associated with higher preterm birth risk; 2) paternal preconception concentrations of MEHP (a DEHP metabolite), but not BPA, appears to be associated with increased preterm birth; 3) a complex biological interplay seems to exist between maternal and paternal preconception exposures, with both progenitors contributing to preterm birth; 4) a cumulative joint effect of the total chemical mixture within couples may exist in relation to preterm birth. Below we discuss the existing biological and toxicological support.

We hypothesize that couples' preconception exposure to phenols and phthalates may affect the male and female germline, especially at the level of epigenetic regulation during gametogenesis (Sun et al., 2017), which may persist and operate during embryogenesis, decidualization and/or placentation, predisposing to adverse pregnancy and birth outcomes, including a shorter gestation (Cha et al., 2012; Li et al., 2012; Zong et al., 2015). Although mechanistic data on preconception exposures are scarce, our maternal findings are plausible considering the established effect of BPA and DEHP in the ovary with related epigenetic modifications in ovary and oocytes which can be transmitted across generations (Eichenlaub-Ritter and Pacchierotti, 2015; Li et al., 2014; Santangeli et al., 2016; Zhang et al., 2016; Zhang et al., 2018).

Regarding the paternal findings, previous epidemiological study found MEHP was associated with decreased sex hormones and increased DNA fragmentation index among males (Pan et al., 2015). Rodent studies have also confirmed the ability of DEHP and BPA to exert heritable epigenetic modifications in sperm, with implications for reproductive health in subsequent generations (Doyle et al., 2013; Shi et al., 2019), including post implantation losses (Doshi et al., 2013).

Although epigenetic marks in gametes are erased during fertilization and then during embryo preimplantation development, imprinted genes can escape this process (Hanna et al., 2018). Genomic imprinting, the monoallelic parent-of-origin-dependent expression of a subset of specific genes, is required for normal development, fetal growth, gestation length and metabolism among other functions (Malnou et al., 2018; Monk et al., 2019). Interestingly, both BPA and DEHP have been shown to alter the epigenetic regulation of imprinted genes in gametes (Liao and Kannan, 2014; Kochmanski et al., 2018; Susiarjo et al., 2013), potentially explaining the contribution of both parents to birth outcomes such as preterm birth.

In relation to the potential cumulative effect of the total chemical mixture on preterm birth, emerging evidence highlights the frequent exacerbation in response to the so-called "cocktail" effect (Kortenkamp and Faust, 2018). For example, co-administration of DEHP in mice reduces the threshold dose at which BPA disrupts blastocyst implantation (Borman et al., 2016). In rats, mixtures of BPA and DEHP led to transgenerational effects including reproductive endpoints (Manikkam et al., 2013), biologically supporting the potential existence of mixture effects mediated by epigenetic mechanisms.

The observed PCA-derived factors in this study, namely DEHP and BPA factor, paraben factor, HMWP factor and LMWP factor, were similar between preconception mothers and fathers, and in line with previously published analyses in both the EARTH Study (Chiu et al., 2018; Mínguez-Alarcón et al., 2019) and other cohorts (Myridakis et al., 2015). The DEHP-BPA factor suggests that both chemicals share exposure sources, perhaps from packaged food and beverages (Martínez et al., 2018). Parabens and LMWP, including MEP, MBP and MiBP are mainly used in cosmetics, fragrance and consumer products. Thus, the paraben factor comprising parabens and MEP seems to indicate cosmetic sources of exposure (Nassan et al., 2017).

The major strength of our study was the implementation of two complementary statistical methods to evaluate the contribution of chemical mixtures on the risk of preterm birth among prospective parents. PCA and BKMR methods complemented each other providing coherent answers to our initial research question (Messerlian et al., 2018). PCA grouped the mixtures based on correlations (O'Rourke and Hatcher, 2013) while BKMR used the information on the mixture groups derived by PCA, examining both the overall mixture effect and the effects of each component within the context of the overall joint exposure. BKMR also provided information on potential interactions and cumulative effects of the total mixture, although we did not observe any interactions. Furthermore, BKMR models coupled to hierarchical variable selection (Valeri et al., 2017; Coull et al., 2015) estimated the relative contribution of maternal and paternal preconception windows. We were furthermore able to account for the increasingly relevant role of both maternal and paternal factors in pregnancy outcomes (Bellavia et al., 2020). Nevertheless, we remained uncertain whether or not our findings were generalizable to fertile couples since subfertile men and women may have increased susceptibility to environmental perturbations, and preterm birth may be associated with underlying treatment or infertility factors (Cavoretto et al., 2018). However, our results remained consistent with the existing literature on BPA and DEHP in relation to adverse outcomes in both subfertile (Mustieles et al., 2018; Messerlian et al., 2018; Messerlian et al., 2017; Mustieles et al., 2019) and non-subfertile study populations (Radke et al., 2019). Another major strength of the present work was our use of repeated urine samples across the preconception period to quantify exposure to phthalates and phenols. This approach reduced exposure misclassification and the probability of attenuation bias (Vernet et al., 2019), though exposure misclassification was still possible given the short biological half-lives and the episodic nature of exposure to these non-persistent chemicals. Our prospective preconception cohort design was a major advantage relative to other designs reported in prior research on this topic (Ferguson et al., 2014; Aung et al., 2019). The modest number of preterm birth cases limited our ability to study the subtypes of preterm birth, including preterm premature rupture of membranes, placental abruption, and spontaneous preterm labor. Caution should be taken when interpreting the couple-based results due to the reduced sample size for couples and the more modest number of preterm cases. Another limitation is that, while human populations are normally exposed to many chemical families at low doses, our mixtures analyses focused on non-persistent chemicals used in plastics manufacturing (e.g., BPA, DEHP) and in personal care products (e.g., parabens). We additionally did not consider potential co-exposure confounding during the prenatal window, given the inherent complexity of the models investigated. However, we did not observe prenatal co-exposure confounding of couple's DEHP and BPA preconception associations with preterm birth in our previous single-pollutant analyses within this same dataset (Mustieles et al., 2020; Zhang et al., 2020).

5. Conclusions

A complex interplay was observed between parental preconception exposure to mixtures of non-persistent chemicals, with both paternal and maternal windows of exposure jointly contributing to the risk of preterm birth. Specifically, maternal BPA and DEHP, and paternal DEHP exposure before conception, appeared to increase the risk of preterm birth in the context of the joint preconception mixture. Additionally, maternal and paternal preconception windows showed similar contributions supporting that preterm birth should be regarded as a couple-based pregnancy outcome. Our results highlight the need to consider couples' preconception exposure to chemical mixtures, showing the suitability and advantages of PCA coupled to BKMR for achieving this purpose. Future studies should deepen the mechanistic understanding of these exposure-outcome associations and validate our findings in a fertile population of pregnancy planners.

CRediT authorship contribution statement

Yu Zhang: Conceptualization, Methodology, Software, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Vicente Mustieles:** Conceptualization, Writing - original draft, Writing - review & editing. **Paige L. Williams:** Methodology, Writing - review & editing. **Blair J. Wylie:** Writing - review & editing. **Irene Souter:** Writing - review & editing. **Antonia M. Calafat:** Writing - review & editing, Data curation. **Melina Demokritou:** Writing - review & editing. **Alexandria Lee:** Writing - review & editing. **Stylianos Vagios:** Writing - review & editing. **Russ Hauser:** Writing - review & editing, Funding acquisition. **Carmen Messerlian:** Conceptualization, Methodology, Writing - review & editing, Supervision.

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.

Acknowledgement

The authors acknowledge all members of the EARTH Study team, and physicians and staff at Massachusetts General Hospital Fertility Center. We are grateful to all study participants and to Xiaoliu Zhou, Tao Jia, and Xiaoyun Ye (deceased) (CDC, Atlanta, GA) for measuring the urinary concentrations of phthalate and phenol biomarkers.

Funding sources

This work was supported by the National Institute of Environmental Health Sciences of the National Institutes of Health (R01ES031657, R01ES009718). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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), the US Government, or the Department of Health and Human Services (DHHS). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or DHHS.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106440.

References

ACOG, 2014. Obstetricians, Gynecologists, Committee opinion no 611: method for estimating due date. Obstet. Gynecol. 124, 863–866.
Aker, A.M., Ferguson, K.K., Rosario, Z.Y., Mukherjee, B., Alshawabkeh, A.N., Cordero, J. F., Meeker, J.D., 2019. The associations between prenatal exposure to triclocarban, phenols and parabens with gestational age and birth weight in northern Puerto Rico. Environ. Res. 169, 41–51.
Aung, M.T., Ferguson, K.K., Cantonwine, D.E., McElrath, T.F., Meeker, J.D., 2019. Preterm birth in relation to the bisphenol A replacement, bisphenol S, and other phenols and parabens. Environ. Res. 169, 131–138.
Bellavia, A., Mitro, S.D., Hauser, R., James-Todd, T., 2020. Paternal bias: the impact of not accounting for paternal confounders in reproductive epidemiological studies. Am. J. Obstet. Gynecol. 222, 87–88.
Bengtsson, J., Thygesen, P.S., Kaerlev, L., Knudsen, L.E., Bonde, J.P., 2017. Potential exposure to endocrine disrupting chemicals and selected adverse pregnancy outcomes: a follow-up study of pregnant women referred for occupational counselling. J. Occup. Med. Toxicol. 12, 6.
Benjamin, S., Masai, E., Kamimura, N., Takahashi, K., Anderson, R.C., Faisal, P.A., 2017. Phthalates impact human health: epidemiological evidences and plausible mechanism of action. J. Hazard. Mater. 340, 360–383.
Birks, L., Casas, M., Garcia, A.M., Alexander, J., Barros, H., Bergstrom, A., Bonde, J.P., Burdorf, A., Costet, N., Danileviciute, A., Eggesbo, M., Fernandez, M.F., Gonzalez-Galarzo, M.C., Hanke, W., Jaddoe, V., Kogevinas, M., Kull, I., Lertxundi, A., Melaki, V., Andersen, A.N., Olea, N., Polanska, K., Rusconi, F., Santa-Marina, L., Santos, A.C., Vrijkotte, T., Zugna, D., Nieuwenhuijsen, M., Cordier, S., Vrijheid, M., 2016. Occupational exposure to endocrine-disrupting chemicals and birth weight and length of gestation: a European meta-analysis. Environ. Health Perspect. 124, 1785–1793.
Birnbaum, L.S., 2012. NIEHS's new strategic plan. Environ. Health Perspect. 120, a298.
Bobb, J.F., Valeri, L., Claus Henn, B., Christiani, D.C., Wright, R.O., Mazumdar, M., Godleski, J.J., Coull, B.A., 2015. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics 16, 493–508.
Bobb, J.F., 2017. Bayesian Kernel Machine Regression. In: CRAN, Implementation of a statistical approach for estimating the joint health effects of multiple concurrent exposure.
Borman, E.D., Foster, W.G., deCatanzaro, D., 2016. Concurrent administration of diethylhexyl phthalate reduces the threshold dose at which bisphenol A disrupts blastocyst implantation and cadherins in mice. Environ. Toxicol. Pharmacol. 49, 105–111.
Braun, J.M., Kalkbrenner, A.E., Just, A.C., Yolton, K., Calafat, A.M., Sjödin, A., Hauser, R., Webster, G.M., Chen, A., Lanphear, B.P., 2014. Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4-and 5-year-old children: the HOME study. Environ. Health Perspect. 122, 513–520.
Braun, J.M., Messerlian, C., Hauser, R., 2017. Fathers matter: why it's time to consider the impact of paternal environmental exposures on children's health. Curr. Epidemiol. Rep. 4, 46–55.
Calafat, A.M., Ye, X., Wong, L.Y., Reidy, J.A., Needham, L.L., 2008. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. Environ. Health Perspect. 116, 39–44.
Carlin, D.J., Rider, C.V., Woychik, R., Birnbaum, L.S., 2013. Unraveling the health effects of environmental mixtures: an NIEHS priority. Environ. Health Perspect. 121, A6–A8.
Carvaillo, J.C., Barouki, R., Coumoul, X., Audouze, K., 2019. Linking Bisphenol S to adverse outcome pathways using a combined text mining and systems biology approach. Environ. Health Perspect. 127, 47005.
Cavoretto, P., Candiani, M., Giorgione, V., Inversetti, A., Abu-Saba, M.M., Tiberio, F., Sigismondi, C., Farina, A., 2018. Risk of spontaneous preterm birth in singleton pregnancies conceived after IVF/ICSI treatment: meta-analysis of cohort studies. Ultrasound Obstet. Gynecol. 51, 43–53.
Centers for Disease Control and Prevention, 2017. Fourth National Report on Human Exposure to Environmental Chemicals Update, in, Atlanta, GA.
Cha, J., Sun, X., Dey, S.K., 2012. Mechanisms of implantation: strategies for successful pregnancy. Nat. Med. 18, 1754–1767.
Chin, H.B., Jukic, A.M., Wilcox, A.J., Weinberg, C.R., Ferguson, K.K., Calafat, A.M., McConnaughey, D.R., Baird, D.D., 2019. Association of urinary concentrations of early pregnancy phthalate metabolites and bisphenol A with length of gestation. Environ. Health 18, 80.
Chiu, Y.-H., Bellavia, A., James-Todd, T., Correia, K.F., Valeri, L., Messerlian, C., Ford, J. B., Mínguez-Alarcón, L., Calafat, A.M., Hauser, R., Williams, P.L., 2018. E.S.T. for the, E.S. Team, Evaluating effects of prenatal exposure to phthalate mixtures on birth weight: a comparison of three statistical approaches. Environ. Int. 113, 231–239.
Coull, B.A., Bobb, J.F., Wellenius, G.A., Kioumourtzoglou, M.-A., Mittleman, M.A., Koutrakis, P., Godleski, J.J., 2015. Part 1. Statistical learning methods for the effects of multiple air pollution constituents. Res. Rep. (Health Effects Institute) 5–50.
De Felice, B., Manfellotto, F., Palumbo, A., Troisi, J., Zullo, F., Di Carlo, C., Di Spiezio Sardo, A., De Stefano, N., Ferbo, U., Guida, M., Guida, M., 2015. Genome-wide microRNA expression profiling in placentas from pregnant women exposed to BPA. BMC Med. Genomics 8, 56.
Doshi, T., D'Souza, C., Vanage, G., 2013. Aberrant DNA methylation at Igf2-H19 imprinting control region in spermatozoa upon neonatal exposure to bisphenol A and its association with post implantation loss. Mol. Biol. Rep. 40.
Doyle, T.J., Bowman, J.L., Windell, V.L., McLean, D.J., Kim, K.H., 2013. Transgenerational effects of di-(2-ethylhexyl) phthalate on testicular germ cell associations and spermatogonial stem cells in mice. Biol. Reprod. 88, 112.
Drakvik, E., Altenburger, R., Aoki, Y., Backhaus, T., Bahadori, T., Barouki, R., Brack, W., Cronin, M.T.D., Demeneix, B., Hougaard Bennekou, S., van Klaveren, J., Kneuer, C., Kolossa-Gehring, M., Lebret, E., Posthuma, L., Reiber, L., Rider, C., Rüegg, J., Testa, G., van der Burg, B., van der Voet, H., Warhurst, A.M., van de Water, B., Yamazaki, K., Öberg, M., Bergman, Å., 2020. Statement on advancing the assessment of chemical mixtures and their risks for human health and the environment. Environ. Int. 134, 105267.
Eichenlaub-Ritter, U., Pacchierotti, F., 2015. Bisphenol a effects on mammalian oogenesis and epigenetic integrity of oocytes: a case study exploring risks of endocrine disrupting chemicals. Biomed Res. Int. 2015, 698795–1698711.
Etzel, R.A., 2020. Is the environment associated with preterm birth? JAMA Netw. Open 3, e202239.
European Chemicals Agency, E., 2016. Member State Committee Support Document for Identification of 4,4'-Isopropylidenediphenol (Bisphenol A) as a Substance of Very High Concern Because of its Toxic For Reproduction (Article 57 C), EC 201-245-8, CAS 80-05-7.
Farland, L.V., Correia, K.F., Wise, L.A., Williams, P.L., Ginsburg, E.S., Missmer, S.A., 2016. P-values and reproductive health: what can clinical researchers learn from the American Statistical Association? Hum. Reprod. 31, 2406–2410.
Ferguson, K.K., Chin, H.B., 2017. Environmental chemicals and preterm birth: biological mechanisms and the state of the science. Curr. Epidemiol. Rep. 4, 56–71.
Ferguson, K.K., McElrath, T.F., Meeker, J.D., 2014. Environmental phthalate exposure and preterm birth. JAMA Pediatr. 168, 61–67.
Freire, C., Molina-Molina, J.M., Iribarne-Duran, L.M., Jimenez-Diaz, I., Vela-Soria, F., Mustieles, V., Arrebola, J.P., Fernandez, M.F., Artacho-Cordon, F., Olea, N., 2019. Concentrations of bisphenol A and parabens in socks for infants and young children in Spain and their hormone-like activities. Environ. Int. 127, 592–600.
Ghazipura, M., McGowan, R., Arslan, A., Hossain, T., 2017. Exposure to benzophenone-3 and reproductive toxicity: a systematic review of human and animal studies. Reprod. Toxicol. 73, 175–183.
Giulivo, M., Lopez de Alda, M., Capri, E., Barcelo, D., 2016. Human exposure to endocrine disrupting compounds: Their role in reproductive systems, metabolic syndrome and breast cancer. A review. Environ. Res. 151, 251–264.
Goldenberg, R.L., Culhane, J.F., Iams, J.D., Romero, R., 2008. Epidemiology and causes of preterm birth. Lancet 371, 75–84.
Govarts, E., Iszatt, N., Trnovec, T., de Cock, M., Eggesbo, M., Palkovicova Murinova, L., van de Bor, M., Guxens, M., Chevrier, C., Koppen, G., Lamoree, M., Hertz-Picciotto, I., Lopez-Espinosa, M.J., Lertxundi, A., Grimalt, J.O., Torrent, M., Goni-Irigoyen, F., Vermeulen, R., Legler, J., Schoeters, G., 2018. Prenatal exposure to endocrine disrupting chemicals and risk of being born small for gestational age: pooled analysis of seven European birth cohorts. Environ. Int. 115, 267–278.
Hanna, C.W., Demond, H., Kelsey, G., 2018. Epigenetic regulation in development: is the mouse a good model for the human? Hum. Reprod. Update 24, 556–576.
Hao, H., Chang, H.H., Holmes, H.A., Mulholland, J.A., Klein, M., Darrow, L.A., Strickland, M.J., 2016. Air pollution and preterm birth in the U.S. State of Georgia (2002–2006): associations with concentrations of 11 ambient air pollutants estimated by combining community multiscale air quality model (CMAQ) simulations with stationary monitor measurements. Environ. Health Perspect. 124, 875–880.
Hornung, R.W., Reed, L.D., 1990. Estimation of average concentration in the presence of nondetectable values. Appl. Occup. Environ. Hyg. 5, 46–51.
Hou, J., Yin, W., Li, P., Hu, C., Xu, T., Cheng, J., Li, T., Wang, L., Yu, Z., Yuan, J., 2020. Joint effect of polycyclic aromatic hydrocarbons and phthalates exposure on telomere length and lung function. J. Hazard. Mater. 386, 121663.
Jamal, A., Rastkari, N., Dehghaniathar, R., Aghaei, M., Nodehi, R.N., Nasseri, S., Kashani, H., Yunesian, M., 2019. Prenatal exposure to parabens and anthropometric birth outcomes: a systematic review. Environ. Res. 173, 419–431.

Johnson, P.I., Koustas, E., Vesterinen, H.M., Sutton, P., Atchley, D.S., Kim, A.N., Campbell, M., Donald, J.M., Sen, S., Bero, L., Zeise, L., Woodruff, T.J., 2016. Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. Environ. Int. 92–93, 716–728.
Kamai, E.M., McElrath, T.F., Ferguson, K.K., 2019. Fetal growth in environmental epidemiology: mechanisms, limitations, and a review of associations with biomarkers of non-persistent chemical exposures during pregnancy. Environ. Health 18, 43.
Kapraun, D.F., Wambaugh, J.F., Ring, C.L., Tornero-Velez, R., Setzer, R.W., 2017. A method for identifying prevalent chemical combinations in the U.S. population. Environ. Health Perspect. 125, 087017.
Karpuzoglu, E., Holladay, S.D., Gogal Jr., R.M., 2013. Parabens: potential impact of low-affinity estrogen receptor binding chemicals on human health. J. Toxicol. Environ. Health B Crit. Rev. 16, 321–335.
Kim, S., Kim, S., Won, S., Choi, K., 2017. Considering common sources of exposure in association studies-Urinary benzophenone-3 and DEHP metabolites are associated with altered thyroid hormone balance in the NHANES 2007–2008. Environ. Int. 107, 25–32.
Klebanoff, M.A., Keim, S.A., 2011. Epidemiology: the changing face of preterm birth. Clin. Perinatol. 38, 339–350.
Kochmanski, J.J., Marchlewicz, E.H., Cavalcante, R.G., Perera, B.P.U., Sartor, M.A., Dolinoy, D.C., 2018. Longitudinal effects of developmental Bisphenol A exposure on epigenome-wide DNA hydroxymethylation at imprinted loci in mouse blood. Environ. Health Perspect. 126, 077006.
Kortenkamp, A., 2007. Ten years of mixing cocktails: a review of combination effects of endocrine-disrupting chemicals. Environ. Health Perspect. 115, 98–105.
Kortenkamp, A., Faust, M., 2018. Regulate to reduce chemical mixture risk. Science 361, 224–226.
Lazarevic, N., Barnett, A.G., Sly, P.D., Knibbs, L.D., 2019. Statistical methodology in studies of prenatal exposure to mixtures of endocrine-disrupting chemicals: a review of existing approaches and new alternatives. Environ. Health Perspect. 127, 026001.
Li, R., Yu, C., Gao, R., Liu, X., Lu, J., Zhao, L., Chen, X., Ding, Y., Wang, Y., He, J., 2012. Effects of DEHP on endometrial receptivity and embryo implantation in pregnant mice. J. Hazard. Mater. 241–242, 231–240.
Li, L., Zhang, T., Qin, X.-S., Ge, W., Ma, H.-G., Sun, L.-L., Hou, Z.-M., Chen, H., Chen, P., Qin, G.-Q., Shen, W., Zhang, X.-F., 2014. Exposure to diethylhexyl phthalate (DEHP) results in a heritable modification of imprint genes DNA methylation in mouse oocytes. Mol. Biol. Rep. 41, 1227–1235.
Liao, C., Kannan, K., 2014. Widespread occurrence of benzophenone-type UV light filters in personal care products from China and the United States: an assessment of human exposure. Environ. Sci. Technol. 48, 4103–4109.
Lin, V.W., Baccarelli, A.A., Burris, H.H., 2016. Epigenetics-a potential mediator between air pollution and preterm birth. Environ. Epigenet. 2, e55387.
Luderer, U., Eskenazi, B., Hauser, R., Korach, K.S., McHale, C.M., Moran, F., Rieswijk, L., Solomon, G., Udagawa, O., Zhang, L., Zlatnik, M., Zeise, L., Smith, M.T., 2019. Proposed key characteristics of female reproductive toxicants as an approach for organizing and evaluating mechanistic data in hazard assessment. Environ. Health Perspect. 127, 75001.
Luu, T.M., Rehman Mian, M.O., Nuyt, A.M., 2017. Long-term impact of preterm birth: neurodevelopmental and physical health outcomes. Clin. Perinatol. 44, 305–314.
Luyckx, V.A., 2017. Preterm birth and its impact on renal health. Semin. Nephrol. 37, 311–319.
Malnou, E.C., Umlauf, D., Mouysset, M., Cavaillé, J., 2018. Imprinted MicroRNA gene clusters in the evolution, development, and functions of mammalian placenta. Front. Genet. 9, 706.
Manikkam, M., Tracey, R., Guerrero-Bosagna, C., Skinner, M.K., 2013. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PLoS ONE 8.
Martínez, M.A., Rovira, J., Sharma, R.P., Nadal, M., Schuhmacher, M., Kumar, V., 2018. Comparing dietary and non-dietary source contribution of BPA and DEHP to prenatal exposure: a Catalonia (Spain) case study. Environ. Res. 166, 25–34.
Menon, R., Conneely, K.N., Smith, A.K., 2012. DNA methylation: an epigenetic risk factor in preterm birth. Reprod. Sci. 19, 6–13.
Messerlian, C., Braun, J.M., Mínguez-Alarcón, L., Williams, P.L., Ford, J.B., Mustieles, V., Calafat, A.M., Souter, I., Toth, T., Hauser, R., 2017. Paternal and maternal urinary phthalate metabolite concentrations and birth weight of singletons conceived by subfertile couples. Environ. Int. 107, 55–64.
Messerlian, C., Williams, P.L., Ford, J.B., Chavarro, J.E., Mínguez-Alarcón, L., Dadd, R., Braun, J.M., Gaskins, A.J., Meeker, J.D., James-Todd, T., Chiu, Y., Nassan, F.L., Souter, I., Petrozza, J., Keller, M., Toth, T.L., Calafat, A.M., Hauser, R., 2018. The environment and reproductive health (EARTH) study: a prospective preconception cohort. Hum. Reprod. 2018, hoy001.
Messerlian, C., Mustieles, V., Minguez-Alarcon, L., Ford, J.B., Calafat, A.M., Souter, I., Williams, P.L., Hauser, R., 2018. Preconception and prenatal urinary concentrations of phenols and birth size of singleton infants born to mothers and fathers from the Environment and Reproductive Health (EARTH) study. Environ. Int. 114, 60–68.
Mínguez-Alarcón, L., Messerlian, C., Bellavia, A., Gaskins, A.J., Chiu, Y.-H., Ford, J.B., Azevedo, A.R., Petrozza, J.C., Calafat, A.M., Hauser, R., Williams, P.L., the Earth Study, T., Earth Study, T., 2019. Urinary concentrations of bisphenol A, parabens and phthalate metabolite mixtures in relation to reproductive success among women undergoing in vitro fertilization. Environ. Int., 126, 355–362.
Monk, D., Mackay, D.J.G., Eggermann, T., Maher, E.R., Riccio, A., 2019. Genomic imprinting disorders: lessons on how genome, epigenome and environment interact. Nat. Rev. Genet. 20, 235–248.
Moster, D., Lie, R.T., Markestad, T., 2008. Long-term medical and social consequences of preterm birth. N. Engl. J. Med. 359, 262–273.
Mustieles, V., Perez-Lobato, R., Olea, N., Fernandez, M.F., 2015. Bisphenol A: human exposure and neurobehavior. Neurotoxicology 49, 174–184.
Mustieles, V., Fernández, M.F., Martin-Olmedo, P., González-Alzaga, B., Fontalba-Navas, A., Hauser, R., Olea, N., Arrebola, J.P., 2017. Human adipose tissue levels of persistent organic pollutants and metabolic syndrome components: combining a cross-sectional with a 10-year longitudinal study using a multi-pollutant approach. Environ. Int. 104, 48–57.
Mustieles, V., Williams, P.L., Fernandez, M.F., Minguez-Alarcon, L., Ford, J.B., Calafat, A. M., Hauser, R., Messerlian, C., 2018. Maternal and paternal preconception exposure to bisphenols and size at birth. Hum. Reprod. 33, 1528–1537.
Mustieles, V., Mínguez-Alarcón, L., Christou, G., Ford, J.B., Dimitriadis, I., Hauser, R., Souter, I., Messerlian, C., 2019. Placental weight in relation to maternal and paternal preconception and prenatal urinary phthalate metabolite concentrations among subfertile couples. Environ. Res. 169, 272–279.
Mustieles, V., Zhang, Y., Yland, J., Braun, J.M., Williams, P.L., Wylie, B.J., Attaman, J.A., Ford, J.B., Azevedo, A., Calafat, A.M., 2020. Maternal and paternal preconception exposure to phenols and preterm birth. Environ. Int. 137, 105523.
Myridakis, A., Fthenou, E., Balaska, E., Vakinti, M., Kogevinas, M., Stephanou, E.G., 2015. Phthalate esters, parabens and bisphenol-A exposure among mothers and their children in Greece (Rhea cohort). Environ. Int. 83, 1–10.
Nassan, F.L., Coull, B.A., Gaskins, A.J., Williams, M.A., Skakkebaek, N.E., Ford, J.B., Ye, X., Calafat, A.M., Braun, J.M., Hauser, R., 2017. Personal care product use in men and urinary concentrations of select phthalate metabolites and parabens: results from the environment and reproductive health (earth) study. Environ. Health Perspect. 125, 087012.
Nowak, K., Ratajczak-Wrona, W., Gorska, M., Jablonska, E., 2018. Parabens and their effects on the endocrine system. Mol. Cell. Endocrinol. 474, 238–251.
O'Rourke, N., Hatcher, L., 2013. A step-by-step Approach to Using SAS for Factor Analysis and Structural Equation Modeling. Sas Institute.
Ouidir, M., Buck Louis, G.M., Kanner, J., Grantz, K.L., Zhang, C., Sundaram, R., Rahman, M.L., Lee, S., Kannan, K., Tekola-Ayele, F., Mendola, P., 2020. Association of maternal exposure to persistent organic pollutants in early pregnancy with fetal growth. JAMA Pediatrics 174, 149.
Pan, Y., Jing, J., Dong, F., Yao, Q., Zhang, W., Zhang, H., Yao, B., Dai, J., 2015. Association between phthalate metabolites and biomarkers of reproductive function in 1066 Chinese men of reproductive age. J. Hazard. Mater. 300, 729–736.
Parets, S.E., Conneely, K.N., Kilaru, V., Menon, R., Smith, A.K., 2015. DNA methylation provides insight into intergenerational risk for preterm birth in African Americans. Epigenetics 10, 784–792.
Pearson, M.A., Lu, C., Schmotzer, B.J., Waller, L.A., Riederer, A.M., 2009. Evaluation of physiological measures for correcting variation in urinary output: implications for assessing environmental chemical exposure in children. J. Expo. Sci. Environ. Epidemiol. 19, 336–342.
Peretz, J., Vrooman, L., Ricke, W.A., Hunt, P.A., Ehrlich, S., Hauser, R., Padmanabhan, V., Taylor, H.S., Swan, S.H., VandeVoort, C.A., Flaws, J.A., 2014. Bisphenol A and reproductive health: update of experimental and human evidence, 2007–2013. Environ. Health Perspect. 122, 775–786.
Philippat, C., Bennett, D., Calafat, A.M., Picciotto, I.H., 2015. Exposure to select phthalates and phenols through use of personal care products among Californian adults and their children. Environ. Res. 140, 369–376.
Porpora, M.G., Piacenti, I., Scaramuzzino, S., Masciullo, L., Rech, F., Benedetti Panici, P., 2019. Environmental contaminants exposure and preterm birth: a systematic review. Toxics 7, 11.
Practice Committee of the American Society for Reproductive Medicine, 2015. Diagnostic evaluation of the infertile female: a committee opinion, Fertil. Steril. 103, e44–e50.
Practice Committee of the American Society for Reproductive Medicine, 2015. Diagnostic evaluation of the infertile male: a committee opinion, Fertil. Steril. 103, e18–e25.
Radke, E.G., Glenn, B.S., Braun, J.M., Cooper, G.S., 2019. Phthalate exposure and female reproductive and developmental outcomes: a systematic review of the human epidemiological evidence. Environ. Int. 130, 104580.
Romero, R., Dey, S.K., Fisher, S.J., 2014. Preterm labor: one syndrome, many causes. Science 345, 760–765.
Santangeli, S., Maradonna, F., Olivotto, I., Piccinetti, C.C., Gioacchini, G., Carnevali, O., 2016. Effects of BPA on female reproductive function: the involvement of epigenetic mechanism. Gen. Comp. Endocrinol. 245, 122–126.
Shi, M., Whorton, A.E., Sekulovski, N., MacLean, J.A., Hayashi, K., 2019. Prenatal exposure to Bisphenol A, E, and S induces transgenerational effects on male reproductive functions in mice. Toxicol. Sci. 172, 303–315.
Sun, Y.-C., Wang, Y.-Y., Ge, W., Cheng, S.-F., Dyce, P.W., Shen, W., 2017. Epigenetic regulation during the differentiation of stem cells to germ cells. Oncotarget 8, 57836.
Susiarjo, M., Sasson, I., Mesaros, C., Bartolomei, M.S., 2013. Bisphenol A exposure disrupts genomic imprinting in the mouse. PLoS Genet. 9, e1003401.
Suteau, V., Briet, C., Lebeault, M., Gourdin, L., Henrion, D., Rodien, P., Munier, M., 2020. Human amniotic fluid-based exposure levels of phthalates and bisphenol A mixture reduce INSL3/RXFP2 signaling. Environ. Int. 138, 105585.
Taylor, K.W., Joubert, B.R., Braun, J.M., Dilworth, C., Gennings, C., Hauser, R., Heindel, J.J., Rider, C.V., Webster, T.F., Carlin, D.J., 2016. Statistical approaches for assessing health effects of environmental chemical mixtures in epidemiology: lessons from an innovative workshop. Environ. Health Perspect. 124, A227–A229.
Valeri, L., Mazumdar, M.M., Bobb, J.F., Claus Henn, B., Rodrigues, E., Sharif, O.I.A., Kile, M.L., Quamruzzaman, Q., Afroz, S., Golam, M., Amarasiriwardena, C., Bellinger, D.C., Christiani, D.C., Coull, B.A., Wright, R.O., 2017. The joint effect of

prenatal exposure to metal mixtures on neurodevelopmental outcomes at 20–40 months of age: evidence from rural Bangladesh. Environ. Health Perspect. 125, 067015.
Vernet, C., Philippat, C., Agier, L., Calafat, A.M., Ye, X., Lyon-Caen, S., Hainaut, P., Siroux, V., Schisterman, E.F., Slama, R., 2019. An empirical validation of the within-subject biospecimens pooling approach to minimize exposure misclassification in biomarker-based studies. Epidemiology 30, 756–767.
Weatherly, L.M., Gosse, J.A., 2017. Triclosan exposure, transformation, and human health effects. J. Toxicol. Environ. Health B Crit. Rev. 20, 447–469.
World Health Organization, Preterm Birth, Retrived August. 30, 2019. From https://www.who.int/en/news-room/fact-sheets/detail/preterm-birth, 2018.
Xu, Z., Xiong, X., Zhao, Y., Xiang, W., Wu, C., 2020. Pollutants delivered every day: phthalates in plastic express packaging bags and their leaching potential. J. Hazard. Mater. 384, 121282.
Zhang, Y., Mu, X., Gao, R., Geng, Y., Liu, X., Chen, X., Wang, Y., Ding, Y., Wang, Y., He, J., 2018. Foetal-neonatal exposure of Di (2-ethylhexyl) phthalate disrupts ovarian development in mice by inducing autophagy. J. Hazard. Mater. 358, 101–112.
Zhang, Y., Mustieles, V., Yland, J., Braun, J.M., Williams, P.L., Attaman, J.A., Ford, J.B., Calafat, A.M., Hauser, R., Messerlian, C., 2020. Association of parental preconception exposure to phthalates and phthalate substitutes with preterm birth. JAMA Netw. Open 3, e202159.
Zhang, T., Shen, W., De Felici, M., Zhang, X.-F., 2016. Di(2-ethylhexyl)phthalate: adverse effects on folliculogenesis that cannot be neglected: Di(2-ethylhexyl)phthalate. Environ. Mol. Mutagen. 57, 579–588.
Zhou, X., Kramer, J.P., Calafat, A.M., Ye, X., 2014. Automated on-line column-switching high performance liquid chromatography isotope dilution tandem mass spectrometry method for the quantification of bisphenol A, bisphenol F, bisphenol S, and 11 other phenols in urine. J. Chromatogr. B 944, 152–156.
Zhou, F., Yin, G., Gao, Y., Liu, D., Xie, J., Ouyang, L., Fan, Y., Yu, H., Zha, Z., Wang, K., Shao, L., Feng, C., Fan, G., 2019. Toxicity assessment due to prenatal and lactational exposure to lead, cadmium and mercury mixtures. Environ. Int. 133, 105192.
Zoeller, R.T., Brown, T.R., Doan, L.L., Gore, A.C., Skakkebaek, N.E., Soto, A.M., Woodruff, T.J., Vom Saal, F.S., 2012. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. Endocrinology 153, 4097–4110.
Zong, T., Lai, L., Hu, J., Guo, M., Li, M., Zhang, L., Zhong, C., Yang, B., Wu, L., Zhang, D., Tang, M., Kuang, H., 2015. Maternal exposure to di-(2-ethylhexyl) phthalate disrupts placental growth and development in pregnant mice. J. Hazard. Mater. 297, 25–33.
Zou, G., 2004. A modified Poisson regression approach to prospective studies with binary data. Am. J. Epidemiol. 159, 702–706.