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Maternal and paternal preconception exposure to bisphenols and size at birth

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STUDY QUESTION: Are maternal and paternal preconception urinary bisphenol A (BPA) or bisphenol S (BPS) concentrations associated with offspring birth size?

SUMMARY ANSWER: Maternal—but not paternal—preconception urinary BPA concentrations were associated with lower birth size among couples seeking fertility evaluation.

WHAT IS KNOWN ALREADY: Prenatal BPA exposure has been previously associated with reduced birth size in some but not all epidemiologic studies. However, the potential effect of BPA exposure before conception in either parent is unknown. Data on BPS is practically absent.

STUDY DESIGN, SIZE, DURATION: Ongoing prospective preconception cohort of women and men seeking fertility evaluation between 2005 and 2016 in a large fertility center in an academic hospital in Boston, MA, USA.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We examined the association between maternal and paternal preconception, as well as maternal prenatal urinary BPA and BPS concentrations, and size at birth among 346 singletons from couples recruited in the Environment and Reproductive Health (EARTH) Study using multivariable linear regression. Infant birth weight and head circumference were abstracted from delivery records. Mean preconception and prenatal exposures were estimated by averaging urinary ln-BPA and ln-BPS concentrations in multiple maternal and paternal urine samples collected before pregnancy, and maternal pregnancy samples collected in each trimester.

MAIN RESULTS AND THE ROLE OF CHANCE: Maternal preconception urinary BPA concentrations were inversely associated with birth weight and head circumference in adjusted models: each ln-unit increase was associated with a decrease in birth weight of 119 g (95% CI: −212, −27), and a head circumference decrease of 0.72 cm (95% CI: −1.3, −0.1). Additional adjustment by gestational age or prenatal BPA exposure modestly attenuated results. Women with higher prenatal BPA concentrations had infants with lower mean birth weight (−75 g, 95% CI: −153, 2) although this did not achieve statistical significance. Paternal preconception urinary BPA concentrations were not associated with either birth weight or head circumference. No consistent patterns emerged for BPS concentrations measured in either parent.

LIMITATIONS, REASONS FOR CAUTION: We observed a strong negative association between maternal—but not paternal—preconception BPA concentrations and offspring birth size among a subfertile population. Although these results are overall consistent with prior studies on prenatal BPA exposure, these findings may not be generalizable to women without fertility concerns.

WIDER IMPLICATIONS OF THE FINDINGS: This study suggests that the unexplored maternal preconception period may be a sensitive window for BPA effects on birth outcomes.

STUDY FUNDING/COMPETING INTEREST(S): Work supported by Grants (ES R01 009718, ES 022955 and ES 000002) from the National Institute of Environmental Health Sciences (NIEHS). C.M. was supported by a post-doctoral fellowship award from the Canadian Institutes of Health Research. There are no competing interests to declare.

Key words: bisphenol A / bisphenol S / birth weight / head circumference / ART / subfertile couples / endocrine disrupting chemicals

Introduction

The Developmental Origins of Health and Disease paradigm maintains that early life environments influence health outcomes later in life (Wadhwa *et al.*, 2009). Birth weight and other measures of infant size at birth are considered important markers of the intrauterine environment, with potential long-term consequences for adult health (Barker, 2007; Basso, 2008; Visentin *et al.*, 2014). There is accumulating epidemiologic evidence associating exposure to non-persistent endocrine disrupting chemicals (EDC), such as bisphenol A (BPA), to adverse reproductive outcomes, including reduced fetal and infant birth weight, with some studies showing differences by infant sex (Veiga-Lopez *et al.*, 2015; Tomza-Marciniak *et al.*, 2018). Moreover, there is a growing body of experimental research showing that EDC exposure before conception may affect offspring health, potentially leading to multigenerational effects (Fan *et al.*, 2013; Xin *et al.*, 2015; Chen *et al.*, 2016). Germ cells are hypothesized to mediate part or the totality of these effects, possibly through epigenetic modifications of oocytes and spermatozoa, which can be inherited by offspring (Fan *et al.*, 2013; Xin *et al.*, 2015; Chen *et al.*, 2016). BPA has been shown to exert epigenetic modifications in mammalian and human sperm (Manikkam *et al.*, 2013; Zheng *et al.*, 2017), oocytes (Trapphoff *et al.*, 2013; Machtinger and Orvieto, 2014) and the placenta (Susiarjo *et al.*, 2013; De Felice *et al.*, 2015). Some of these modifications have been shown to affect the expression of genes and transcription factors related to fetal growth and nutrition (Susiarjo *et al.*, 2013).

BPA is a synthetic high production volume chemical used in the manufacturing of polycarbonate plastics and epoxy resins food can liners, among other consumer products (Vandenberg *et al.*, 2007). Consequently, human exposure is widespread as suggested by the fact that more than 90% of the US population has detectable BPA concentrations in their urine (Calafat *et al.*, 2008). Well-conducted experimental and a small but growing number of epidemiologic studies show that BPA can interfere with several aspects of hormone action, and may produce pleiotropic effects on reproduction, behavior and metabolism (Peretz *et al.*, 2014; Giulivo *et al.*, 2016; Mustieles *et al.*, 2015, 2018). Increasing concern over BPA has prompted its substitution in some consumer products often labeled as 'BPA-free'. However, some replacements are structural analogs such as bisphenol S (BPS), which are also hormonally active (Rochester and Bolden, 2015) and increasingly detected in human urine (Yang *et al.*, 2014; Ye *et al.*, 2015).

Emerging research suggests that the preconception period may be highly sensitive to environmental perturbations, highlighting the importance of considering paternal in addition to maternal exposures (Rando, 2012; Braun *et al.*, 2017). While BPA exposure during pregnancy has been inversely associated with infant size at birth in some epidemiologic studies, the effect of preconception exposure is unknown. Furthermore, epidemiologic data on BPS are practically absent. Therefore, our study aimed to examine whether paternal and maternal preconception, as well as maternal prenatal urinary BPA and BPS concentrations were associated with infant birth weight and head circumference in a prospective preconception cohort of couples attending a large fertility clinic.

Materials and Methods

Study cohort

The Environment and Reproductive Health (EARTH) Study is an ongoing prospective preconception cohort of couples recruited from the Massachusetts General Hospital (MGH) Fertility Center. The study was designed to evaluate the effects of environmental exposures and diet on fertility and pregnancy outcomes. To date, the study has recruited ~800 women ages 18–46 years and 500 men ages 18–55 years. Details of the study have been described elsewhere (Messerlian *et al.*, 2018). Briefly, participants enroll independently or as a couple and are followed from study entry and throughout their fertility care, pregnancy and delivery. Participants complete staff-administered baseline questionnaires and provide urine samples at enrollment and then again at each fertility treatment cycle.

The present study included male and female participants from the EARTH Study with a singleton infant born between 2005 and 2016 (N = 385 singletons). Out of these 385 singletons infants, BPA concentration measurements were available in at least one urine sample before conception of the index pregnancy for 346 mother–child pairs (Fig. 1). As measurement of BPS began in 2015, urinary concentrations were available for only 107 mother–child pairs and 37 father–child pairs. Trained study staff described the study protocol to all participants and answered questions, before participants provided signed informed consent. 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).

Bisphenol exposure assessment

Men and women provided a single spot urine sample at study entry. Women provided up to two additional urine samples per fertility treatment cycle. During pregnancy, women also provided one spot urine sample per trimester (median: 6, 21 and 35 weeks gestation). Men provided one additional spot urine sample per treatment cycle at the time when

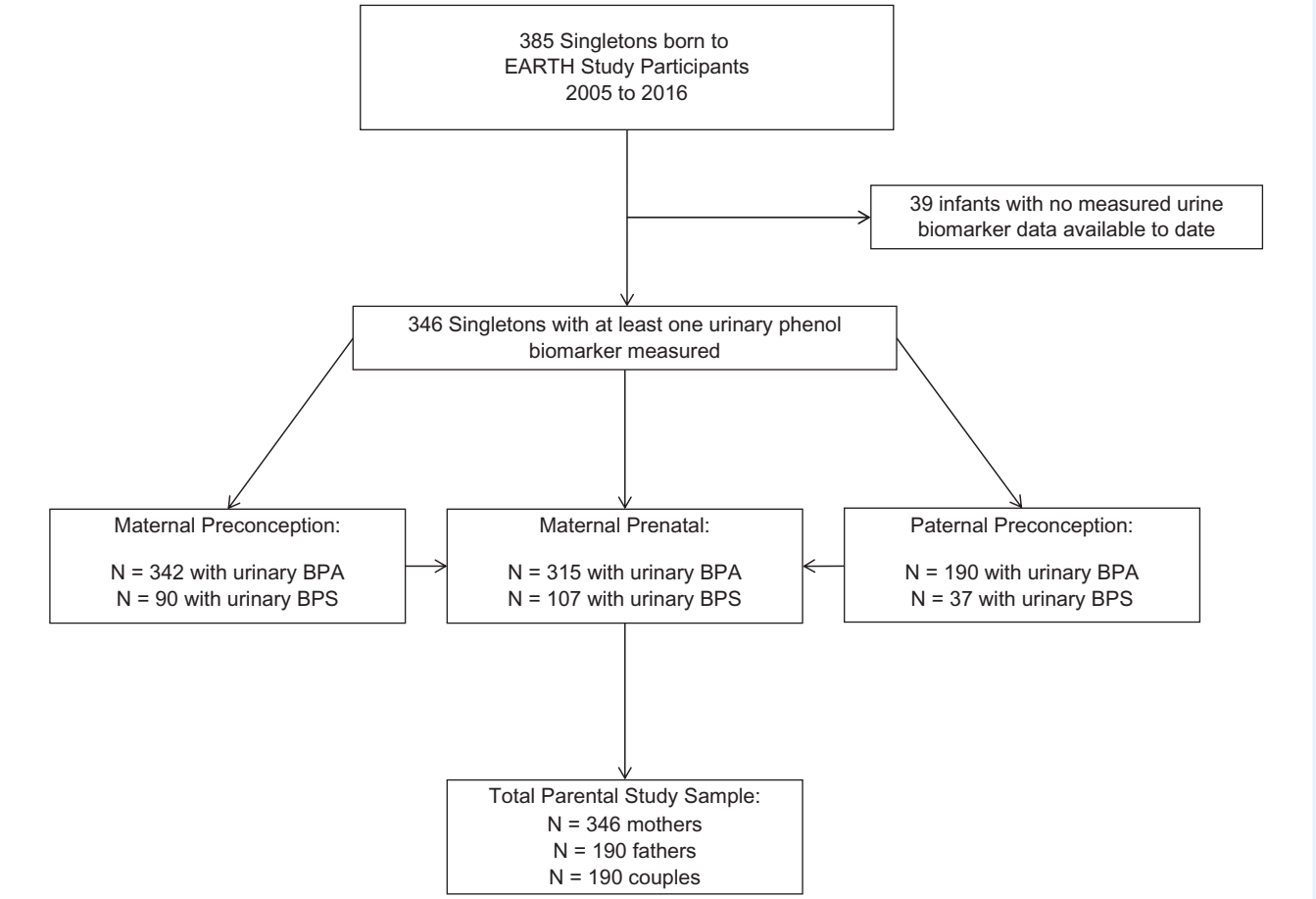

Figure 1 Participant flow chart and bisphenol biomarker data available in the Environment and Reproductive Health (EARTH) study.

their female partner underwent oocyte retrieval or IUI. We used multiple urine samples collected by each participant to examine BPA and BPS in three separate windows of exposure—paternal preconception, maternal preconception and maternal prenatal (Fig. 2).

Urine was collected in a polypropylene specimen cup and analyzed for specific gravity with a handheld refractometer (National Instrument Company, Inc., Baltimore, MD, USA), divided into aliquots, and frozen for long-term storage at −80°C. Samples were shipped on dry ice overnight to the CDC (Atlanta, GA, USA) for quantification of urinary BPA and BPS concentrations using online solid phase extraction coupled with high performance liquid chromatography–isotope dilution tandem mass spectrometry (Silva *et al.*, 2007). The limits of detection (LOD) were 0.4 and 0.1 ng/ml for BPA and BPS, respectively. Concentrations below the LOD were assigned the LOD divided by the square root of two (Hornung, 1990). We excluded paternal BPS from analyses given the small number of male participants with available BPS data ($N = 37$).

Birth weight and head circumference outcome assessment

Birth weight (g) and head circumference (cm) were abstracted from hospital delivery records by trained study staff. Gestational age in days was also abstracted from delivery records and validated using the American College of Obstetricians and Gynecologists (ACOG) guidelines to estimate gestational age for births following medically assisted reproduction (ACOG, 2014). For IVF based conceptions, we estimated gestational age as: (outcome date − date of transfer) + 14 + cycle day of transfer. For IUI and non-medically assisted/naturally conceived pregnancies, we used birth date minus cycle start date. Gestational age was corrected if delivery record estimates (gold standard) differed by over 6 days from the clinically estimated age (corrected for three infants through additional chart verification). Implausible birth weight values were examined through additional verification of delivery record by study nurse (corrected for two infants).

Covariates

Race, age and education of study participants were obtained from the enrollment questionnaire. A study nurse measured the height and weight of the parents at study entry, and BMI (kg/m^2) was calculated. Smoking status was self-reported at baseline. Infant sex and mode of delivery (vaginal versus caesarian) was abstracted by study staff from maternal delivery records. The treating infertility physician diagnosed the underlying cause of infertility using the Society for Assisted Reproductive Technology (ART) definitions. Type of medically assisted reproduction used in the conception cycle of the index birth was abstracted from the electronic medical records by trained study staff and dichotomized: ART procedures (e.g. fresh or frozen IVF protocols, including ICSI) versus non-ART protocols (e.g. IUI with or without ovulation induction/stimulation; ovulation induction/stimulation with timed intercourse, or non-medically assisted/naturally conceived).

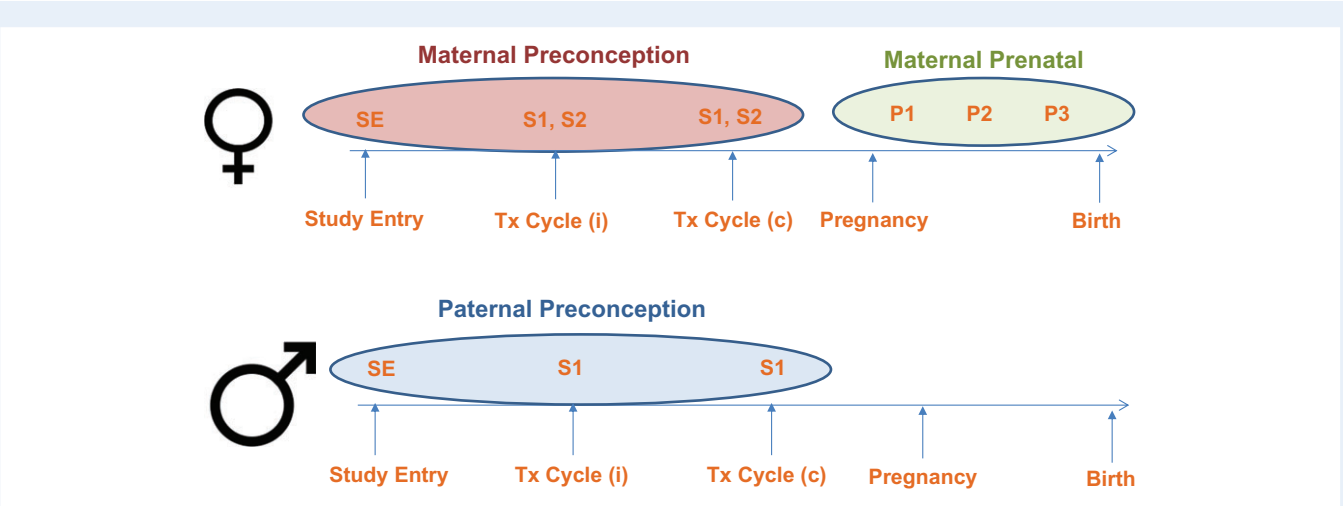

Figure 2 Maternal and paternal assessment in the Environment and Reproductive Health (EARTH) study. Female participants: Study Entry (SE) Assessment includes: baseline urine and completion of the Baseline and Full Questionnaires. Treatment (Tx) Cycle (i) connotes any number of followed cycles including those treated with IVF based technologies or non-IVF based procedures. Assessment occurs at two points in time during each Treatment (Tx) Cycle: S1—includes the first spot urine sample during the follicular phase of the cycle (Days 3–9). S2—includes the second spot urine sample collected at the time of scheduled treatment procedure (oocyte retrieval, embryo transfer or intrauterine insemination). All SE, S1 and S2 samples represent the maternal preconception BPA/BPS exposure period. Treatment (Tx) Cycle (c) connotes the index cycle of conception. Clinical information about the mode of conception (IVF-based, non-IVF based, or non-medically assisted) is abstracted from electronic medical records by trained study staff. Assessment in pregnancy: P1, P2 and P3—includes a single urine sample collected in the first, second and third trimesters of pregnancy, respectively. P1, P2 and P3 samples collected following the index conception represent the maternal prenatal BPA/BPS exposure period. Male participants: Study Entry (SE) Assessment includes: baseline urine and completion of the Baseline and Full Questionnaires. Assessment at Treatment (Tx) cycle: S1 includes a spot urine sample collected on the day their female partner undergoes their scheduled fertility treatment procedure. All SE and S1 samples collected up to and including Tx Cycle (c)—the index cycle of conception—represent the paternal preconception BPA/BPS exposure period. Republished from Messerlian *et al.* (2018).

Statistical analysis

Urinary BPA and BPS concentrations were adjusted for urine dilution by multiplying each concentration by $[(SG_p - 1)/(SG_i - 1)]$, where SG_i is the specific gravity of the participant's sample and SG_p is the mean specific gravity for all male or all female participants included in the study samples (Pearson *et al.*, 2009). The specific gravity-adjusted bisphenol concentrations were natural log-transformed to standardize the distribution and reduce the influence of extreme values. We estimated mean paternal and maternal preconception BPA and BPS concentrations by averaging each participant's natural log-bisphenol A or S concentration obtained from study entry and at each treatment cycle up to and including the cycle of the index conception of the singleton (Fig. 2). We estimated mean maternal prenatal bisphenol concentration by averaging all trimester-specific natural log-bisphenol A or S concentrations obtained from women during the index pregnancy. When only one urine sample was available the bisphenol concentration for that single sample was used. We calculated descriptive statistics for BPA and BPS concentrations for the three exposure windows as well as the percentage of values below the LOD. We also calculated Pearson correlation coefficients for each natural log-bisphenol concentration between couples (paternal versus maternal) and within women across exposure windows (maternal preconception versus maternal prenatal).

We estimated associations of paternal and maternal preconception and maternal prenatal natural log-bisphenol A or S concentrations and birth weight and head circumference using multivariable linear regression. Beta coefficients and 95% CIs represent the mean difference in birth weight (g) and head circumference (cm) for each natural log-unit increase in urinary bisphenol concentration. In order to assess potential non-linear associations, we fit multivariable linear models to evaluate change in birth weight and head circumference across tertiles of urinary BPA concentrations using the lowest tertile as the reference. We conducted statistical tests for trend across tertiles using the urinary bisphenol concentration as an ordinal level indicator variable (1, 2, 3) of each tertile in the regression model.

We selected *a priori* covariates as potential confounders based on substantive knowledge using a directed acyclic graph and examined unadjusted and covariate-adjusted results (Supplementary Fig. S1). Maternal preconception/prenatal window covariate-adjusted models included: maternal age and BMI (continuous); maternal education (<college, college, graduate degree); smoking status (never smoked versus ever smoked, defined as a current or former smoker); and ART versus non-ART-based treatment. Paternal preconception window covariate-adjusted models included paternal and maternal age and BMI (continuous); paternal and maternal smoking (ever/never); maternal education (<college, college, graduate degree); ART versus non-ART-based treatment. As gestational age may be a causal intermediate between bisphenol exposure and birth outcomes (Wilcox *et al.*, 2011), we initially did not include this in our main covariate-adjusted model. However, we additionally adjusted for gestational age in separate models to assess the potential change in estimates (Ananth and Schisterman, 2017). We also adjusted for bisphenol co-exposures by partner or prenatal window by adding the specific bisphenol concentration into each individual multivariable model. That is, concentrations of BPA (or BPS) from two different windows were entered into the same model in order to account for possible differences in effects by exposure window (Messerlian *et al.*, 2017). In models examining head circumference, we also controlled for mode of delivery (vaginal versus caesarian birth).

Given previously reported sex-specific differences between BPA exposure and size at birth (Veiga-Lopez *et al.*, 2015; Tomza-Marciniak *et al.*,

2018), we conducted a stratified sensitivity analysis by adding a cross-product term for interaction (bisphenol concentration * sex), with a *P*-value for the interaction term <0.20 indicating possible effect measure modification by infant sex on the multiplicative scale. We also conducted post-hoc analyses to assess the relationship between urinary BPA concentrations and gestational age (days, continuous) using multivariable linear regression. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, USA). The significance level was set at $P \leq 0.05$, and all tests were two-tailed.

Results

Study cohort

The study cohort included 346 mothers and 190 fathers (190 couples) with an average age of 34.8 and 35.8 years, respectively, at the time of enrollment. Table I shows parental characteristics of study participants. Among the 346 singletons, the mean (SD) for birth weight and head circumference was 3373 (534) g and 34.3 (2.5) cm respectively; 7.5% were born preterm (<37 weeks gestation) and 3.5% at low birth weight (<2.5 kg) (see Supplementary Table SI).

Table I Parental characteristics from 346 mothers and 190 fathers participating in the Environment and Reproductive Health (EARTH) Study.

Parental characteristic	Mothers *N* = 346	Fathers *N* = 190
Age (years)		
Mean (SD)	34.8 (3.9)	35.8 (4.4)
Age > 35, *n* (%)	145 (42)	104 (55)
Race, *n* (%)		
White	298 (86)	167 (88)
Black	7 (2)	3 (2)
Asian	28 (8)	13 (7)
Other	13 (4)	7 (4)
BMI (kg/m^2)		
Mean (SD)	24.1 (4.2)	27.1 (4.3)
BMI > 25, *n* (%)	107 (31)	130 (68)
Education, *n* (%)		
<College	20 (6)	26 (14)
College graduate	112 (32)	50 (26)
Graduate degree	189 (55)	76 (40)
Missing	25 (7)	38 (20)
Smoking status, *n* (%)		
Never	256 (74)	132 (69)
Ever (former or current)	90 (26)	58 (31)
Infertility diagnosis, *n* (%)		
Female factor	87 (25)	58 (31)
Male factor	114 (33)	56 (29)
Unexplained	145 (42)	76 (40)
Nulliparous, *n* (%)	287 (83)	

Urinary bisphenol concentrations

Geometric means of the specific gravity-adjusted urinary BPA concentrations were 1.6, 1.5 and 1.2 ng/ml for paternal preconception, maternal preconception, and maternal prenatal BPA, respectively (Supplementary Table SII). The specific gravity-adjusted geometric means for BPS were: 0.51, 0.45 and 0.33 ng/ml for the corresponding exposure windows. BPA detection frequencies ranged between 61 and 81% and between 53 and 68% for BPS. These values were within ranges reported for US adults (Calafat *et al.*, 2008; Ye *et al.*, 2015). Bisphenol concentrations were weakly correlated between couples and within subjects across exposure windows, with Pearson correlation coefficients ranging from 0.10 to 0.26 (Supplementary Table SIII).

Maternal preconception window

Maternal preconception urinary BPA concentrations were inversely associated with birth weight (Table II). After adjusting for covariates in the main model, each log-unit increase in urinary BPA concentration was associated with a 119 g (95% CI: −212, −27) decrease in birth weight. Further adjustment for gestational age attenuated the magnitude of the association (β = −79; 95% CI: −153, −5) (Table II). Models that additionally adjusted for maternal prenatal BPA concentrations did not substantially change the results (Table II). When maternal preconception urinary BPA concentrations were categorized in tertiles, a significant negative trend in birth weight over increasing BPA tertiles was observed (test for *P*-trend, 0.03) (Table III). Additionally, maternal urinary preconception BPA concentrations were inversely associated with head circumference in adjusted models (Table IV). Each log-unit increase in BPA concentration was associated with a 0.72 cm (95% CI: −1.3, −0.1) decrease in head circumference (Table IV). Although BPA tertiles were not significantly associated with head circumference in adjusted models, a suggestive trend was observed (data not shown). No sex-specific associations or interaction by sex were observed between maternal preconception urinary BPA concentrations and birth weight (Supplementary Table SIV). Maternal preconception urinary BPS concentrations were not associated with birth weight or head circumference (Tables II and IV).

Maternal prenatal window

Maternal prenatal BPA concentrations were associated with non-significant birth weight decrement. After adjustment for covariates, each log-unit increase in urinary BPA concentration during pregnancy was associated with a 75 g (95% CI: −153, 2) decrease in birth weight (Table II). This association did not differ by newborn sex (Supplemental Table IVA). Models that additionally adjusted for maternal preconception BPA concentrations substantially attenuated this association (Table II). Maternal prenatal BPS concentrations were not associated with birth weight (Tables II). However, there was some evidence of effect measure modification by infant sex (*P*-interaction, 0.10) with boys exhibiting non-significant decreased birth weight compared with increased birth weight in girls in relation to higher BPS concentrations (Supplementary Table SIV). Neither maternal prenatal BPA nor prenatal BPS concentrations were associated with head circumference (Table IV).

Table II Association of natural log-unit increase in paternal preconception, maternal preconception, and maternal prenatal urinary bisphenol A (BPA) and bisphenol S (BPS) concentrations and birth weight (g) among all singletons.

Model 1[a]	Paternal preconception			Maternal preconception			Maternal prenatal		
	Beta (95% CI)	*P*-value	*N*	Beta (95% CI)	*P*-value	*N*	Beta (95% CI)	*P*-value	*N*
BPA	−58 (−158, 43)	0.26	190	−113 (−203, −24)	0.01	342	−78 (−155, −2)	0.05	315
BPS[f]	–	–	–	−8 (−139, 124)	0.91	90	22 (−82, 126)	0.68	107
Model 2	**Paternal preconception[b]**			**Maternal preconception[c]**			**Maternal prenatal[c]**		
	Beta (95% CI)	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***
BPA	−45 (−146, 55)	0.38	178	−119 (−212, −27)	0.01	318	−75 (−153, 2)	0.06	292
BPS[f]	–	–	–	9 (−119, 138)	0.89	83	24 (−78, 127)	0.64	100
Model 3	**Paternal preconception[d]**			**Maternal preconception[d]**			**Maternal prenatal[d]**		
	Beta (95% CI)	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***
BPA	−54 (−143, 35)	0.23	178	−79 (−153, −5)	0.04	318	−38 (−101, 25)	0.24	292
BPS[f]	–	–	–	23 (−85, 131)	0.68	83	13 (−83, 109)	0.79	100
Model 4	**Paternal preconception[e]**			**Maternal preconception[e]**			**Maternal prenatal[e]**		
	Beta (95% CI)	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***
BPA	−48 (−151, 55)	0.36	166	−89 (−186, 8)	0.07	289	−46 (−127, 36)	0.27	289
BPS[f]	–	–	–	144 (2, 286)	0.05	73	−67 (−210, 76)	0.36	73

[a]Model 1: Unadjusted model.
[b]Model 2: Covariate-Adjusted Paternal Preconception Model: adjusted for maternal and paternal age (continuous); maternal and paternal BMI (continuous); maternal education (<college, college, graduate degree); maternal and paternal smoking (ever/never); and ART (yes/no).
[c]Model 2: Covariate-Adjusted Maternal Preconception and Prenatal Models: adjusted for maternal age (continuous); maternal BMI (continuous); maternal education (<college, college, graduate degree); maternal smoking (ever/never); and ART (yes/no).
[d]Model 3: Covariate Adjusted + Gestational Age Model: covariates from Model 2 plus additional adjustment for gestational age (continuous, days).
[e]Model 4: Co-Adjusted Model: covariates from Model 2 plus additional co-adjustment for:
Paternal Preconception Model includes respective maternal prenatal bisphenol concentration.
Maternal Preconception Model includes respective maternal prenatal bisphenol concentration.
Maternal Prenatal Model includes respective maternal preconception bisphenol concentration.
[f]Paternal BPS concentrations not analyzed due to the small number of male participants with available BPS data ($N = 37$).

Paternal preconception window

No associations were observed between paternal preconception urinary BPA concentrations and birth weight or head circumference: $\beta = -45$ g; 95% CI: −146, 55 and $\beta = -0.15$ cm; 95% CI: −0.68, 0.37, respectively (Tables II and IV).

Discussion

Maternal preconception BPA concentrations—but not paternal preconception BPA concentrations—were negatively associated with both birth weight and head circumference among singletons born to subfertile couples from a large fertility center. Maternal prenatal BPA concentrations also showed suggestive associations with birth size. No sex-specific differences were evident. There was also no evidence of associations with BPS concentrations across all exposure windows. However, given the limited detection frequencies (53–68%), the smaller sample size with BPS measured in our cohort, and the fact that this is the first epidemiologic study on BPS exposure during the preconception period, more research is warranted.

Our main results showed a robust inverse association between maternal preconception urinary BPA concentrations and birth size, while associations in relation to maternal prenatal BPA concentrations were more tenuous. In support of a maternal preconception effect, the observed negative association with birth weight was maintained even after additional adjustment for maternal prenatal BPA concentrations, whereas the converse did not occur in the prenatal BPA exposure models. Furthermore, a dose–response trend was observed across increasing BPA tertiles for the maternal preconception—but not maternal prenatal—window. Because additional adjustment for gestational age attenuated both preconception and prenatal BPA associations, we conducted a post-hoc analysis to assess the relationship between urinary BPA concentrations and gestational age (Supplementary Table SV). Negative trends were observed between both maternal preconception and maternal prenatal BPA concentrations and gestational age ($\beta = -1.5$ days; 95% CI: −3.6, 0.55 and $\beta = -1.5$ days; 95% CI: −3.4, 0.34, respectively), suggesting the possibility of a partial mediating effect by gestational age (Supplementary Table SV). Although maternal preconception BPA associations were attenuated after adjusting for covariates, gestational age, as well as maternal prenatal BPA co-exposure, associations resisted all these adjustments and were particularly robust.

BPA has been classified as an ovarian toxicant based on both experimental and human evidence (Souter *et al.*, 2013; Peretz *et al.*, 2014), and there is sufficient experimental evidence to support adverse

Table III Change in birth weight (g) by tertile (T) of urinary bisphenol A (BPA) concentrations in paternal preconception, maternal preconception and maternal prenatal windows of exposure among all singletons.

Model 2	Paternal preconception[a]			Maternal preconception[b]			Maternal prenatal[b]		
	Beta (95% CI)	*P*-value	*N*	Beta (95% CI)	*P*-value	*N*	Beta (95% CI)	*P*-value	*N*
BPA									
T1	Ref.		60	Ref.		106	Ref.		98
T2	−117 (−303, 70)	0.22	59	−53 (−196, 89)	0.46	106	−58 (−86, 201)	0.43	97
T3	−40 (−219, 140)	0.67	59	−157 (−300, −13)	0.03	106	−70 (−215, 75)	0.34	97
P-trend		0.68			0.03			0.30	
Model 3	**Paternal preconception[c]**			**Maternal preconception[c]**			**Maternal prenatal[c]**		
	Beta (95% CI)	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***
BPA									
T1	Ref.		60	Ref.		106	Ref.		98
T2	−95 (−262, 72)	0.26	59	−66 (−180, 47)	0.25	106	32 (−84, 148)	0.59	97
T3	−53 (−213, 107)	0.52	59	−130 (−245, −15)	0.03	106	−16 (−133, 102)	0.79	97
P-trend		0.53			0.03			0.80	

[a]Model 2: Covariate-Adjusted Paternal Preconception Model: adjusted for maternal and paternal age (continuous); maternal and paternal BMI (continuous); maternal education (<college, college, graduate degree); maternal and paternal smoking (ever/never); and ART (yes/no).
[b]Model 2: Covariate-Adjusted Maternal Model: adjusted for maternal age (continuous); maternal BMI (continuous); maternal education (<college, college, graduate degree); maternal smoking (ever/never); and ART (yes/no).
[c] Model 3: Covariate Adjusted + Gestational Age Model: covariates from Model 2 plus additional adjustment for gestational age (continuous, days).

Table IV Association of natural log-unit increase in paternal preconception, maternal preconception, and maternal prenatal urinary bisphenol A (BPA) and bisphenol S (BPS) concentrations and head circumference (cm) among all singletons.

Model 1[a]	Paternal preconception			Maternal preconception			Maternal prenatal		
	Beta (95% CI)	*P*-value	*N*	Beta (95% CI)	*P*-value	*N*	Beta (95% CI)	*P*-value	*N*
BPA	−0.01 (−0.55, 0.53)	0.97	133	−0.47 (−1.04, 0.10)	0.10	210	−0.25 (−0.70, 0.19)	0.26	196
BPS[e]	–	–	–	−0.09 (−1.10, 0.91)	0.86	62	0.27 (−0.56, 1.1)	0.53	77
Model 2	**Paternal preconception[b]**			**Maternal preconception[c]**			**Maternal prenatal[c]**		
	Beta (95% CI)	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***
BPA	−0.15 (−0.68, 0.37)	0.57	126	−0.72 (−1.3, −0.16)	0.01	210	−0.33 (−0.77, 0.11)	0.14	196
BPS[e]	–	–	–	0.11 (−1.2, 0.95)	0.84	62	−0.09 (−1.05, 0.87)	0.85	77
Model 3	**Paternal preconception[d]**			**Maternal preconception[d]**			**Maternal prenatal[d]**		
	Beta (95% CI)	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***	**Beta (95% CI)**	***P*-value**	***N***
BPA	−0.14 (−0.66, 0.37)	0.59	126	−0.63 (−1.2, −0.09)	0.02	210	−0.31 (−0.74, 0.11)	0.14	196
BPS[e]	–	–	–	−0.11 (−1.2, 0.96)	0.84	62	−0.02 (−0.99, 0.94)	0.96	77

[a]Model 1: Unadjusted model.
[b]Model 2: Covariate-Adjusted Paternal Preconception Model: adjusted for maternal and paternal age (continuous); maternal and paternal BMI (continuous); maternal education (<college, college, graduate degree); maternal and paternal smoking (ever/never); ART (yes/no); and mode of delivery (vaginal versus c-section).
[c]Model 2: Covariate-Adjusted Maternal Preconception and Prenatal Models: adjusted for maternal age (continuous); maternal BMI (continuous); maternal education (<college, college, graduate degree); maternal smoking (ever/never); ART (yes/no); and mode of delivery (vaginal versus c-section).
[d]Model 3: Covariate Adjusted + Gestational Age Model: covariates from Model 2 plus additional adjustment for gestational age (continuous, days).
[e]Paternal BPS concentrations not analyzed due to the small number of male participants with available BPS data (*N* = 37).

effects on female reproductive physiology (Santangeli *et al.*, 2017). BPA has been shown to affect early oogenesis and follicle formation, female steroidogenesis, oocyte quantity, quality and fertilization, uterine receptivity and implantation, embryo development and the placenta in experimental and some epidemiologic studies (Susiarjo *et al.*, 2013; Peretz *et al.*, 2014). Increasing evidence also highlights the

potential of BPA to interfere with epigenetic mechanisms, which may mediate part of its effects on female reproduction (Santangeli *et al.*, 2017). As we found the strongest BPA-associations when maternal exposure was assessed before conception, and BPA has shown to alter the epigenetic programming of human and mammalian oocytes leading to functional impairments (Eichenlaub-Ritter and Pacchierotti, 2015), a potential early effect of BPA at the ovary (Ikezuki *et al.*, 2002) affecting oocyte quality and later resulting in reduced embryo viability/development might be proposed (Yuan *et al.* 2018).

Epidemiologic studies have provided inconsistent results regarding size at birth. Some studies reported lower birth size in response to higher urinary BPA concentrations during pregnancy, in line with our maternal prenatal results (Chou *et al.*, 2011; Snijder *et al.*, 2013; Troisi *et al.*, 2014; Huo *et al.*, 2015; Veiga-Lopez *et al.*, 2015), whereas others found no association (Wolff *et al.*, 2008; Philippat *et al.*, 2011, 2014; Casas *et al.*, 2015) or even higher birth size (Lee *et al.*, 2014; Ding *et al.*, 2017). Most studies used a single spot urine sample for exposure characterization, which might partially explain discrepancies (Snijder *et al.*, 2013; Perrier *et al.*, 2016). Conversely, only one study has evaluated associations between paternal and maternal preconception urinary BPA concentrations and birth outcomes (Smarr *et al.*, 2015). This study also relied on a single spot urine sample for BPA exposure characterization. Although the authors observed some trends between maternal preconception quartiles of BPA concentrations and smaller size at birth, no obvious associations were found (Smarr *et al.*, 2015). Our results are overall consistent with existing research and expand these findings by reporting clear evidence of the maternal preconception period as a potentially critical window for BPA effects on perinatal outcomes.

Only one previous study analyzed the relationship between urinary BPS concentrations during pregnancy and birth weight, reporting that mothers with a detectable concentration of BPS at any of the study visits had lower weight females (Ferguson *et al.*, 2018). Although we did not observe associations between BPS concentrations and birth size—probably influenced by the small subsample and low detection frequencies—increasing experimental research points to a similar or even worse reprotoxic and/or embryofetotoxic potential of BPS compared to BPA (Žalmanová *et al.* 2017; Campen *et al.* 2018; Gingrich *et al.* 2018). Additional epidemiologic research is needed, especially in new cohorts with more recent recruitments, since the substitution of BPA with BPS is already taking place in consumer products, and this process seems to be occurring relatively faster in the US than other countries (Wu *et al.* 2018). Future follow-up of the EARTH Study will lead to more detailed analyses of the relationship between BPS exposure and reproductive health.

A major strength of our study is the prospective preconception design of the EARTH cohort. Studying subfertile couples from a large fertility center allowed us to assess three critical windows of exposure, including mother's and father's exposure before conception. Although the generalizability of our findings to non-subfertile couples is uncertain, a previous analysis in the EARTH cohort studying paternal preconception exposure to phthalates and birth size (Messerlian *et al.*, 2017) was in line with results from a non-subfertile preconception cohort (Smarr *et al.*, 2015). Because we were limited by a lower number of fathers compared to mothers, future analyses with a higher number of male participants will further address whether paternal preconception exposure to bisphenols is associated with perinatal outcomes. Another major strength is that most participants provided multiple urine samples for each critical window of exposure, allowing us to better characterize exposure to bisphenols, and thus reduce the chances of exposure misclassification and its expected attenuation bias (Perrier *et al.*, 2016). Even so, some level of exposure misclassification cannot be disregarded given the short biological half-lives of these non-persistent chemicals and episodic nature of the exposures.

Conclusions

Our main results show a clear and robust inverse association between maternal preconception urinary BPA concentrations and infant birth weight and head circumference. Although maternal prenatal BPA concentrations also showed a suggestive association towards decreased birth weight, maternal preconception associations tended to remain after additional adjustment for maternal prenatal BPA exposure, whereas the opposite was not observed. No associations were found for paternal preconception BPA exposure. Although limited by small numbers, and low detection frequencies, no associations were observed for BPS exposure across exposure windows. Taken together, our findings highlight the maternal preconception period as a sensitive, yet largely unexplored critical window for BPA effects on birth size. Given the ubiquity of bisphenol exposures (Calafat *et al.*, 2008), the predictive value of size at birth for future health (Basso, 2008), and that BPA has been classified as a reproductive toxicant and endocrine disruptor based on both experimental and human evidence (ECHA, 2016 and 2017; Peretz *et al.*, 2014), we consider these findings to be of public health importance.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' role

C.M. conceived and designed the study and analysis plan. A.M.C. conducted the chemical analysis of urine samples and produced the chemical database. J.B.F contributed to the acquisition of data and follow-up of the participants. All statistical analyses were conducted by C.M. in consultation with P.W., V.M. and L.M. V.M. and C.M. prepared the first draft of the article and all authors critically revised the article for important intellectual content, approving the final version.

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Conflict of interest

The authors declare no actual or potential competing financial conflicts of interest. 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 names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.

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