1-2019

Blood pressure changes during pregnancy in relation to urinary paraben, triclosan and benzophenone concentrations: A repeated measures study

Hongxiu Liu
State Key Laboratory of Environmental Health (Incubation), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Jiufeng Li

Wei Xia
State Key Laboratory of Environmental Health (Incubation), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Bin Zhang

Yang Peng
State Key Laboratory of Environmental Health (Incubation), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

See next page for additional authors

APA Citation

Liu, H., Li, J., Xia, W., Zhang, B., Peng, Y., State Key Laboratory of Environmental Health (Incubation), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China., Zhou, Y., Fang, J., Zhao, H., Jiang, Y., Liu, W., Sun, X., Hu, C., Cai, Z., & Xu, S. (2019). Blood pressure changes during pregnancy in relation to urinary paraben, triclosan and benzophenone concentrations: A repeated measures study. *Environment International, 122*, 185-192. https://doi.org/10.1016/j.envint.2018.11.003

Environment International 122 (2019) 185–192

Contents lists available at ScienceDirect

Environment International

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

Blood pressure changes during pregnancy in relation to urinary paraben, triclosan and benzophenone concentrations: A repeated measures study

Hongxiu Liu[a,b,1], Jiufeng Li[c,1], Wei Xia[a,b], Bin Zhang[d], Yang Peng[a,b], Yuanyuan Li[a,b], Yanqiu Zhou[c], Jing Fang[c], Hongzhi Zhao[c], Yangqian Jiang[a,b], Wenyu Liu[a,b], Xiaojie Sun[a,b], Cheng Hu[a,b], Zongwei Cai[c,*], Shunqing Xu[a,b,**]

[a] Key Laboratory of Environment and Health (HUST), Ministry of Education & Ministry of Environmental Protection, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430000, Hubei, China
[b] State Key Laboratory of Environmental Health (Incubation), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430000, Hubei, China
[c] State Key Laboratory of Environmental and Biological Analysis, Department of Chemistry, Hong Kong Baptist University, Hong Kong, China
[d] Women and Children Medical and Healthcare Center of Wuhan, Wuhan 430000, Hubei, China

ARTICLE INFO

Handling Editor: Lesa Aylward

ABSTRACT

Previous studies have proven the endocrine-disrupting properties and health hazards of parabens, triclosan, and benzophenones, but their relationship with blood pressure during pregnancy remains unknown. Therefore, we investigated the associations of repeated measures of urinary parabens, triclosan, and benzophenones with blood pressure during pregnancy and evaluated whether the associations were modified by fetal sex. From a prospective birth cohort in Wuhan, China, we collected urine samples from 644 pregnant women in the first, second, and third trimesters between 2014 and 2015. Five parabens, triclosan, and three benzophenones were quantified in all urine samples. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in each trimester after urine sampling. Mixed linear models were used to estimate the associations between urinary chemical levels and blood pressure during pregnancy among all pregnant women and subgroups stratified by fetal sex. In the women carrying male fetuses, urinary triclosan and selected benzophenone concentrations were associated with a slight change of SBP during pregnancy. In the women carrying female fetuses, no chemical was associated with SBP, while urinary concentration of triclosan was inversely associated with DBP, though the magnitude was small. Urinary paraben levels weren't associated with blood pressure during pregnancy. Our results suggest that triclosan and selected benzophenone exposure might be associated with blood pressure during pregnancy in a potential fetal sex-different manner. Replicated research studies in pregnant women with higher triclosan and benzophenone exposure levels are needed in the future.

1. Introduction

Parabens, triclosan, and benzophenones are three classes of synthetic organic chemicals with preservative, antimicrobial, and ultraviolet radiation proof properties. They are widely used in personal care products, such as cosmetics, soaps, toothpastes, and sunscreens, and are commonly added in pharmaceuticals, food commodities, as well as industrial products (Asimakopoulos et al., 2014; Bledzka et al., 2014). Humans are widely exposed to these chemicals through direct dermal absorption, oral intake, or inhalation (Heffernan et al., 2015; Larsson et al., 2014). Parabens, triclosan, and benzophenone have been associated with various adverse health effects, including increased risks of breast cancer, obesity, metabolic disturbance, and adverse birth outcomes in previous studies (Darbre and Harvey, 2014; Geer et al., 2017; Giulivo et al., 2016). Nevertheless, limited data are available on the adverse effects of these chemicals on the cardiovascular system.

The risk of cardiovascular disease increases linearly with blood pressure in adults (Kshirsagar et al., 2006). Pregnant women are more susceptible to high blood pressure than general adults because of endocrine alteration, plasma flow increment, and stress elevation over the

* Corresponding author.
** Correspondence to: S. Xu, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.
E-mail addresses: zwcai@hkbu.edu.hk (Z. Cai), xust@hust.edu.cn (S. Xu).
[1] Both the authors contributed equal to the article.

https://doi.org/10.1016/j.envint.2018.11.003
Received 7 June 2018; Received in revised form 30 October 2018; Accepted 1 November 2018
Available online 28 November 2018

course of pregnancy (Sanghavi and Rutherford, 2014). Elevated blood pressure during pregnancy, even that not exceeding the clinical hypertension threshold, can pose a risk of pregnancy complications and adverse birth outcomes, including preeclampsia, intrauterine growth restriction, preterm birth, placental abruption, and cesarean delivery (Hennington and Alexander, 2013; Macdonald-Wallis et al., 2014; Van den Hooven et al., 2011). Further, it can cause long-term consequences later in life by increasing the risk of future cardiovascular disease of both the mother and child (Hennington and Alexander, 2013; Intapad and Alexander, 2013).

Recently, exposure to endocrine-disrupting chemicals (EDCs) has been associated with increased risk of cardiovascular diseases and increased blood pressure status (Bae and Hong, 2015; Werner et al., 2015). Studies revealed EDCs increased blood pressure partly via binding to nuclear receptors, interfering with sex hormone and thyroid hormone, and disrupting the endocrine system, consequently leading to endothelial dysfunction (Bae and Hong, 2015; Bonefeld-Jorgensen et al., 2007; Kataria et al., 2017; Kirkley and Sargis, 2014; Mendelsohn, 2009; Moriyama et al., 2002; Shiue, 2014). Like bisphenols and phthalates, parabens, triclosan, and benzophenones are also capable of disrupting sex hormones and thyroid hormones (Aker et al., 2016; Schmutzler et al., 2007), which allows us to hypothesize that these chemicals might influence blood pressure, especially in vulnerable populations such as pregnant women.

Therefore, in the present study, we assessed exposure levels by measuring urinary chemical concentrations in three trimesters and investigated the associations of paraben, triclosan, and benzophenone exposure levels with blood pressure status during pregnancy based on a prospective birth cohort in Wuhan, China. In addition, we evaluated whether the associations varied by fetal sex, since fetal sex has the potential to affect the occurrence of hypertensive disorders of pregnancy (HDP) (Al-Qaraghouli and Fang, 2017).

2. Methods

2.1. Study population

The present study is based on an ongoing birth cohort and was conducted at the Wuhan Women and Children Medical Care Center in Wuhan, Hubei Province, China. Pregnant women were recruited when they visited the study hospital for their first routine prenatal care based on the following criteria: 1) < 16 weeks of gestation; 2) conceived a singleton baby; 3) a resident of Wuhan city and not planning to move out of Wuhan for the foreseeable future; 4) planned to follow prenatal care during pregnancy and give birth at the study hospital; and 5) agreed to have in-person interviews and repeatedly provide urine samples during pregnancy. We initially recruited 1244 pregnant women in this cohort during the period of 2014–2015. For the present study, we excluded 388 women without urine samples and 212 women without blood pressure measurements in any of first, second, or third trimesters. Finally, a total of 644 (51.77%) pregnant women with urine samples and blood pressure measurements in all three trimesters (gestational weeks: first trimester 13.0 ± 1.1, second trimester 23.6 ± 3.2, third trimester 36.0 ± 3.2) participated in the present study. In addition, we compared the basic information between excluded women (n = 600) and included women (n = 644) in the present study and found that all characteristics, except passive smoking, did not vary statistically between the two groups (data not shown). Among the 644 participants, no woman had hypertension or renal or heart disease before pregnancy. At enrollment, all women were informed about the details of the study and provided written informed consent forms. Both the Ethics Committee of the Tongji Medical College and the Wuhan Women and Children Medical Care Center granted the ethical permission by approving the study protocols.

2.2. Exposure assessment

Urine samples were collected in a polyethylene container when women came to the study hospital for prenatal care in each trimester and were frozen at −20 °C until further processing. Five parabens (methylparaben [MeP], ethylparaben [EtP], propylparaben [PrP], butylparaben [BuP], and benzylparaben [BzP]), triclosan, and three benzophenones (2,4-dihydroxybenzophenone [BP-1], 2-hydroxy-4-methoxybenzophenone [BP-3], and 4-hydroxybenzophenone [4-OH-BP]) were analyzed by an Ultimate 3000 ltra-high performance liquid chromatography system (Dionex, Sunnyvale, CA, USA) coupled to a Thermo Scientific™ TSQ Quantiva™ Triple Quadrupole mass spectrometer (Thermo Scientific, San Jose, CA, USA) (UPLC-MS/MS). The detailed procedures of the sample preparation and the parameters of the UPLC-MS/MS were described in our previous study (Zhao et al., 2017). To monitor instrument background, contamination during preparation, and the instrumental drift, we incorporated the pure blank solution, procedural blanks, and quality control samples in each batch of detection. This method had good accuracy and recovery. The coefficient of variation (CV) was assessed to evaluate performance. CV was calculated by the following equation: CV = standard deviation/average 100. All CVs were < 5% and considered satisfactory. The intraday and interday precisions of all chemicals of this method were within the acceptable variability limits (i.e., within 15%). The limits of detection (LODs) of MeP, EtP, PrP, BuP, BzP, triclosan, BP-1, BP-3, and 4-OH-BP were 0.05, 0.01, 0.05, 0.05, 0.01, 0.1, 0.1, 0.2, and 0.1 ng/mL, respectively. The levels of all chemicals below the LODs were treated as LOD divided by 2.

In addition, given that structurally similar chemicals usually have similar toxicity (Braun et al., 2014), we calculated the sum of parabens (μmol/L) by adding the molar urinary concentrations of the five parabens together (Σparabens = BzP/228.247 + EtP/166.174 + BuP/194.227 + PrP/180.203 + MeP/152.149). The molar sum of the three benzophenones was also calculated using the same method (Σbenzophenones = BP-1/214.22 + BP-3/228.247 + 4-OH-BP/198.221).

Immediately after the urine samples were thawed for determination, we measured the specific gravity (SG) by a refractometer (Atago PAL-10S, Atago, Tokyo, Japan) to control urine dilution. The median of all urinary SG values was 1.012. SG-corrected concentrations of urinary chemicals were calculated according to the formula: SG-corrected concentration = measured concentration × [(1.012 − 1) / (SG − 1)].

2.3. Outcomes and covariates

Blood pressure of pregnant women was measured using an automated sphygmomanometer (A&D Medical Life Source TM-2655 Digital Blood Pressure Monitors, Ibaraki-ken, Japan) at their prenatal care visits at the study hospital (Kobalava et al., 2006). First, women were asked to take at least a 5-minute rest and sit in an upright position. Then, the specially trained clinic nurses guided them to insert their right arm into the cuff at the proper depth and measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) according to the standard procedures (Kobalava et al., 2006). The nurses documented the SBP and DBP values in both the prenatal care system and the personal prenatal care records. Pulse pressure (PP) was calculated by SBP minus DBP. Mean arterial pressure (MAP) was calculated using the following formula: MAP = 1/3 × SBP + 2/3 × DBP (Von Dadelszen et al., 2000).

Interviewers were specially trained to administer the questionnaire according to standardized procedures. Face-to-face interviews were conducted by the specially trained interviewers to collect sociodemographic information, including age, marital status, occupation, education, and annual family income status, and lifestyle habits, including alcohol drinking (defined as pregnant women who consumed alcoholic beverages at least once throughout pregnancy), active smoking during pregnancy (defined as pregnant women who smoked

tobacco at least once throughout pregnancy), and passive smoking status (defined as nonsmoking women exposed to tobacco smoke during pregnancy from her spouse or other family member living in the same household or the workplace) (Zairina, 2016). Medical records provided us information about body weight before pregnancy, height, last menstrual period, parity, and diseases, including gestational diabetes mellitus (GDM), HDP, original heart disease, and hypertension history before pregnancy. Pregnant women were diagnosed with GDM based on the recommendations of the International Association of Diabetes and Pregnancy Study Group (American Diabetes Association, 2011). We calculated pre-pregnancy body mass index (BMI) (kg/m^2) as the ratio of body weight (kg) divided by the height squared (m^2). Gestational age (weeks) was obtained based on the first-trimester ultrasound examination. Neonatal sex was obtained from delivery records in the study hospital.

2.4. Statistical analysis

We summarized the relevant characteristics of the participants stratified by fetal sex and compared them using Student *t*-test for continuous variables and chi-square for categorized variables. Geometric means (GMs) and selected percentiles of SG-corrected concentrations of parabens, triclosan, and benzophenones at each trimester were calculated among all participants and in the subgroups divided by fetal sex. Intraclass correlation coefficients (ICCs) of the chemicals across three trimesters were calculated by a random intercept-only mixed linear model to measure the variability of the urinary concentrations of chemicals. To assess the overall exposures during pregnancy, we calculated GMs and medians of concentrations of these chemicals for each individual using three measurements in the first, second, and third trimesters, respectively. The difference of ln-transformed urinary chemical levels across three trimesters was tested by one-way repeated-measures analysis of variance, followed by the Bonferroni test. The ln-transformed concentrations of chemicals across three trimesters between the mothers with male fetuses and those with female fetuses were compared by two-way repeated-measures analysis of variance.

In the following analyses, we estimated associations of blood pressure with chemicals that had a detection rate of > 50% (including MeP, EtP, PrP, triclosan, BP-1, BP-3, and 4-OH-BP) and Σparabens as well as Σbenzophenones. We transformed all SG-corrected concentrations of those chemicals by natural logarithm (ln) because of the skewed distributions. We used mixed linear models with subject-specific random intercepts to estimate the coefficients (βs) and 95% confidence intervals (CIs) between the repeated chemical levels (ln-transformed) in three trimesters and blood pressure values (mm Hg) during pregnancy. Generalized estimating equations were used to examine the associations between the repeated measurements of parabens, triclosan, and benzophenones (ln-transformed) across the three trimesters and HDP occurrence. We used generalized additive models (GAMs) to assess the shape of the relationships of parabens, triclosan, and benzophenones with SBP, DBP, PP, and MAP during pregnancy. The results of the GAMs showed no evidence of significant departure from linearity (all nonlinearity *P*-values > 0.05). We also divided the average chemical concentrations (GMs) across the whole pregnancy into tertiles to further test the potential nonlinear dose-response relationships with average blood pressure (GMs) during pregnancy, with the lowest exposure levels as the reference. Linear trends were tested using the Wald test by assigning the median values of tertiles of chemicals as continuous variables. We adjusted for age (continuous variable), pre-pregnancy BMI (continuous variable), fetal sex (male or female), annual family income (< 100,000 or ≥100,000 yuan/year), and GDM (yes or no) in the final models because these factors were significantly associated with blood pressure in bivariate analyses ($P < 0.1$). We also included parity in the adjusted models, because it was previously proved to affect blood pressure status in pregnant women (Gleicher et al., 1986). The adjustment for the potential confounders was not applied to tobacco or alcohol consumption, since only one woman reported active smoking and none reported drinking during pregnancy.

Considering the association between GDM and blood pressure status during pregnancy (Vanlalhruaii et al., 2013), sensitivity analyses were performed after excluding participants who developed GDM. The final model was adjusted for the aforementioned covariates, except for GDM. We also performed sensitivity analyses by fixing uncorrected chemical concentrations as independent variables and further adjusted for SG to test the robustness of the associations.

To explore the sex-different effects of these chemical exposures on blood pressure during pregnancy, we conducted the above analyses after stratifying by fetal sex and adjusted for potential confounders mentioned above, except for fetal sex.

In addition, to adjust for multiple tests of significance, we used the false-discovery rate (FDR) to correct the *P* values and calculated the FDR-adjusted *P*-values ($P_{\text{-}FDR}$) by the available spreadsheet software developed by Pike (2011).

An alpha level of 0.05 was defined as statistical significance, and we performed all statistical analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Demographic characteristics of the present population are shown in Table 1. The average age of pregnant women at enrollment was 28.7 years. The average pre-pregnancy BMI was 20.8 kg/m^2. The average age and pre-pregnancy BMI did not differ between women with male fetuses and those with female fetuses (both $P > 0.05$). Approximately 80% of the women had a college education. Most pregnant women in this population had not given birth before (79%) and had no second-hand smoke exposure during pregnancy (62%). Of the 644 pregnant women, only 14 (2%) women developed HDP and 56 (9%) women developed GDM. Annual family income, education levels, parity, passive smoking during pregnancy, and the incidence of HDP and GDM did not vary between mothers carrying male and female fetuses (all $P > 0.05$). We summarized average blood pressure values in each trimester among women with male fetuses and those with female fetuses (Table S1) and found that blood pressure values, including SBP, DBP, PP, and MAP, in the three trimesters showed no difference between the two groups (all $P > 0.05$).

Table 2 describes the detection rates, ICCs, and concentrations of urinary parabens, triclosan, and benzophenones among all participants. MeP, EtP, and PrP were detected in > 90% of urine samples. The urinary GMs of MeP, EtP, PrP, BzP, BuP, and Σparabens were 15.49 μg/L, 0.48 μg/L, 0.66 μg/L, < LOD, < LOD, and 0.15 μmol/L, respectively. Urinary concentrations of MeP, EtP, and PrP were higher in the first trimester than those in the third trimester (all $P < 0.05$). Triclosan was detected in approximately 80% of urine samples in the present population. Compared with our previous report (Zhao et al., 2017), the detection rate of triclosan was higher in this work because of the obtained lower LOD. For the three benzophenones, BP-1 had the highest detection rate (89%), followed by 4-OH-BP (85%) and BP-3 (71%). Concentrations of BP-1 and BP-3 also varied by trimester (both $P < 0.05$). The ICC values of all analyzed chemicals in the three trimesters were < 0.4. Percentiles of the tested chemicals are presented in Table S2. We compared urinary concentrations of parabens, triclosan, and benzophenones between women with male fetuses and those with female fetuses and found only BP-3 was significantly varied between the two groups (see Table S3).

The associations of repeated measures of all chemicals and blood pressure from mixed linear models were similar before and after adjustment for covariates. Therefore, the βs (95% CIs) and $P_{\text{-}FDR}$ values are shown only after adjustment in Table 3. Among all pregnant women, we observed no significant association between any chemical and SBP or DBP. Only a slightly change in PP (β = 0.34, $P_{\text{-}FDR} = 0.02$) was observed when related to triclosan. Interestingly, the associations were in

Table 1
Basic characteristics of the pregnant women among all participants and groups stratified by fetal sex (mean ± SD or n [%]).

Contents	All women (N = 644)	Women with male fetus (n = 336)	Women with female fetus (n = 308)	*P*
Maternal age (years)	28.63 ± 3.32	28.67 ± 3.38	28.60 ± 3.27	0.58
Pre-pregnancy BMI (kg/m^2)	20.81 ± 2.81	20.82 ± 2.84	20.81 ± 2.79	0.89
Annual family income				0.62
< 100,000 yuan/year	367 (56.99)	192 (57.14)	175 (56.82)	
≥100,000 yuan/year	276 (42.86)	143 (42.56)	133 (43.18)	
Missing	1 (0.16)	1 (0.30)	0 (0.00)	
Education status				0.21
≤9 years	35 (5.43)	25 (7.44)	10 (3.25)	
9–12 years	97 (15.06)	47 (13.99)	50 (16.23)	
≥12 years	512 (79.50)	264 (78.57)	248 (80.52)	
Parity				0.05
Nulliparous	546 (84.78)	276 (82.14)	270 (87.66)	
Multiparous	98 (15.22)	60 (17.86)	38 (12.34)	
Passive smoking during pregnancy				0.66
No	402 (62.42)	207 (61.61)	195 (63.31)	
Yes	242 (37.58)	129 (38.39)	113 (36.69)	
Hypertension disorders during pregnancy				0.71
No	630 (97.83)	328 (97.62)	302 (98.05)	
Yes	14 (2.17)	8 (2.38)	6 (1.95)	
Gestational diabetes mellitus				0.53
No	588 (91.30)	309 (91.96)	279 (90.58)	
Yes	56 (8.70)	27 (8.04)	29 (9.42)	

Abbraviations: pre-pregnancy BMI: pre-pregnancy body mass index.

different directions in fetal sex–stratified groups. For almost all chemicals, we observed positive associations with SBP, DBP, and MAP in women carrying male fetuses but negative though nonsignificant associations in women carrying female fetuses. Among women with male fetuses, per ln-unit increase in triclosan, BP-1, 4-OH-BP, and Σbenzophenones were significantly associated with 0.32 (P_{-FDR} = 0.03), 0.58 (P_{-FDR} = 0.02), 0.75 (P_{-FDR} = 0.03), and 0.76 (P_{-FDR} = 0.02) mmHg change in SBP, respectively, whereas no chemical was significantly associated with SBP in women with female fetuses. DBP was not associated with any chemical in women carrying male fetuses but was inversely associated with triclosan in women carrying female fetuses, though the magnitude was small (β = −0.38, P_{-FDR} = 0.03). No chemical was associated with PP, neither in women with male fetuses nor in women with female fetuses. In addition, BP-1 and Σbenzophenones were significantly associated with a slight change of MAP in women carrying male fetuses, while no significant association with MAP was observed in women carrying female fetuses. Further, we observed a null association of urinary paraben, triclosan, and benzophenone levels with the onset of HDP, both in all participants and in analyses stratified by fetal sex (see Table S4).

The results of GAMs suggested no strong evidence for departure from linearity (all nonlinearity *P*-values > 0.05). In addition, the significant estimates in the tertile models have shown trends of linear dose-response relationships between triclosan, benzophenone and blood pressure measurements, though the *P*-values for trend of most associations in tertile models were > 0.05 (Table S5). After excluding women with GDM, the associations between chemicals and blood pressure were mostly unchanged (see Table S6). When using the uncorrected chemical concentrations as independent variables, and additionally adjusting for urinary SG in the final model, associations between triclosan, benzophenones and PP were robust (see Table S7).

4. Discussion

To the best of our knowledge, this is the first epidemiological study estimating the associations of urinary parabens, triclosan, and benzophenones with blood pressure during pregnancy. Taking advantage of the prospective birth cohort, we found that SBP during pregnancy was significantly associated with urinary triclosan and some benzophenones, although the magnitude was tiny. Furthermore, the significant associations with SBP were observed only among women carrying male fetuses, indicating a potential modifier role of fetal sex in the associations of triclosan and benzophenone exposure with blood pressure during pregnancy.

Table 2
Urinary concentrations of parabens, triclosan, and benzophenones in women (N = 644).

Chemical[a] (μg/L)	LOD	Detection rate (%)	GM over pregnancy	GM 1st, 2nd, 3rd trimesters	Median over pregnancy	Median 1st, 2nd, 3rd trimesters	*P*[b]	ICC
MeP	0.05	97.20	15.09	18.06, 15.68, 12.16	15.49	18.97, 16.68, 11.88	0.00	0.37
EtP	0.01	93.99	0.58	0.66, 0.63, 0.48	0.48	0.54, 0.49, 0.42	0.02	0.06
PrP	0.05	96.06	0.85	1.10, 0.94, 0.61	0.66	0.92, 0.82, 0.43	0.00	0.19
BzP	0.01	22.29	ND	ND, ND, ND	ND	ND, ND, ND	/	/
BuP	0.05	36.44	ND	ND, ND, ND	ND	ND, ND, ND	/	/
Σparabens (μmol/L)	/	/	0.14	0.17, 0.15, 0.11	0.15	0.19, 0.17, 0.11	0.00	/
Triclosan	0.1	78.95	0.41	0.47, 0.38, 0.38	0.51	0.55, 0.44, 0.51	0.05	0.38
BP-1	0.1	89.06	0.28	0.35, 0.27, 0.23	0.27	0.31, 0.24, 0.23	0.00	0.29
BP-3	0.2	71.12	0.41	0.51, 0.38, 0.36	0.57	0.65, 0.52, 0.53	0.01	0.30
4-OH-BP	0.1	84.86	0.14	0.12, 0.16, 0.16	0.16	0.13, 0.19, 0.18	0.00	0.34
Σbenzophenones (μmol/L)	/	/	0.006	0.007, 0.006, 0.005	0.006	0.006, 0.005, 0.005	0.01	/

Abbreviations: LOD, limit of detection; ND, estimate below the laboratory's LOD; GM, geometric mean; ICC, intraclass correlation coefficient.
[a] Corrected by specific gravity (SG) using the formula: values × (1.012 − 1) / (measured SG − 1).
[b] Compared chemical levels in the first, second, and third trimesters using repeated-measures analysis of variance.

Table 3
Associations of urinary parabens, triclosan, and benzophenones with blood pressure among all women or subgroups categorized by fetal sex.

Chemical[a]	SBP		DBP		PP		MAP	
	Adjusted β (95% CI)[b]	P_{-FDR}[c]	Adjusted β (95% CI)[b]	P_{-FDR}[c]	Adjusted β (95% CI)[b]	P_{-FDR}[c]	Adjusted β (95% CI)[b]	P_{-FDR}[c]
All participants (N = 644)								
MeP	0.15 (−0.12, 0.43)	0.47	0.19 (−0.05, 0.43)	0.55	−0.02 (−0.25, 0.21)	0.74	0.17 (−0.04, 0.39)	0.77
EtP	−0.08 (−0.32, 0.16)	0.47	0.04 (−0.15, 0.24)	0.91	−0.13 (−0.33, 0.07)	0.24	0.03 (−0.17, 0.22)	0.83
PrP	0.03 (−0.21, 0.27)	0.92	0.05 (−0.15, 0.25)	0.91	−0.02 (−0.23, 0.18)	0.74	0.02 (−0.17, 0.22)	0.83
Σparabens	0.11 (−0.21, 0.43)	0.58	0.20 (−0.06, 0.45)	0.55	−0.09 (−0.37, 0.18)	0.73	0.18 (−0.07, 0.42)	0.77
Triclosan	0.20 (−0.04, 0.43)	0.24	−0.16 (−0.35, 0.03)	0.55	**0.34 (0.14, 0.54)**	**0.02**	−0.03 (−0.22, 0.15)	0.83
BP-1	0.25 (−0.06, 0.55)	0.24	0.01 (−0.24, 0.27)	0.91	0.22 (−0.05, 0.50)	0.14	0.13 (−0.12, 0.38)	0.77
BP-3	0.32 (0.06, 0.59)	0.17	0.07 (−0.15, 0.29)	0.91	0.23 (0.01, 0.45)	0.09	0.16 (−0.05, 0.37)	0.77
4-OH-BP	0.38 (−0.03, 0.80)	0.24	−0.04 (−0.37, 0.30)	0.91	0.37 (0.03, 0.71)	0.09	0.12 (−0.21, 0.45)	0.83
Σbenzophenones	0.39 (0.04, 0.73)	0.17	0.09 (−0.21, 0.39)	0.91	0.36 (0.07, 0.66)	0.06	0.15 (−0.13, 0.42)	0.77
Women with male fetus (n = 336)								
MeP	0.35 (−0.03, 0.72)	0.13	0.16 (−0.14, 0.46)	0.47	0.20 (−0.11, 0.52)	0.60	0.20 (−0.10, 0.50)	0.20
EtP	0.02 (−0.31, 0.35)	0.95	0.11 (−0.16, 0.38)	0.53	−0.11 (−0.40, 0.17)	0.60	0.07 (−0.19, 0.34)	0.70
PrP	0.24 (−0.11, 0.60)	0.13	0.19 (−0.09, 0.47)	0.39	0.12 (−0.17, 0.41)	0.60	0.24 (−0.03, 0.51)	0.16
Σparabens	0.39 (−0.05, 0.84)	0.09	0.29 (−0.06, 0.64)	0.31	0.21 (−0.15, 0.57)	0.60	0.31 (−0.04, 0.66)	0.16
Triclosan	**0.32 (0.01, 0.64)**	**0.03**	0.09 (−0.16, 0.35)	0.51	0.31 (0.04, 0.58)	0.13	0.11 (−0.14, 0.36)	0.16
BP-1	**0.58 (0.14, 1.02)**	**0.02**	0.45 (0.10, 0.81)	0.05	0.12 (−0.25, 0.49)	0.60	**0.53 (0.18, 0.87)**	**0.01**
BP-3	0.32 (−0.05, 0.68)	0.13	0.22 (−0.07, 0.52)	0.31	0.08 (−0.22, 0.39)	0.63	0.26 (−0.03, 0.54)	0.16
4-OH-BP	**0.75 (0.17, 1.34)**	**0.03**	0.18 (−0.31, 0.67)	0.47	0.55 (0.05, 1.04)	0.13	0.39 (−0.07, 0.85)	0.16
Σbenzophenones	**0.76 (0.26, 1.26)**	**0.02**	0.50 (0.10, 0.91)	0.05	0.27 (−0.16, 0.70)	0.60	**0.59 (0.20, 0.98)**	**0.01**
Women with female fetus (n = 308)								
MeP	−0.10 (−0.50, 0.30)	0.76	0.20 (−0.14, 0.54)	0.38	−0.31 (−0.64, 0.03)	0.13	0.11 (−0.21, 0.43)	0.61
EtP	−0.19 (−0.54, 0.16)	0.74	−0.03 (−0.32, 0.26)	0.78	−0.16 (−0.45, 0.13)	0.29	−0.09 (−0.37, 0.19)	0.61
PrP	−0.27 (−0.61, 0.08)	0.74	−0.09 (−0.38, 0.20)	0.67	−0.17 (−0.46, 0.11)	0.29	−0.14 (−0.42, 0.13)	0.56
Σparabens	−0.27 (−0.71, 0.17)	0.74	0.08 (−0.29, 0.46)	0.75	−0.36 (−0.73, 0.01)	0.13	−0.03 (−0.38, 0.33)	0.90
Triclosan	−0.07 (−0.39, 0.25)	0.76	**−0.38 (−0.65, −0.10)**	**0.03**	0.30 (0.03, 0.58)	0.11	−0.27 (−0.53, −0.01)	0.23
BP-1	−0.11 (−0.55, 0.32)	0.76	−0.42 (−0.79, −0.06)	0.08	0.31 (−0.05, 0.68)	0.20	−0.32 (−0.67, 0.03)	0.23
BP-3	0.18 (−0.19, 0.55)	0.76	−0.20 (−0.51, 0.11)	0.38	0.39 (0.08, 0.70)	0.11	−0.07 (−0.37, 0.22)	0.61
4-OH-BP	−0.10 (−0.66, 0.46)	0.76	−0.29 (−0.76, 0.18)	0.38	0.19 (−0.28, 0.66)	0.46	−0.23 (−0.68, 0.22)	0.56
Σbenzophenones	0.01 (−0.47, 0.50)	0.95	−0.41 (−0.82, −0.01)	0.12	0.43 (0.03, 0.84)	0.11	−0.27 (−0.66, 0.12)	0.45

Abbreviations: CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure.
Significance of bold: $P_{-FDR} < 0.05$.

[a] Natural logarithm transformed specific gravity–corrected concentrations.

[b] Adjusted for age, pre-pregnancy BMI, fetal sex, parity, annual family income, and gestational diabetes mellitus in all population. Adjusted for above covariates except for fetal sex in the stratified analyses.

[c] *P* values for estimating false-discovery rate (FDR) to correct multiple comparisons.

Parabens, triclosan, and benzophenones were rapidly metabolized and mainly excreted as conjugated urinary metabolites after absorption (Sandborgh-Englund et al., 2006; Soni et al., 2005; Wang and Kannan, 2013); thus, urinary concentrations were primary exposure biomarkers to assess the valid exposures. Notably, a single urine sample may not be sufficient to reflect long-term individual exposure because of the fast excretion of those chemicals in the human body, usually within several hours to several days (Sandborgh-Englund et al., 2006; Soni et al., 2005; Wang and Kannan, 2013). This was further supported by the low ICCs (< 0.4) of parabens, triclosan, and benzophenones we observed across three different trimesters. Therefore, we used repeated urinary measurements in each trimester to make valid exposure assessments of those chemicals across pregnancy. In the present study, we observed that almost all chemicals, except for 4-OH-BP, had higher urinary concentrations in the first trimester than in the second and/or third trimester, possibly because the physiological and biochemical changes associated with pregnancy may alter the physiological response to environmental pollutants (Abduljalil et al., 2012). Another potential explanation is that women may reduce their exposure to personal care products, especially cosmetics, which are common sources of these chemicals, in mid and late pregnancy, after their pregnancy has been confirmed.

The high detection rates (70%–97%) of the analyzed chemicals, except for BzP and BuP, indicated that the Chinese pregnant women were widely exposed to selected parabens, triclosan, and benzophenones. We compared the tested chemical levels in this study and other reported populations in Table 4. The median levels of MeP, EtP, and PrP (15.1, 0.6, 0.9 μg/L) in the present population were comparable to that of pregnant women from Denmark (median, 20.7, 1.01, 4.17 μg/L) (Tefre et al., 2014) but much lower than those from France (median, 97.8, 4.1, 12.5 μg/L) (Philippat et al., 2012) and the United States (median, 279.0, 1.4, 75.3 μg/L) (Pycke et al., 2015). Urinary triclosan levels in our study population (median, 0.4 μg/L) were much lower than in pregnant women from France (median, 24.1 μg/L) (Philippat et al., 2012), Canada (median, 9.2 μg/L) (Arbuckle et al., 2015), and the United States (median, 26.5 μg/L) (Watkins et al., 2015) and slightly lower than those from Denmark (GM, 0.96 μg/L) (Lassen et al., 2016). Compared with Denmark, pregnant women in the present study were exposed to lower levels of BP-1 (median, 0.3 vs. 0.5 μg/L) and higher levels of 4-OH-BP (median, 0.2 μg/L vs. < LOD) (Krause et al., 2017). Urinary BP-3 concentrations in the pregnant women of the present study (GM, 0.4 μg/L; median, 0.6 μg/L) were lower than in the same population from France (median, 1.7 μg/L) (Philippat et al., 2012), Norway (GM, 6.1 μg/L) (Guidry et al., 2015), and Denmark (median, 2.6 μg/L) (Krause et al., 2017) but were comparable to those of children (median 0.6 μg/L) and adults (median, 0.7 μg/L) in China (Wang and Kannan, 2013). In summary, the detection rates and concentrations of urinary parabens, triclosan, and benzophenones in the present population were comparable to populations from Denmark and other cities in China but lower than that of most developed countries, including the United States, Canada, and France, perhaps because of the differences in regions, economic status, lifestyle, usage rate of personal care products, as well as the timing of sample collection during pregnancy (Zhang et al., 2013). EDCs at low dose can lead to effects on human

Table 4
Comparison of paraben, triclosan, and benzophenone concentrations in the urine of pregnant women from the present study and previous studies.

Reference	Nation	Population	Concentration (median or GM)								
			MeP	EtP	PrP	BuP	BzP	TCS	BP-1	BP-3	4-OH-BP
Present study	China	Pregnant women	14.8	0.6	0.9	ND	ND	0.6	0.3	0.6	0.2
Philippat et al. (2012)	France	Pregnant women	122.0	4.7	17.0	2.0	/	30.0	/	2.2	/
Watkins et al. (2015)	USA	Pregnant women	152.0	/	45.4	/	/	26.5	/	34.5	/
Arbuckle et al. (2015)	Canada	Pregnant women	/	/	/	/	/	9.2	/	/	/
Claire Philippat et al.	France	Pregnant women	97.8	4.1	12.5	1.7	/	24.1	/	1.7	/
Pycke et al. (2015)	USA	Pregnant women	279.0	1.4	75.3	0.4	/	/	/	/	/
Krause et al. (2017)	Denmark	Pregnant women	/	/	/	/	/	/	0.5	2.6	ND
Tefre et al. (2014)	Denmark	Pregnant women	20.7	1.0	4.2	/	/	/	/	3.2	/
Guidry et al. (2015)	Norway	Pregnant women	1235.7[a]	/	32.3[a]	6.3[a]	/	/	/	6.1[a]	/
Lassen et al. (2016)	Denmark	Pregnant women	/	/	/	/	/	0.96[a]	/	/	/
Shirai et al. (2013)	Japan	Pregnant women	108.0	7.3	33.3	0.8	ND	/	/	/	/
Kang et al. (2013)	Korea	Pregnant women	169.9	44.6	8.6	/	/	/	/	/	/
Shiue (2014)	USA (NHANES)	Adults	214.7	15.5	50.6	/	/	/	/	/	/
Wang and Kannan (2013)	China	Children	/	/	/	/	/	/	/	0.6	/
Wang and Kannan (2013)	China	Adults	/	/	/	/	/	/	/	0.7	/

Abbreviation: GM, geometric mean.
[a] GMs.

health (Vandenberg et al., 2012); thus, the potential adverse health effects of parabens, triclosan, and benzophenones, even with the relatively low exposure levels in the present population, should not be neglected. Further, a previous study indicated that EDC exposure levels were associated with age (Meeker et al., 2013), but no significant associations between age and levels of paraben, triclosan, and benzophenone were observed in the present study (data not shown).

Blood pressure, the most common indicator of circulation system condition and a strong contributor to the risk of cardiovascular events, was previously suggested to be influenced by EDCs (such as bisphenol A, polychlorobiphenyls, and organochlorine pesticides) in the general population (Bae and Hong, 2015; Henriquez-Hernandez et al., 2014). However, limited research related EDCs to blood pressure among pregnant women, who are more vulnerable to environmental contaminments compared with adults in the general population. As far as we know, only one study reported that monobenzyl phthalate (MBzP) exposure was associated with DBP among 369 pregnant women in the United States (Werner et al., 2015). Those findings provided a clue to the potential associations of EDCs with blood pressure and highlighted the needs of further research on adverse cardiovascular effects of EDC exposure, particularly among pregnant women.

No previous data were available on the association of parabens with blood pressure in pregnant women, but a study based on the National Health and Nutrition Examination Survey investigated the association between urinary parabens and high blood pressure (SBP ≥ 140 and DBP ≥ 90 mm Hg) in the general population with an average age of 31.4 ± 24.6 (mean ± SD) years. In agreement with our findings, they found no significant associations between paraben exposures and high blood pressure occurrence (Shiue, 2014). This null association may be explained by the weak estrogen activity of parabens (Bledzka et al., 2014). Since the paraben levels of the present pregnant women were much lower than that of pregnant women in most developed countries (Table 4), further replicated research in other populations is needed to make a conclusion about the associations between parabens and blood pressure during pregnancy.

Our results suggested the four blood pressure indicators (SBP, DBP, PP, and MAP) showed different sensitivity with the chemicals in the groups stratified by fetal sex. In women carrying male fetuses, SBP was the most sensitive indicator, as it was affected by triclosan and almost all benzophenones. However, the SBP-dominant effects disappeared in women carrying female fetuses. The diverse results suggest the need for further studies to take fetal sex susceptibility into consideration for research on the sensitivity of blood pressure measures of pregnant women.

The exposures of parabens, triclosan, and benzophenones had no significant associations with HDP. The limited number of HDP cases (n = 14) in the present population may be one possible reason, and the other explanation may be that the magnitude of the adverse effects on blood pressure did not reach the hypertension threshold in the present exposure levels. Although changes in blood pressure values of only 0.3 to 0.8 mm Hg were observed to be associated with triclosan or benzophenones in the present study, this is a hazard that warrants concern. A tiny change in blood pressure may seem negligible for individuals, but it can have a non-ignorable impact at the population scale. Further, this tiny change in blood pressure was observed in a population with much lower triclosan and benzophenone levels than those found in most developed countries (Table 4). This highlights the necessity of evaluating the effects of triclosan and benzophenones on blood pressure and related diseases in populations with different exposure levels, especially those with higher exposure levels of triclosan and benzophenone.

Although the underlying mechanisms that related triclosan and benzophenones to blood pressure alteration during pregnancy have not yet been studied, previous studies that researched other EDC-related blood pressure increments provided a clue as to the possible pathways. Estrogen and androgen play important roles in maintaining endothelial function and the cardiovascular system and can stimulate the renin-angiotensin-aldosterone system and consequently modulate blood pressure. Triclosan and benzophenones, which are well-documented EDCs, have the ability to disrupt estrogen and androgen functions, which might then affect blood pressure (Dos Santos et al., 2014). Also, triclosan and benzophenones may alter blood pressure via disruption of the thyroid hormone (Aker et al., 2016; Koeppe et al., 2013), which is also associated with blood pressure regulation (Fommei and Iervasi, 2002). The associations may be explained by the potential effects of triclosan and benzophenones on oxidative stress and systemic inflammation, although both are great contributors to blood pressure increment (Cullinan et al., 2015; Dinh et al., 2014; Liu et al., 2015; Watkins et al., 2015). Further, the findings regarding blood pressure increment were most prominently observed in women carrying male fetuses. Exposure levels could not explain the dominant effects associated with mothers of male fetuses, since concentrations of those chemicals, except for BP-3, did not differ between pregnant women carrying female fetuses and those with male fetus in the present study. The possible explanation for the potential fetal sex-different associations is that EDC exposure is thought to disrupt maternal hormones and placental secretion in a fetal sex–specific way (Sood et al., 2017). In addition, the reported fetal sex differences in maternal inflammatory and immune function (i.e., women carrying male fetuses face higher

levels of inflammation) may also contribute to the stronger associations observed in these women (Enninga et al., 2015).

The major strength of the present study is the prospective cohort design, which allowed us to repeatedly measure chemical exposures and blood pressure over three trimesters, to make a valid exposure, and to investigate the relationship with outcome measurement. Moreover, the detailed information obtained from interviews and medical records enabled us to control socioeconomic, perinatal, and environmental confounders.

Our study also has some limitations. First, the magnitude of blood pressure changes associated with contaminant exposures observed in this study was tiny, which was possibly the result of measurement error or internal variation. Because the tiny change in blood pressure was associated with relatively low exposure levels of triclosan and benzophenone in this study, future replicated research, especially in populations with higher triclosan and benzophenone exposure levels, is needed to make the conclusion. Then, detailed information about the use of personal care products during pregnancy was not available in the present population, which prohibited us from clarifying the sources of chemical exposure. Other factors that may impair blood pressure, such as salt intake and maternal stress, were not adjusted because of unavailable information.

5. Conclusions

In summary, the present study suggested that exposure to triclosan and benzophenones during pregnancy has the potential to alter blood pressure in pregnant women, and the associations may differ by fetal sex. Further, as cardiovascular morbidity and mortality are rising worldwide, the potential risk of later-life cardiovascular diseases in mothers and children exposed prenatally to environmental pollutants is a critical area of investigation.

Acknowledgements

This work was supported by the National Key Research and Development Plan of China (grant nos. 2016YFC0206700, 2016YFC0206203) and the National Natural Science Foundation of China (grant nos. 81372959, 21437002, 81402649, 91643207, and 21777010).

Declaration of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.11.003.

References

Abduljalil, K., Furness, P., Johnson, T.N., Rostami-Hodjegan, A., Soltani, H., 2012. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. Clin. Pharmacokinet. 51, 365–396.

Aker, A.M., Watkins, D.J., Johns, L.E., Ferguson, K.K., Soldin, O.P., Anzalota Del Toro, L.V., et al., 2016. Phenols and parabens in relation to reproductive and thyroid hormones in pregnant women. Environ. Res. 151, 30–37.

Al-Qaraghouli, M., Fang, Y.M.V., 2017. Effect of fetal sex on maternal and obstetric outcomes. Front. Pediatr. 5, 144.

American Diabetes Association, 2011. Diagnosis and classification of diabetes mellitus. Diabetes Care 34 (Suppl. 1), S62–S69.

Arbuckle, T.E., Marro, L., Davis, K., Fisher, M., Ayotte, P., Belanger, P., et al., 2015. Exposure to free and conjugated forms of bisphenol A and triclosan among pregnant women in the mirec cohort. Environ. Health Perspect. 123, 277–284.

Asimakopoulos, A.G., Thomaidis, N.S., Kannan, K., 2014. Widespread occurrence of bisphenol A diglycidyl ethers, *p*-hydroxybenzoic acid esters (parabens), benzophenone type-UV filters, triclosan, and triclocarban in human urine from Athens, Greece. Sci. Total Environ. 470–471, 1243–1249.

Bae, S., Hong, Y.C., 2015. Exposure to bisphenol A from drinking canned beverages increases blood pressure: randomized crossover trial. Hypertension 65, 313–319.

Bledzka, D., Gromadzinska, J., Wasowicz, W., 2014. Parabens. From environmental studies to human health. Environ. Int. 67, 27–42.

Bonefeld-Jorgensen, E.C., Long, M., Hofmeister, M.V., Vinggaard, A.M., 2007. Endocrine-disrupting potential of bisphenol A, bisphenol A dimethacrylate, 4-*n*-nonylphenol, and 4-*n*-octylphenol in vitro: new data and a brief review. Environ. Health Perspect. 115 (Suppl. 1), 69–76.

Braun, J.M., Just, A.C., Williams, P.L., Smith, K.W., Calafat, A.M., Hauser, R., 2014. Personal care product use and urinary phthalate metabolite and paraben concentrations during pregnancy among women from a fertility clinic. J. Expo. Sci. Environ. Epidemiol. 24 (5), 459–466.

Cullinan, M.P., Palmer, J.E., Faddy, M.J., Westerman, B., Carle, A.D., West, M.J., et al., 2015. The influence of triclosan on biomarkers of cardiovascular risk in patients in the cardiovascular and periodontal study (CAPS): a randomized controlled trial. J. Periodontol. 86, 847–855.

Darbre, P.D., Harvey, P.W., 2014. Parabens can enable hallmarks and characteristics of cancer in human breast epithelial cells: a review of the literature with reference to new exposure data and regulatory status. J. Appl. Toxicol. 34, 925–938.

Dinh, Q.N., Drummond, G.R., Sobey, C.G., Chrissobolis, S., 2014. Roles of inflammation, oxidative stress, and vascular dysfunction in hypertension. Biomed. Res. Int. 2014, 406960.

Dos Santos, R.L., Da Silva, F.B., Ribeiro Jr., R.F., Stefanon, I., 2014. Sex hormones in the cardiovascular system. Horm. Mol. Biol. Clin. Invest. 18, 89–103.

Enninga, E.A., Nevala, W.K., Creedon, D.J., Markovic, S.N., Holtan, S.G., 2015. Fetal sex based differences in maternal hormones, angiogenic factors,and immune mediators during pregnancy and the postpartum period. Am. J. Reprod. Immunol. 73 (3), 251–262. https://doi.org/10.1111/aji.12303. (Epub 2014 Aug 4).

Fommei, E., Iervasi, G., 2002. The role of thyroid hormone in blood pressure homeostasis: evidence from short-term hypothyroidism in humans. J. Clin. Endocrinol. Metab. 87, 1996–2000.

Geer, L.A., Pycke, B.F.G., Waxenbaum, J., Sherer, D.M., Abulafia, O., Halden, R.U., 2017. Association of birth outcomes with fetal exposure to parabens, triclosan and triclocarban in an immigrant population in Brooklyn, New York. J. Hazard. Mater. 323, 177–183.

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.

Gleicher, N., Boler Jr., L.R., Norusis, M., Del Granado, A., 1986. Hypertensive diseases of pregnancy and parity. Am. J. Obstet. Gynecol. 154, 1044–1049.

Guidry, V.T., Longnecker, M.P., Aase, H., Eggesbo, M., Zeiner, P., Reichborn-Kjennerud, T., et al., 2015. Measurement of total and free urinary phenol and paraben concentrations over the course of pregnancy: assessing reliability and contamination of specimens in the Norwegian mother and child cohort study. Environ. Health Perspect. 123, 705–711.

Heffernan, A.L., Baduel, C., Toms, L.M., Calafat, A.M., Ye, X., Hobson, P., et al., 2015. Use of pooled samples to assess human exposure to parabens, benzophenone-3 and triclosan in Queensland, Australia. Environ. Int. 85, 77–83.

Hennington, B.S., Alexander, B.T., 2013. Linking intrauterine growth restriction and blood pressure: insight into the human origins of cardiovascular disease. Circulation 128, 2179–2180.

Henriquez-Hernandez, L.A., Luzardo, O.P., Zumbado, M., Camacho, M., Serra-Majem, L., Alvarez-Leon, E.E., et al., 2014. Blood pressure in relation to contamination by polychlorobiphenyls and organochlorine pesticides: results from a population-based study in the canary islands (Spain). Environ. Res. 135, 48–54.

Intapad, S., Alexander, B.T., 2013. Future cardiovascular risk: interpreting the importance of increased blood pressure during pregnancy. Circulation 127, 668–669.

Kang, S., Kim, S., Park, J., Kim, H.J., Lee, J., Choi, G., et al., 2013. Urinary paraben concentrations among pregnant women and their matching newborn infants of Korea, and the association with oxidative stress biomarkers. Sci. Total Environ. 461–462, 214–221.

Kataria, A., Levine, D., Wertenteil, S., Vento, S., Xue, J., Rajendiran, K., et al., 2017. Exposure to bisphenols and phthalates and association with oxidant stress, insulin resistance, and endothelial dysfunction in children. Pediatr. Res. 81, 857–864.

Kirkley, A.G., Sargis, R.M., 2014. Environmental endocrine disruption of energy metabolism and cardiovascular risk. Curr. Diab. Rep. 14, 494.

Kobalava, Z.D., Kotovskaya, Y.V., Babaeva, L.A., Moiseev, V.S., 2006. Validation of tm-2655 oscillometric device for blood pressure measurement. Blood Press. Monit. 11, 87–90.

Koeppe, E.S., Ferguson, K.K., Colacino, J.A., Meeker, J.D., 2013. Relationship between urinary triclosan and paraben concentrations and serum thyroid measures in NHANES 2007–2008. Sci. Total Environ. 445–446, 299–305.

Krause, M., Frederiksen, H., Sundberg, K., Jorgensen, F.S., Jensen, L.N., Norgaard, P., et al., 2017. Presence of benzophenones commonly used as UV filters and absorbers in paired maternal and fetal samples. Environ. Int. 110, 51–60.

Kshirsagar, A.V., Carpenter, M., Bang, H., Wyatt, S.B., Colindres, R.E., 2006. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. Am. J. Med. 119, 133–141.

Larsson, K., Ljung Bjorklund, K., Palm, B., Wennberg, M., Kaj, L., Lindh, C.H., et al., 2014. Exposure determinants of phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children. Environ. Int. 73, 323–333.

Lassen, T.H., Frederiksen, H., Kyhl, H.B., Swan, S.H., Main, K.M., Andersson, A.M., et al., 2016. Prenatal triclosan exposure and anthropometric measures including anogenital distance in Danish infants. Environ. Health Perspect. 124, 1261.

Liu, H., Sun, P., Liu, H., Yang, S., Wang, L., Wang, Z., 2015. Hepatic oxidative stress biomarker responses in freshwater fish Carassius auratus exposed to four

benzophenone UV filters. Ecotoxicol. Environ. Saf. 119, 116–122.
Macdonald-Wallis, C., Tilling, K., Fraser, A., Nelson, S.M., Lawlor, D.A., 2014. Associations of blood pressure change in pregnancy with fetal growth and gestational age at delivery: findings from a prospective cohort. Hypertension 64, 36–44.
Meeker, J.D., Cantonwine, D.E., Rivera-Gonzalez, L.O., Ferguson, K.K., Mukherjee, B., Calafat, A.M., et al., 2013. Distribution, variability, and predictors of urinary concentrations of phenols and parabens among pregnant women in Puerto Rico. Environ. Sci. Technol. 47, 3439–3447.
Mendelsohn, M.E., 2009. Estrogen actions in the cardiovascular system. Climacteric 12 (Suppl. 1), 18–21.
Moriyama, K., Tagami, T., Akamizu, T., Usui, T., Saijo, M., Kanamoto, N., et al., 2002. Thyroid hormone action is disrupted by bisphenol A as an antagonist. J. Clin. Endocrinol. Metab. 87, 5185–5190.
Philippat, C., Mortamais, M., Chevrier, C., Petit, C., Calafat, A.M., Ye, X., et al., 2012. Exposure to phthalates and phenols during pregnancy and offspring size at birth. Environ. Health Perspect. 120, 464–470.
Pike, N., 2011. Using false discovery rates for multiple comparisons in ecology and evolution. Methods Ecol. Evol. 2, 278–282.
Pycke, B.F.G., Geer, L.A., Dalloul, M., Abulafia, O., Halden, R.U., 2015. Maternal and fetal exposure to parabens in a multiethnic urban U.S. population. Environ. Int. 84, 193–200.
Sandborgh-Englund, G., Adolfsson-Erici, M., Odham, G., Ekstrand, J., 2006. Pharmacokinetics of triclosan following oral ingestion in humans. J. Toxicol. Environ. Health A 69, 1861–1873.
Sanghavi, M., Rutherford, J.D., 2014. Cardiovascular physiology of pregnancy. Circulation 130, 1003–1008.
Schmutzler, C., Bacinski, A., Gotthardt, I., Huhne, K., Ambrugger, P., Klammer, H., et al., 2007. The ultraviolet filter benzophenone 2 interferes with the thyroid hormone axis in rats and is a potent in vitro inhibitor of human recombinant thyroid peroxidase. Endocrinology 148, 2835–2844.
Shirai, S., Suzuki, Y., Yoshinaga, J., Shiraishi, H., Mizumoto, Y., 2013. Urinary excretion of parabens in pregnant Japanese women. Reprod. Toxicol. 35, 96–101.
Shiue, I., 2014. Higher urinary heavy metal, phthalate, and arsenic but not parabens concentrations in people with high blood pressure, U.S. NHANES, 2011–2012. Int. J. Environ. Res. Public Health 11, 5989–5999.
Soni, M.G., Carabin, I.G., Burdock, G.A., 2005. Safety assessment of esters of *p*-hydroxybenzoic acid (parabens). Food Chem. Toxicol. 43, 985–1015.
Sood, S., Shekhar, S., Santosh, W., 2017. Dimorphic placental stress: a repercussion of interaction between endocrine disrupting chemicals (EDCs) and fetal sex. Med. Hypotheses 99, 73–75.
Tefre, dRK, Frederiksen, H., Christensen, J.S., Boye, K.H., Andersson, A.M., Husby, S., et al., 2014. Current exposure of 200 pregnant Danish women to phthalates, parabens and phenols. Reproduction 147, 443–453.
Van den Hooven, E.H., De Kluizenaar, Y., Pierik, F.H., Hofman, A., van Ratingen, S.W., Zandveld, P.Y., et al., 2011. Air pollution, blood pressure, and the risk of hypertensive complications during pregnancy: the generation R study. Hypertension 57, 406–412.
Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs Jr., D.R., Lee, D.H., et al., 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr. Rev. 33, 378–455.
Vanlalhruaii, Ranabir S., Prasad, L., Singh, N.N., Singh, T.P., 2013. Prevalence of gestational diabetes mellitus and its correlation with blood pressure in Manipuri women. Indian J. Endocr. Metab. 17, 957–961.
Von Dadelszen, P., Ornstein, M.P., Bull, S.B., Logan, A.G., Koren, G., Magee, L.A., 2000. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. Lancet 355, 87–92.
Wang, L., Kannan, K., 2013. Characteristic profiles of benzonphenone-3 and its derivatives in urine of children and adults from the United States and China. Environ. Sci. Technol. 47, 12532–12538.
Watkins, D.J., Ferguson, K.K., Anzalota Del Toro, L.V., Alshawabkeh, A.N., Cordero, J.F., Meeker, J.D., 2015. Associations between urinary phenol and paraben concentrations and markers of oxidative stress and inflammation among pregnant women in Puerto Rico. Int. J. Hyg. Environ. Health 218, 212–219.
Werner, E.F., Braun, J.M., Yolton, K., Khoury, J.C., Lanphear, B.P., 2015. The association between maternal urinary phthalate concentrations and blood pressure in pregnancy: the HOME study. Environ. Health 14, 75.
Zairina, E., 2016. Maternal passive smoking and the risk of developing wheeze in children: how should we deal with it? Eur. Respir. J. 48, 3–5.
Zhang, T., Sun, H., Qin, X., Wu, Q., Zhang, Y., Ma, J., et al., 2013. Benzophenone-type UV filters in urine and blood from children, adults, and pregnant women in China: partitioning between blood and urine as well as maternal and fetal cord blood. Sci. Total Environ. 461–462, 49–55.
Zhao, H., Huo, W., Li, J., Ma, X., Xia, W., Pang, Z., et al., 2017. Exposure to benzophenones, parabens and triclosan among pregnant women in different trimesters. Sci. Total Environ. 607–608, 578–585.