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Exposure to phthalate metabolites, phenols and organophosphate pesticide metabolites and blood pressure during pregnancy

Charline Warembourg[a,b,c], Xavier Basagaña[a,b,c], Chiara Seminati[a,b,c,1], Jeroen de Bont[a,b,c], Berit Granum[d], Sarah Lyon-Caen[e], Cyntia B. Manzano-Salgado[a,b,c,2,3], Isabelle Pin[e,f], Amrit K. Sakhi[d], Valérie Siroux[e], Rémy Slama[e], Jose Urquiza[a,b,c], Martine Vrijheid[a,b,c], Cathrine Thomsen[d], Maribel Casas[a,b,c,*]

[a] ISGlobal, Barcelona, Spain
[b] Universitat Pompeu Fabra, Barcelona, Spain
[c] CIBER Epidemiología y Salud Pública (CIBERESP), Spain
[d] Norwegian Institute of Public Health, Oslo, Norway
[e] Team of Environmental Epidemiology Applied to Reproduction and Respiratory Health, Inserm, CNRS, University Grenoble Alpes, Institute of Advanced Biosciences, Joint Research Center (U1209), La Tronche, Grenoble, France
[f] Grenoble University Hospital (CHU-GA), Pediatric Department, Grenoble, France

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ABSTRACT

Introduction: Hypertensive disorders during pregnancy are one of the leading causes of maternal and offspring mortality and morbidity. Exposure to environmental chemicals is suspected to increase blood pressure (BP) but few studies have investigated the impact of non-persistent chemicals, in particular among pregnant women.
Methods: Women included in the study were 152 volunteer participants in the Human Early-Life Exposome (HELIX) project. They provided 3 urine samples daily over one week in two pregnancy trimesters (at around 18 and 32 weeks of gestation) to assess their exposure to phthalates (10 metabolites), phenols (7 compounds) and organophosphate pesticides (4 metabolites). BP was measured at the end of the two collection weeks. Associations between biomarkers of exposure and BP were investigated using generalized estimating equations (GEE) and linear regression, and adjusted for potential confounders.
Results: A significant decrease in systolic and/or diastolic BP was observed with exposure to some phthalate metabolites, BPA, and parabens (e.g. β GEE models for systolic BP = −0.91 mmHg (95%CI: −1.65; −0.17) per doubling of BPA concentrations). These associations were more frequently observed in the second trimester of pregnancy and remained statistically significant after correction for multiple testing for BPA only. No associations were observed with organophosphate pesticides.
Conclusion: This study investigates the effect of exposure to non-persistent chemicals assessed using multiple biospecimens per subject on BP during pregnancy and suggests that higher exposure to some phthalates and phenols but not pesticides is associated with lower BP during pregnancy.

1. Introduction

Hypertensive disorders during pregnancy are one of the leading causes of maternal and offspring mortality and morbidity (Say et al., 2014). Hypertension can be chronic or start during pregnancy and can be associated with additional comorbidities that may lead to pre-eclampsia and preterm delivery. Many factors are known to increase the risk of high blood pressure (BP) during pregnancy, including overweight and obesity, primiparity, age over 40 years, smoking and alcohol consumption, low physical activity, or familial predisposition (Umesawa and Kobashi, 2017). More recently, environmental factors such as air pollution and exposure to chemicals present in the en-

* Corresponding author. ISGlobal, Barcelona, Spain.
E-mail address: maribel.casas@isglobal.org (M. Casas).
[1] Departament de Sanitat i d'Anatomia Animals, Universitat Autònoma de Barcelona.
[2] Institut Universitari d'Investigació en Atenció Primària (IDIAP) Jordi Gol, Barcelona, Spain.
[3] Universitat Autónoma de Barcelona, Barcelona, Spain.

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vironment have also been suggested to contribute to the risk of hypertensive disorders (Leow, 2015).

Among environmental chemicals suspected to affect BP, phthalates, phenols, and organophosphate (OP) pesticides are non-persistent chemicals widely used in consumer and personal care products for which widespread exposure has been documented in pregnant women (Gore et al., 2015). Several cross-sectional studies have raised concerns of a possible association between exposure to these chemicals and BP or hypertension in adults outside the context of pregnancy. Most of them reported positive associations between at least one group of non-persistent chemicals and BP or hypertension (Aekplakorn et al., 2015; Bae et al., 2012; James-Todd et al., 2016; Ranjbar et al., 2015; Shankar and Teppala, 2012; Zhang et al., 2018) and one reported a negative association for Bisphenol A (BPA) (Wang et al., 2015). In addition, a randomized control trial reported a positive association between BPA exposure and BP in elderly (Bae and Hong, 2015). However, there is only one previous study in pregnant women which examined the effect of exposure to phthalates only; they observed that a higher spot urine concentration of mono benzyl phthalate (MBzP) metabolite at around 16 weeks of gestation was associated with increased BP assessed before 20 weeks (Werner et al., 2015).

A major limitations in the study of the health effects of non-persistent chemicals lies in the assessment of exposure because these compounds have short half-life and high within-subject variability (Cantonwine et al., 2014; Lewis et al., 2015; Meeker et al., 2013). To date, almost all existing studies used a spot urine sample to assess the exposure of these compounds, leading to exposure misclassification and possibly strong attenuation bias (in particular for the most variable compounds such as BPA) under the assumption of classical-type error (Perrier et al., 2016). Therefore, there is a need to study the potential effects of exposure to non-persistent chemicals on BP in pregnant women with a more accurate assessment of exposure, as provided e.g. by relying on within-subject biospecimens pooling (Perrier et al., 2016).

The aim of this study was to assess the association between exposure to phthalate metabolites, phenols, and OP pesticide metabolites and BP in pregnant women using repeated measurements of urinary non-persistent chemicals in two weeks during the second and third trimesters of pregnancy.

2. Materials and methods

2.1. Study population

Between 2014 and 2015, a total of 154 pregnant women were recruited within the framework of the Human Early-Life Exposome (HELIX) project, a collaborative research project with the aim of understanding how different environmental exposures (described globally as the *exposome*) that mothers and children are exposed to, can influence the health, growth and development of children (Vrijheid et al., 2014). Pregnant woman were recruited by gynecologists, ultrasonographers, midwifes/nurses, or research staff at their first visit (around 12 weeks). They conducted an intensive follow-up during one week in the second trimester (around 20 weeks; range = 11–24) and one week in the third trimester of pregnancy (around 32 weeks; range = 26–38), each week ending by a clinical examination (Maitre et al., 2018). The study included around 50 women from each of the three European regions under study: 52 from Barcelona (Spain), 46 from Grenoble (France) and 55 from Oslo (Norway). Criteria for inclusion were having a singleton pregnancy, age ≥18 years at the time they got pregnant, first visit to be conducted before week 20 of pregnancy, non-complicated pregnancy, and residence in the area under study. For the present study, we included a total of 152 pregnant women with information on exposures and BP in both weeks (i.e., 2 women with missing BP and/or exposures were excluded). The study was approved by the Ethic Committees of each country and all participants gave their written informed consent.

2.2. Urine collection and pooling procedure

The women collected 2–3 urines per day during one week in the second trimester and one week in the third trimester. Urines collected were first morning, midday (when possible) and last night-time void. Urines were collected in 70 ml polypropylene containers and stored in a domestic freezer (typically at −20 °C). At the end of each monitoring week, all samples were transported to each study centre, using cool box ice packs to prevent thawing, and stored in a freezer. Urines were defrosted overnight at 4 °C, placed at room temperature for 30 min prior aliquoting, aliquoted, and then stored at −80 °C until analysis. All urine samples from each subject were processed at the same time. Each pregnant woman collected around 21 urines per week (mean: 20.0 urines per week; SD: 1.7; min = 12; max = 22); in total, 6134 urine samples were collected. We pooled all the urines collected in a week by taking 0.3 ml from each aliquot. In all study centers, collection and processing of the samples were performed in a completely harmonized way, using the same protocols and equipment.

2.3. Determination of phthalate metabolites, phenols, and OP pesticide metabolites

We analyzed a total of 10 phthalate metabolites originating from 6 different phthalates (monoethyl phthalate [MEP], mono-iso-butyl phthalate [MiBP], mono-n-butyl phthalate [MnBP], mono benzyl phthalate [MBzP], mono-2-ethylhexyl phthalate [MEHP], mono-2-ethyl-5-hydroxyhexyl phthalate [MEHHP], mono-2-ethyl-5-oxohexyl phthalate [MEOHP], mono-2-ethyl 5-carboxypentyl phthalate [MECPP], mono-4-methyl-7-hydroxyoctyl phthalate [OH-MiNP] and mono-4-methyl-7-oxooctyl phthalate [oxoMiNP]), 7 phenols (4 parabens [methyl-, ethyl-, propyl-, and butylparaben], BPA, triclosan and benzophenone-3 [OXBE]), and 6 non-specific OP pesticide metabolites (dimethyl phosphate [DMP], diethyl phosphate [DEP], dimethyl thiophosphate [DMTP], diethyl thiophosphate [DETP], dimethyl dithiophosphate [DMDTP] and diethyl dithiophosphate [DEDTP]. Samples were analyzed at the Department of Environmental Exposure and Epidemiology at the Norwegian Institute of Public Health (NIPH) in Norway, following the methods described in detail elsewhere (Haug et al., 2018). Briefly, phthalate metabolites were quantified using liquid chromatography coupled with mass spectrometry system (LC-MS/MS) (Sabaredzovic et al., 2015), phenols using ultra performance liquid chromatography - tandem mass spectrometer system (UPLC-MS/MS) (Sakhi et al., 2018), and OP pesticide metabolites using the ultra-performance liquid chromatography-time-of-flight system (UPLC-TOF) (Cequier et al., 2016). Creatinine was measured at Fürst Medisinsk Laboratorium (Norway) using AU680 Chemistry System form Beckman Coulter using DRI® Creatinine-Detect® Test. Limits of detection (LODs) ranged from 0.03 µg/L for most of phenols to 0.61 µg/L for some phthalate metabolites (Haug et al., 2018). Concentrations of phthalate metabolites, phenols, and OP pesticide metabolites were divided by urinary creatinine concentration to control for urine dilution (concentration are expressed in micrograms per gram of creatinine). For all methods, we included internal quality control samples in each batch and results were evaluated according to method specific criteria. Further, NIPH participated in at least one inter-laboratory comparison for some phenols during the period when HELIX samples were analysed (Haug et al., 2018). Because of their low detection rate, DMDTP (18% > LOD) and DEDTP (1% > LOD) were no longer studied.

After conversion to their molecular basis, the sum of DEHP metabolites (ΣDEHP = MEHP + MEHHP + MEOHP + MECPP) and the sum of dialkylphosphate metabolites (ΣDAP = DMP + DMTP + DEP + DETP) were calculated and expressed in µmol/g creatinine. The individual metabolites included in these sums were not considered in the main analyses but their associations with BP are reported in the appendix (Tables A1 to A4).

2.4. Blood pressure measurements

BP measurement was performed at the end of each week using the OMRON 705-CPII automated oscillometry by specially trained personnel and following the recommendations made by the American Heart Association (Pickering et al., 2005). The same protocol was followed in each study centre. Cuff bladder was chosen according to the arm size of each participant, in order to obtain the most precise measurement of BP and avoid possible over or underestimations. Both systolic and diastolic BP were recorded and measured in the right arm in a sitting position, according to the following steps: after 5 min of rest, 2 consecutives measurements were taken with 2 min interval between them. If the difference between the first two measurements was greater than 5 mmHg, then a third one was performed. The average of the two or three BP measurements was calculated and retained as outcome in the present study.

2.5. Covariates

Information on socio-demographic and lifestyle characteristics was obtained by questionnaires completed by women and during face-to-face interviews conducted by trained interviewers at the beginning of the first week. Each pregnant women provided information on education level, ethnicity, pre-pregnancy weight, parity, marital status, employment status, smoking habits during pregnancy (active and passive), health history (diabetes type I and II, heart disease, renal and suprarenal disease, alteration of blood coagulation, and alteration of thyroid gland), and complications of current pregnancy (hypertension, pre-eclampsia, eclampsia, and gestational diabetes). At the beginning of the second follow-up week, women provided information of changes in the civil and employment status, onset of pathologies related to pregnancy, and changes in smoking habits (active and passive). Height and weight were recorded during the clinical examinations at the end of each week (in Grenoble, height measured during the first examination only). In addition, physical activity during each week was evaluated using accelerometer (Maitre et al 2018). Finally, a food-frequency questionnaire of 43 items was fulfilled during the first week of follow-up. For the present study, particular attention was made on items potentially related to both exposure to non-persistent chemicals and BP (i.e., fruit and vegetables consumption, ultra-processed food consumption including heat-and-serve food, fast-food, and snack).

2.6. Statistical analysis

Urinary concentrations of phthalate metabolites, phenols, and OP pesticide metabolites below the LOD were imputed by a distribution-based single imputation method (*truncdist* function) assuming a log-normal distribution (Jin et al., 2011). Creatinine-standardized concentrations of pollutants were $\log_2$ transformed to approach normality and reduce influence of outliers. For each chemical, results are expressed as mean change in systolic or diastolic BP (in mmHg) for a doubling urinary concentration of the weekly pool. Missing data on covariates were imputed using chained equations. Five datasets were created and Rubin's rules were used to aggregate the results (White et al., 2011). The association between each biomarker of exposure (considered separately) and BP was first examined using generalized estimating equations (GEE) to take into account the repeated measurement of both exposure and outcome and was then examined independently in each period using linear regression models. In addition, prospective associations were examined studying the effect of exposure measured at the first period on BP measured at the second period. A directed acyclic graph (DAG) was used to determine the variables included in the multivariate models (Shrier and Platt, 2008). Based on the DAGs, the final multivariate models were adjusted for study centre (Barcelona; Grenoble; Oslo), ethnicity (Caucasian; Non-Caucasian), gestational age (weeks), age (years), body mass index at examination (BMI, kg/m^2), smoking status at examination (non-smoker not exposed to passive smoking; non-smoker exposed to passive smoking; current smoker), physical activity (low, medium, high), fruit and vegetables consumption (< 7 servings/day; ≥7 servings/day; included to study OP pesticide metabolites only), and ultra-processed food consumption (< 1 serving/week; ≥1 serving/week; included to study phthalate metabolites and phenols only) (Appendix Figure A1). Some of these covariates were time-varying (see Table 1). To account for multiple comparisons, a family wise error rate correction was used to correct the p-value threshold (5% divided by the effective number of tests) (Li et al., 2012); after correction the p-value was 0.005. All the statistical analyses were performed under R3.4.0.

Table 1
Characteristics of the study population (n = 152).

	Fixed characteristics or 2nd/3rd trimester	
	N (%) or mean ± sd	% missing
Study centre		0%
Barcelona, Spain	52 (27.6)	
Grenoble, France	45 (29.6)	
Oslo, Norway	55 (36.2)	
Maternal age (years)	32.9 ± 4.2	0%
Ethnicity		5%
Caucasian	131 (91.0)	
Non-Caucasian	13 (9.0)	
Marital status		5%/5%
Cohabitant or married	143 (98.6)/142 (97.9)	
Single	2 (1.4)/3 (2.1)	
Maternal pre-pregnancy BMI (kg/m^2)	22.6 ± 3.5	3%
Maternal BMI at examination (kg/m^2)	24.3 ± 3.5/26.7 ± 3.4	0%/0%
Maternal height (cm)	164.7 ± 6.8	0%
Maternal education		0%
Primary or secondary	18 (11.8)	
University	134 (88.2)	
Working status		3%/20%
Non active worker	15 (10.1)/13 (10.7)	
Active worker	133 (89.9)/109 (89.3)	
Parity		0%
Primiparous	84 (55.3)	
Multiparous	68 (44.7)	
Physical activity		7%/21%
Low (not active > 70% of the day)	44 (31.2)/38 (31.7)	
Medium (light active > 30% of the day and moderate to vigorous < 5%)	47 (33.3)/50 (41.7)	
High (moderate or vigorous > 5% of the day)	50 (35.5)/32 (26.7)	
Fruits and vegetables consumption		5%
< 7 servings/day	111 (77.1)	
≥7 servings/day	33 (22.9)	
Ultra-processed food consumption		5%
< 1 serving/week	94 (65.3)	
≥1 serving/week	50 (34.7)	
Gestational age (weeks)	18.0 ± 2.3/32.0 ± 2.1	6%/7%
Smoking status at examination		16%/36%
Non-smoker not exposed to passive smoking	114 (79.7)/90 (89.1)	
Non-smoker exposed to passive smoking	19 (13.3)/6 (5.9)	
Current smoker	10 (7.0)/5 (5.0)	
Blood pressure		0%/0%
Systolic (mmHg)	106 ± 10/105 ± 13	
Diastolic (mmHg)	65 ± 7/66 ± 10	

Abbreviations: sd: standard deviation; BMI: body mass index.

2.7. Sensitivity analyses

Different sensitivity analysis sets were performed to test the robustness of our results: 1) excluding women with specific conditions (n = 11 thyroid disease, n = 4 blood coagulation disease, n = 4 heart disease, n = 2 pregnancy-induced hypertension [diagnosed after the second visit]); 2) adjusting the models for creatinine instead of standardizing the concentration of chemicals for creatinine; 3) testing for

statistical interactions between the chemicals and maternal BMI at examination (≤ 25 and $> 25\,kg/m^2$) because of the hormonal activity of the adipose tissue; and 4) stratifying models by study centre.

3. Results

3.1. Study population

The characteristics of the study population are given in Table 1. Women included in the study were 33 years old on average, more likely to be European (91%), most (88%) had university degree, lived with their partner (98%), were primiparous (55%), and few smoked during the pregnancy (7% in the second trimester and 5% in the third). The measurement weeks took place on average at 18 (± 2.3) and 32 (± 2.1) weeks of gestation.

At the first measurement week, mean value for systolic BP was 106 mmHg (min-max: 81–132 mmHg) and for diastolic BP was 65 mmHg (min-max: 50–89 mmHg) (Table 1). No difference in mean systolic BP was observed between periods (second and the third trimesters of pregnancy) while mean diastolic BP was slightly higher in the third trimester ($p < 0.10$).

3.2. Distribution of biomarkers concentrations in urine

The distribution of phthalate metabolites, phenols, and OPs pesticide metabolites in urine samples is shown in Table 2. Phthalate metabolites were detected in all urine samples, phenols were detected in most of urine samples (> 95%), while OP pesticide metabolites were variably detected (from 1% detection frequency for DEDTP to 98% for DEP). Of the ten phthalate metabolites studied, MEP, MiBP, and MnBP were found in the highest concentrations and MEHP and OXO-MiNP the lowest. Of the seven phenols, methylparaben had the highest concentrations. Finally, concentrations of OP pesticide metabolites were all on the same range. Overall, no differences in the levels of exposure were observed between the follow-up weeks.

3.3. Associations of the non-persistent chemicals and systolic BP

In overall, higher exposure to non-persistent chemicals was associated with a decrease or no change in systolic BP during pregnancy (Fig. 1). In the GEE models, considering simultaneously both follow-up weeks, a decrease in systolic BP was observed with increasing levels of MEP ($\beta = -0.75$ mmHg; 95% CI: -1.44, -0.07 per doubling of MEP concentrations) (Fig. 1). Higher concentrations of BPA during the pregnancy were also associated with a decrease in systolic BP ($\beta = -0.91$ mmHg; 95%CI: -1.65, -0.17), as suggested for other phenols. When we estimated the effects separately by trimester, the above-mentioned effect estimates were consistent across the two time periods for MEP but stronger in the second than the third trimester for BPA. In addition, decreases in systolic BP were observed in association with higher concentrations of MiBP, ethylparaben, and triclosan, in the second trimester only (e.g., $\beta = -2.14$ mmHg; 95%CI: -4.02, -0.25

Table 2
Distribution of urinary concentrations[a] (μg/g creatinine unless otherwise specified) of phthalate metabolites, phenols, and OP pesticide metabolites in pregnant women (n = 152).

Biomarker	N analyzed	2nd trimester		N analyzed	3rd trimester		p-value[b]
		% > LOD	Median (25-75th centiles)		% > LOD	Median (25–75th centiles)	
Phthalate metabolites							
MEP	146	100	47.1 (21.5–90.2)	147	100	49.1 (24.5–106.2)	0.42
MiBP	152	100	25.2 (18.0–33.3)	152	100	26.3 (19.4–36.3)	0.08
MnBP	152	100	15.2 (11.7–21.3)	152	100	15.8 (11.8–24.4)	0.10
MBzP	150	100	3.9 (2.4–6.7)	151	100	4.1 (2.4–7.1)	0.52
MEHP	147	100	3.2 (2.2–5.1)	147	100	2.7 (1.8–4.8)	**0.03**
MEHHP	151	100	9.2 (6.7–12.2)	152	100	8.3 (6.5–12.0)	0.21
MEOHP	152	100	6.0 (4.5–7.9)	152	100	5.7 (4.4–8.0)	0.51
MECPP	152	100	14.9 (12.1–20.2)	152	100	14.1 (11.7–20.2)	0.39
ΣDEHP[c]	147	-	0.12 (0.09–0.15)	147	-	0.11 (0.08–0.15)	0.23
OH-MiNP	152	100	5.6 (3.2–11.0)	152	100	5.1 (3.4–11.7)	0.65
OXO-MiNP	152	100	3.0 (1.9–6.3)	152	100	3.1 (2.0–6.3)	0.90
Phenols							
Methylparaben	151	100	44.6 (13.7–128.6)	152	100	42.9 (12.0–122.6)	0.30
Ethylparaben	152	99.3	1.4 (0.6–13.4)	151	100	1.2 (0.6–7.5)	0.39
Propylparaben	151	99.3	7.9 (1.5–22.4)	151	98.7	7.5 (2.0–28.4)	0.22
Butylparaben	152	98.0	0.1 (0.1–0.6)	151	96.0	0.1 (0.1–0.4)	0.40
BPA	152	97.4	3.1 (2.0–4.5)	149	98.0	3.5 (2.0–5.7)	0.65
OXBE	152	100	6.5 (2.5–27.9)	152	100	6.6 (2.2–22.0)	0.72
Triclosan	152	100	1.0 (0.3–4.1)	152	100	0.9 (0.4–5.8)	0.80
OP pesticide metabolites							
DMP	152	84.2	3.8 (2.3–5.7)	152	82.9	3.8 (2.0–5.7)	0.73
DMTP	152	96.1	4.3 (2.7–6.9)	152	88.2	4.1 (2.4–7.1)	0.14
DEP	152	96.7	3.9 (2.4–5.6)	152	98.0	3.4 (2.1–5.5)	0.33
DETP	147	70.1	1.4 (0.2–2.8)	147	66.7	1.3 (0.2–2.7)	0.32
ΣDAP[c]	147	–	0.1 (0.07–0.15)	147	–	0.1 (0.06–0.15)	0.18

Abbreviations: OP, Organophosphate. Q, quartile. Phthalates metabolites: MEP, Monoethyl phthalate; MiBP, Mono-iso-butyl phthalate; MnBP, Mono-n-butyl phthalate;,MBzP, Mono benzyl phthalate; MEHP, Mono-2-ethylhexyl phthalate; MEHHP, Mono-2-ethyl-5-hydroxyhexyl phthalate; MEOHP, Mono-2-ethyl-5-oxohexyl phthalate; MECPP, Mono-2-ethyl 5-carboxypentyl phthalate; ΣDEHP, sum of Di(2-ethylhexyl) phthalate metabolites (sum of MEHP, MEHHP, MEOHP and MECPP); OH-MiNP, Mono-4-methyl-7-hydroxyoctyl phthalate; OXO-MiNP, Mono-4-methyl-7-oxooctyl phthalate. Phenols: BPA, Bisphenol A; OXBE, Oxybenzone or Benzophenone-3; Organophosphate pesticide metabolites: DMP, Dimethyl phosphate; DMTP, Dimethyl thiophosphate; DEP, Diethyl phosphate; DETP, Diethyl thiophosphate. ΣDAP, Sum of dialkylphosphate metabolites.

[a] A total of 21 urines in each of the two periods were collected (mean: 20.0 urines, standard deviation: 1.7).

[b] Paired-sample Student test.

[c] Expressed in μmol/g creatinine.

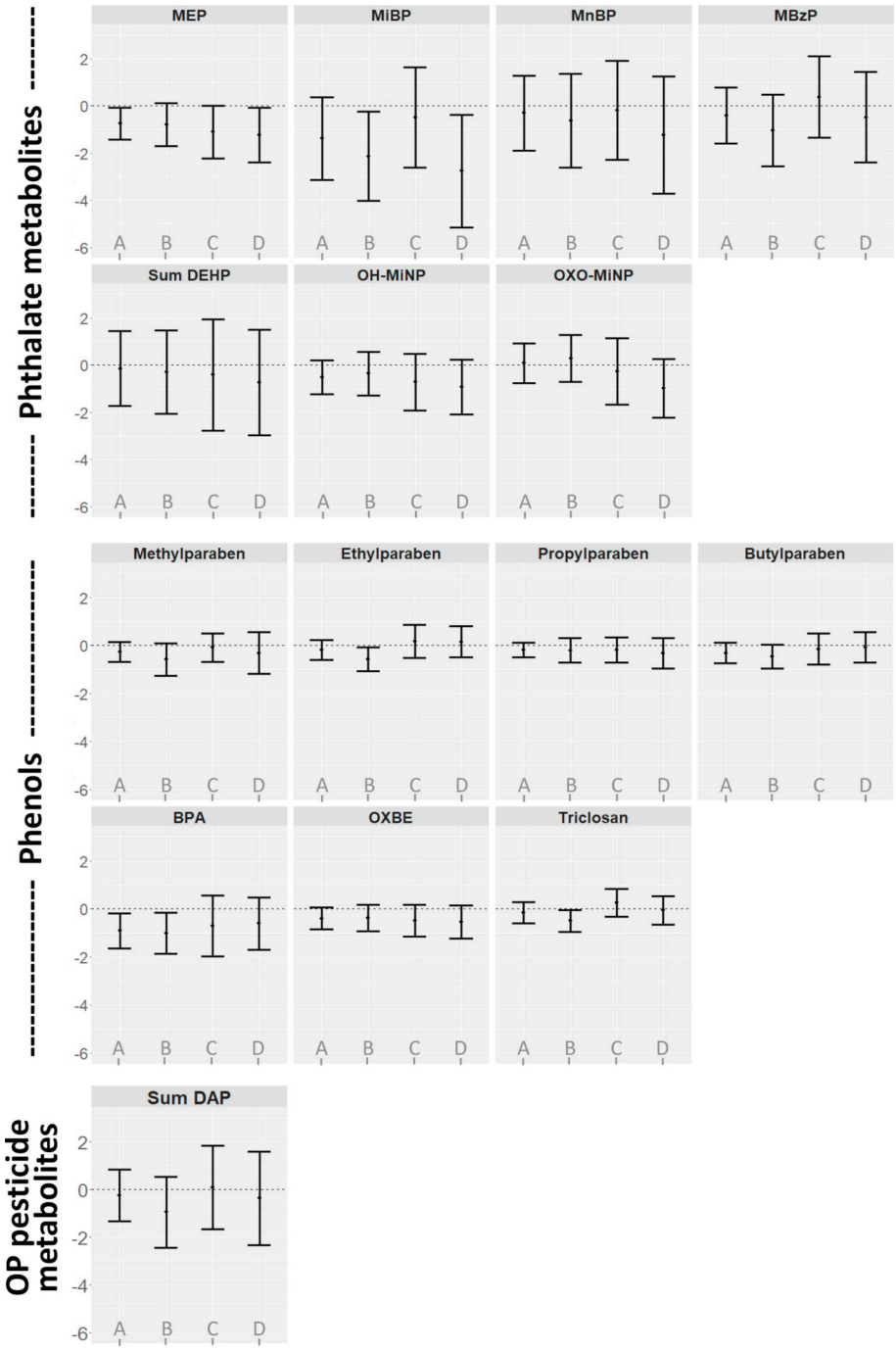

Fig. 1. Adjusted beta coefficient and 95% confidence interval between maternal urinary phthalate metabolites, phenols, and OP pesticide metabolites and systolic blood pressure.
Abbreviations: Phthalate metabolites: MEP, Monoethyl phthalate; MiBP, Mono-iso-butyl phthalate; MnBP, Mono-n-butyl phthalate;,MBzP, Mono benzyl phthalate; ΣDEHP, sum of Di(2-ethylhexyl) phthalate metabolites (sum of MEHP, MEHHP, MEOHP and MECPP); OH-MiNP, Mono-4-methyl-7-hydroxyoctyl phthalate; OXO-MiNP, Mono-4-methyl-7-oxooctyl phthalate. Phenols: BPA, Bisphenol A; OXBE, Oxybenzone or Benzophenone-3. Organophosphate pesticide metabolites: ΣDAP, Sum of dialkylphosphate metabolites. BP, Blood pressure. GEE, Generalized estimating equation. OP, Organophosphate.
A: GEE models, B: linear regression between exposure and BP measured during the 2nd trimester, C: linear regression between exposure and BP measured during the 3rd trimester; D: linear regression between exposure measured during the 2nd trimester and BP measured during the 3rd trimester. Estimates are expressed as change in BP (mmHG) for doubling exposure levels. All models are adjusted for study centre, ethnicity, maternal age, maternal BMI at examination, gestational age, physical activity, smoking status at examination, fruit & vegetables consumption (OP pesticide metabolites only) and ultra-processed food (phthalate metabolites and phenols only). GEE models are additionally adjusted for period.

per doubling of MiBP concentrations) (Fig. 1). In the prospective analyses (i.e., exposure during the second trimester in association with BP during the third trimester), the decrease in systolic BP in association with MEP and MiBP, but not with BPA, were even stronger (e.g., $\beta = -2.77$ mmHg; 95% CI: -5.14, -0.39 per doubling of MiBP concentrations). None of the OP pesticide metabolites were associated with systolic BP.

After p-value correction for multiple testing, only the association observed with BPA during the second trimester remained statistically significant. The estimates and their 95% CI from the minimally adjusted (adjusted for study centre) and the full-adjusted models are presented in appendix Table A1 and Table A2, respectively.

3.4. Associations of the non-persistent chemicals and diastolic BP

Similarly to systolic BP, we observed a decrease or no change in diastolic BP with increasing exposure to non-persistent chemicals (Fig. 2). From the GEE models, only BPA was associated with a decrease in diastolic BP ($\beta = -0.82$ mmHg (95%CI: -1.34, -0.30) per doubling of BPA concentrations) (Fig. 2). In the models separately by trimester, we additionally observed decreases in diastolic BP associated with exposure to parabens including methylparaben, ethylparaben, and butylparaben in the second trimester ($\beta = -0.62$ mmHg; 95%CI: -1.16, -0.08 per doubling of methylparaben concentrations). The prospective analyses showed similar trend in lowering diastolic BP

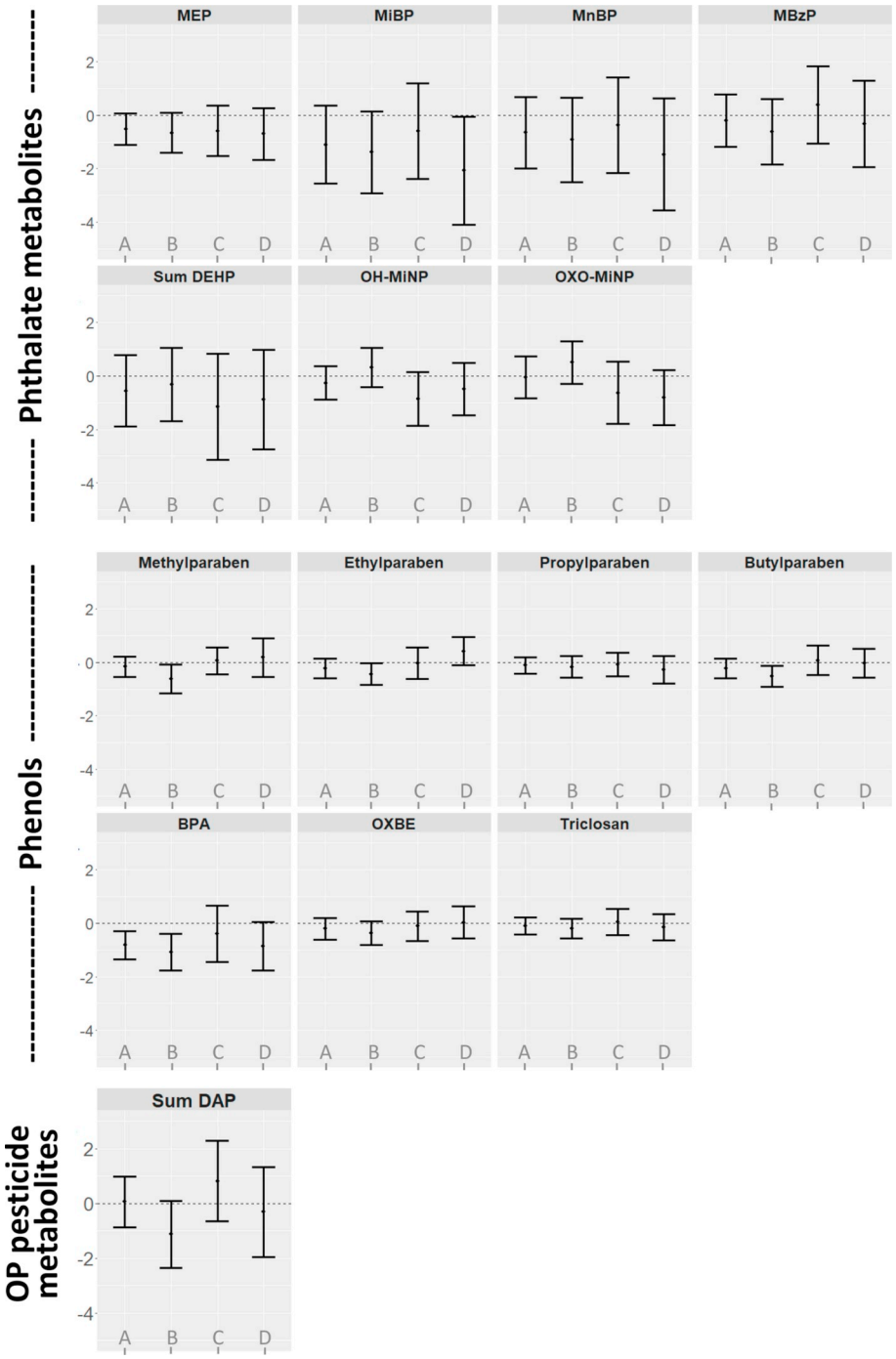

Fig. 2. Adjusted beta coefficient and 95% confidence interval between maternal urinary phthalate metabolites, phenols, and OP pesticide metabolites and diastolic blood pressure.
A: GEE models, B: linear regression between exposure and BP measured during the 2nd trimester, C: linear regression between exposure and BP measured during the 3rd trimester; D: linear regression between exposure measured during the 2nd trimester and BP measured during the 3rd trimester. Estimates are expressed as change in BP (mmHG) for doubling exposure levels. All models are adjusted for study centre, ethnicity, maternal age, maternal BMI at examination, gestational age, physical activity, smoking status at examination, fruit & vegetables consumption (OP pesticide metabolites only) and ultra-processed food (phthalate metabolites and phenols only). GEE models are additionally adjusted for period.
Abbreviations: Phthalate metabolites: MEP, Monoethyl phthalate; MiBP, Mono-iso-butyl phthalate; MnBP, Mono-n-butyl phthalate; MBzP, Mono benzyl phthalate; ΣDEHP, sum of Di(2-ethylhexyl) phthalate metabolites (sum of MEHP, MEHHP, MEOHP and MECPP); OH-MiNP, Mono-4-methyl-7-hydroxyoctyl phthalate; OXO-MiNP, Mono-4-methyl-7-oxooctyl phthalate. Phenols: BPA, Bisphenol A; OXBE, Oxybenzone or Benzophenone-3. Organophophate pesticide metabolites: ΣDAP, Sum of dialkylphosphate metabolites. BP, Blood pressure. GEE, Generalized estimating equation. OP, Organophosphate.

during the third trimester in association with exposure to BPA during the second trimester. A decrease in diastolic BP in association with exposure to MiBP was also observed. No associations were observed between concentrations of OP pesticide metabolites and diastolic BP.

After p-value correction for multiple testing, only the two associations observed with BPA remained significant. The estimates and their 95% CI from the minimally adjusted (adjusted for study centre) and the full-adjusted models are presented in appendix Table A3 and Table A4, respectively.

3.5. Sensitivity analyses

All the associations reported above remained statistically significant (p-value before correction < 0.05) and with similar estimates after exclusion of women with specific pregnancy conditions and using non-standardized creatinine concentrations of chemicals (data not shown). Significant interactions were observed between maternal BMI and exposure to phenols (ethylparaben and triclosan) during the 2nd trimester: the decrease in systolic and/or diastolic BP reported above were only observed among overweight/obese women (i.e., BMI > 25 kg/m^2; p-value for interaction < 0.05) (data not shown). The associations by study centre are presented in Appendix Figure A2 and Figure A3. The most consistent findings across countries are those reported for MEP with systolic BP, and BPA with diastolic BP. On the contrary, the results for parabens are more heterogeneous with an overall decrease in BP observed in Oslo and an overall increase in BP in Barcelona.

4. Discussion

In this prospective pregnancy cohort study, we observed that exposure to phthalate metabolites, BPA, and parabens was associated with a decrease in both systolic and diastolic BP during pregnancy, especially in the 2nd trimester of pregnancy. No associations were reported with exposure to OP pesticide metabolites.

To our knowledge, there is only one previous study assessing the association of exposure to phthalates with BP during pregnancy (Werner et al., 2015). This study was performed among 369 pregnant women from the HOME study and showed that higher urinary concentrations of MBzP measured in a spot urine sample around 16 weeks of gestation (range = 10–23 weeks) was associated with increased diastolic BP before 20 weeks of gestation (range = 4–20 weeks) and higher risk of pregnancy-induced hypertensive diseases. Other phthalate metabolites showed no significant associations and nor did phthalate concentrations measured at 26 weeks gestation (range = 19–35 weeks); a negative tendency for the sum of DEHP metabolites could be noted. The contradictory results in respect to our study could be explained by the difference in levels of exposure. Median concentrations of phthalate metabolites in the HOME study were 3 times higher than in our study (i.e. MEP: HOME = 132 μg/g creatinine; present study = 47 μg/g creatinine), which means that the level of exposure of our pregnant women corresponds to the 1st tertile of exposure of the HOME's participants. If a non-linear exposure-response relationship exists, we could expect a negative association in the lowest range of exposure and a positive association in the highest range of exposure. In addition, the study populations were quite different (i.e., in the HOME study 40% were non-Caucasians, 50% have a university degree, 9% treated for hypertensive disorders). Finally, the HOME study might be more at risk of exposure and outcome misclassification since it only relies on 2 urines collected during the whole pregnancy and BP measures were derived from medical records retaining the first two measures during pregnancy and the two highest in late pregnancy. Few case-control studies, including one using multiple biospecimens, reported higher levels of phthalate metabolites, and BPA among women with preeclampsia than in non-complicated pregnancy (Cantonwine et al., 2016; Leclerc et al., 2014; Ye et al., 2017). Other phenols and OP pesticides have not been studied before in relation to BP during pregnancy, giving very little data for comparison of our results.

Studies in non-pregnant populations (children, adults, elderly) have predominantly reported increases in BP and hypertension risk associated with increasing urinary levels of phthalate metabolites, BPA, and OP pesticide metabolites (Aekplakorn et al., 2015; Bae et al., 2012; James-Todd et al., 2016; Ranjbar et al., 2015; Shankar and Teppala, 2012; Shiue, 2014; Trasande et al., 2013; Trasande and Attina, 2015; Zhang et al., 2018). One study in adults reported a decreased risk of hypertension associated with urinary levels of BPA (Wang et al., 2015). It is important to note that most of these studies were cross-sectional and assessed exposure to non-persistent chemicals using spot urine samples, which may be at risk for residual confounding or reverse causation. The chemicals of interest have short biological half-lives, ranging from hours to days, and levels of exposure may vary between days; therefore, previous studies are at high risk of exposure misclassification (Perrier et al., 2016). In our study, the use of around 21 urinary samples per subject at two time points during pregnancy limits exposure measurement error and reflects better the level of exposure. However, although the reliability of these 2 weekly pools is good for certain phthalate metabolites and phenols like oxybenzone, with intraclass-correlation coefficients (ICCs) above 0.60, it is still not good enough for other phenols like BPA and OP pesticide metabolites, with ICCs below 0.40 (Casas et al., 2018). These low reliability coefficient highlight the necessity to adopt a thoughtful sampling design based on many pooled urines rather than collecting one spot sample per subject in studies assessing the health effects of these compounds (Casas et al., 2018).

Our findings do not support the assumption of a hypertensive effect of phthalates, phenols or OP pesticides during pregnancy. This apparent contradiction with studies in non-pregnant populations may reflect physiological changes during pregnancy. Indeed, BP is regulated by various mechanisms involving different systems (cardiovascular, neural, renal, and endocrine) but the physiological changes encountered during pregnancy additionally affect BP: the increase in blood volume and cardiac output, and the vasodilatation of blood vessels lead to lower BP than normal in the first two trimesters but returns to normal in the third (Macdonald-Wallis et al., 2015; Soma-Pillay et al., 2016). We can hypothesize that the non-persistent chemicals of interest may expand the effect of lowering BP secondary to the pregnancy-related physiological changes. This could also explain the small difference we observed between the periods of interest. Pregnancy also affects the kidney physiology which is highly related to the control of BP (Cheung and Lafayette, 2013). Glomerular filtration rate varies during pregnancy and could affect the excretion of chemicals. In the present study, we used chemical concentrations standardized by creatinine to try to take this into account since creatinine is highly correlated with glomerular filtration rate (Carrieri et al., 2001). The sensitivity analyses performed using non-standardized creatinine concentrations and adjusting the models for creatinine lead to similar findings.

Endocrine disruption is among the potential mechanisms that may explain how environmental chemicals may affect BP, particularly through the rennin-angiotensin-aldosterone sytem (RAAS), a major regulator of systemic BP (e.g., inhibition of the RAAS is associated with lower BP) (Cheung and Lafayette, 2013). Phthalate metabolites are known agonist of PPARγ receptor and previous studies have reported that PPARγ plays an important role in the regulation of BP by inhibiting the RAAS (Bility et al., 2004; Kvandová et al., 2016; Rőszer and Ricote, 2010). PPARγ is also involved in the control of vascular tone, inflammation, oxidative stress, and energy homeostasis, all these biological mechanisms being involved in the control of BP (Kvandová et al., 2016; Rőszer and Ricote, 2010). In contrary to phthalate metabolites, there is no evidence of BPA affinity with PPARγ receptor, nevertheless BPA is known to interfere with thyroid and steroid hormones and especially to have estrogenic activity (Rubin, 2011). Evidence suggests that estrogens are involved in the regulation of multiple RAAS pathways and it is well-documented that estrogens have cardioprotective effects (e.g., reduction of the risk of cardiovascular diseases among premenopausal women, improvement of vascular function, and reduction of the risk of atherosclerosis) (Murphy, 2011). Parabens, share these two endocrine properties: they are PPARγ agonists and have estrogenic activity (Nowak et al., 2018). We therefore speculate that the decrease in BP we observed in association with exposure to phthalate metabolites, BPA and parabens, may be mediated by the RAAS, either through the activation of PPARγ or through estrogenic pathways.

The major strength of this study lies in its repeated (in two pregnancy trimesters) and prospective (exposure was measured in the week before the outcome) design and the use of multiple biospecimens per subject. However, there are some limitations that should be considered. First, the present study is of relative small sample size; however, the use of GEE models allowed gaining in statistical power by controlling for time-invariant, unobservable differences between individuals. Moreover, it is worth mentioning that Perrier et al. (2016) showed that studies relying in fewer subjects but more samples per subject are more efficient in terms of bias compared with studies including more subjects but one spot biospecimen per subject. Second, we cannot exclude the possibility of residual confounding. Diet is the main source of exposure to the non-persistent chemicals of interest, by direct consumption of contaminated food or by chemical migration from packaging into food; other sources of exposure include cosmetics or drugs (especially for phenols and phthalate metabolites) and indoor air pollution (Giovanoulis et al., 2018; US EPA, 2015). Since an unhealthy diet, especially high salt diet, is known to increase BP, we tried to control for

this potential confounding factor by adjusting our models on frequency of ultra-processed food eating, that we considered as a marker of a less healthy diet and source of exposure to phthalates and phenols, or on frequency of fruit and vegetable consumption, as a marker of a more healthy diet and source of exposure to OP pesticides. However, we were not able to take into account other dietary sources of exposure to phthalates and phenols, such as canned food or beverages, or food preparation habits (e.g., heating food within their packaging). In addition, some risk factors for high BP were not collected including family history of hypertension or alcohol consumption; hence, residual confounding cannot be ruled out. Third, we should consider that our study population is quite homogeneous and included pregnant women with few risk factors for BP and in normotensive range (i.e. no values above 140 mmHg or 90 mmHg, for diastolic and systolic BP, respectively). In comparison with BP reference ranges across pregnancy calculated in a population of > 10,000 pregnant women in England, the average systolic and diastolic BP of our population are close to the reference range for low risk group (Macdonald-Wallis et al., 2015). This has hindered us to explore the exposure-response associations at high levels of BP. Fourth, our study did not cover the late pregnancy period (i.e., > 32 weeks), which is at risk for onset of hypertensive disorders. No conclusion can therefore be drawn on the effect of late pregnancy exposure on blood pressure. Finally, we estimated quite a large number of associations between exposures and outcomes, which increased the risk for false positives. After correction for multiple testing, only few associations remained statistically significant. However, we cannot exclude that we missed some associations because of a lack of power due to the relative small sample size of our study population.

5. Conclusion

This study investigates the effect of exposure to non-persistent chemicals assessed by multiple biospecimens per subject on BP during pregnancy. Findings suggest that higher exposure to some phthalates and phenols but not pesticides is associated with lower systolic and diastolic BP during pregnancy. These results need to be confirmed in other studies of pregnant women.

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Nothing to declare.

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Appendix A. Supplementary data

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