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## Original Article

### **The association between maternal urinary phthalate metabolites concentrations and pregnancy induced hypertension: Results from the EDEN Mother-Child Cohort**

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## **Abstract**

**Background:** Studies have suggested that exposure to endocrine disruptors such as phthalates that are widely used in our daily life (food wrapping, cosmetics, toys, medical devices, polyvinyl chloride flooring, and building materials) might be related to raised blood pressure and increased risk of cardiovascular diseases. Phthalates might induce a pro-inflammatory response and increased oxidative stress and may be a cause of pregnancy induced hypertension.

**Methods:** We evaluated the association between maternal exposure to phthalates during pregnancy and pregnancy induced hypertension. 604 pregnant women were included and eleven phthalate metabolites were quantified in spot maternal urine samples collected between the 23rd and 28th week of gestation in a French EDEN mother-child cohort. The associations were assessed by applying multiple logistic regression analysis.

**Results:** Twenty nine (4,8%) mothers developed pregnancy induced hypertension. Two low molecular weight phthalate metabolites: Monoethyl phthalate (MEP) and Mono-n-butyl phthalate (MBP) were positively associated with pregnancy induced hypertension in crude (Odds Ratio: 1.43, 95% Confidence Interval: 1.04-1.96, p-value = 0.02 and 1.48, 1.10-2.01, p-value = 0.01) and in adjusted (1.47, 1.01-2.14, p-value = 0.04 and 1.66, 1.11-2.47, p-value = 0.01) models respectively.

**Conclusion:** Our data suggest that prenatal exposure to some phthalates, including MEP and MBP, might play a role in pregnancy induced hypertension.

**Key words:**

Phthalate, prenatal exposure, endocrine disruptor, urinary biomarkers, mother-child cohort, pregnancy induced hypertension

## **Introduction**

Phthalates are widely used in our daily life and are contained within products ranging from food wrappers, personal care products, cosmetics, toys, polyvinyl chloride flooring, building materials and medical devices. Despite their usefulness, however, phthalates can interfere and disrupt the endocrine system and might be related with raised blood pressure and increased risk of cardiovascular diseases [1, 2]. Phthalates are a broad class of chemical compounds with a wide range of consumer product and medical device applications that vary based on their molecular weight. Phthalates are classified into two main groups. Low molecular weight (LMW) phthalates are frequently added to cosmetic products, shampoos, lotions, and other personal care products to preserve scent. Whereas high molecular weight (HMW) phthalates are used as plasticizers of polyvinyl chloride (PVC) because of their flexibility and resistant kinking properties.

Phthalates are ubiquitous in the environment. Exposure to phthalates can occur through inhalation, ingestion (including dietary ingestion and incidental ingestion), skin absorption (including air-to-skin transport), use of personal care products and/or contact with contaminated surfaces [3]. After exposure the phthalates are metabolized in monoester metabolites and conjugated before being excreted in the urine; hence urinary phthalate metabolites can be used as a biomarker of exposure [4]. Studies have revealed that phthalates can also cross the fetoplacental barrier and enter the amniotic fluid and fetal circulation [4-6]. Therefore, it is hypothesized that the prenatal and early years of life are very critical in the development of immune system and during this period the exposure to toxic pollutants can result in an increased risk of adverse health outcomes during pregnancy including

preeclampsia (high blood pressure plus proteinuria after 20<sup>th</sup> week of gestation) as well as later in life, which may also cause hypertension in children or adult population. However, the exact mechanism through which phthalate exposure can influence cardiovascular health effects is still unknown. However, it is hypothesized that as phthalates are endocrine disruptors, they affect the metabolism and actions of androgens, thyroid hormones and cortisol [7, 8]. Another possible mechanism, by which endocrine disruptors may cause a pro-inflammatory response, vascular dysfunction and increased oxidative stress [9, 10].

A cross-sectional study in US children and adolescents aged 6-19 years, assessed LMW and HMW phthalates and suggested that the increased urinary phthalate concentrations of HMW phthalate metabolites were associated with higher blood pressure [2]. Another cross-sectional study from Uppsala, Sweden in older adults (aged 70 years) showed that increased serum concentrations of monobenzyl phthalate (MBzP) were related to multiple cardiovascular risk factors [11]. However, there is only one prospective birth cohort study from Cincinnati, USA that examined the relationship between urinary phthalate metabolite concentrations (both LMW and HMW) during pregnancy (16 to 26 weeks of gestation) with maternal blood pressure and the risk of pregnancy induced hypertensive diseases, which needs to be confirmed [12].

The main objective of our study was to evaluate the association between maternal exposure to phthalates during pregnancy and pregnancy induced hypertension in a population-based sample of pregnant mothers.

## **Methods and Materials**

### ***Study population and data collection***

This is a nested cross-sectional study in design. The population included in this study is a subgroup of French EDEN (Etude des Déterminants pré et post natals du développement de

la santé de l'Enfant) mother-child prospective birth cohort (<https://eden.vjf.inserm.fr>). The study was conducted in two cities of France i.e Nancy and Poitiers. The mothers' recruitment, follow-up procedures, and methodological assumptions have been published in previous studies [13]. Women were given an appointment between the 24<sup>th</sup> and 28<sup>th</sup> gestational weeks, by a study midwife during which an interview on lifestyle factors were conducted and biological samples were collected. The information on the mothers and their newborns, including parity, mode of delivery, gestational age, season of birth, birth weight, behavioral and environmental data were collected by the use of questionnaires, interviews and from obstetric and pediatric records. The current study includes mothers of all male offspring for whom maternal urine samples were analyzed for phthalate metabolites as a part of earlier studies [3, 14-16]. Further, we also excluded all the mothers with previous history of hypertension, diabetes or kidney diseases before their pregnancy.

The blood pressure of the mothers was measured during their routine monthly visits, with the subject in supine position, using a standard sphygmomanometer. One set of measures was taken by the study midwife between 24 and 28 weeks using a different (semi-automated) device, with the two measurements averaged to determine the values for that visit. Measurements taken within each gestational trimester (T1, T2, and T3) were averaged to determine the values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) assigned to each period.

Women were classified as having pregnancy induced hypertension based on SBP  $\geq$  140 mmHg and /or DBP  $\geq$  90 mmHg measured during at least two visits after 22<sup>nd</sup> week of gestation, such that the elevated measures could have occurred during or across any of the three periods, at any point after 22 weeks. Consequently, no diagnosis of pregnancy induced hypertension was made before 24 weeks. All cases of pregnancy induced hypertension were reviewed by a physician. Further, two devices were used to counter check the results.

### *Urine collection and analysis*

Women were invited for a clinical examination and to provide a first morning urine at home before the hospital study visit between the 24<sup>th</sup> and 28<sup>th</sup> gestational weeks (second trimester of the pregnancy). If forgotten, the urine sample was collected at the hospital. A polypropylene container (FP40VPS manufactured by Centre Européen de Biotechnologie SA (CEB) in Angers, France) was used. The urine samples were aliquoted and then frozen at  $-80^{\circ}\text{C}$ . The analyses of the samples were conducted at the National Center for Environment Health Laboratory at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia (USA) for eleven metabolites of eight phthalates: Diethyl phthalate (DEP), Di-n-butyl phthalate (DBP), Di-isobutyl phthalate (DiBP), Di(2-ethylhexyl) phthalate (DEHP), Benzylbutyl phthalate (BBzP), Di-isononyl phthalate (DiNP), Di-n-octyl phthalate (DOP), and Di-isodecyl phthalate (DiDP).

The targeted phthalate metabolites measured were monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), mono-isobutyl phthalate (MiBP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethylhexyl) phthalate (MEHP), monobenzyl phthalate (MBzP), monocarboxy-isooctyl phthalate (MCOP), mono(3-carboxypropyl) phthalate (MCP) and monocarboxy-isononyl phthalate (MCNP).

Quantification of the phthalate metabolite concentrations was performed using online solid phase extraction high performance liquid chromatography electrospray ionization isotope dilution tandem mass spectrometry. Creatinine concentrations were also quantified following an identical analytical procedure as described previously [15]. The concentrations of metabolites below the limit of detection (LOD)  $<3\%$  were replaced by instrumental reading values or by the compound specific lowest instrumental reading value divided by the square

root of two ( $LOD/\sqrt{2}$ ) when the instrumental value was found missing. The vast majority of the samples/metabolites (>97%) were above the LOD. A two-step standardization was performed to reduce variability in the biomarker urinary concentrations due to sampling conditions as described previously [15]. There was no significant difference in the concentrations of phthalates in the morning urine samples collected at the participants homes compared to those of the urine sampled collected later in the day at the hospital.

### ***Other Variables***

Information on potential confounders including: gestational age (two-class variable: < 37 gestational week,  $\geq 37$  gestational week), parity, number of siblings (0, 1, 2  $\geq 3$ ), maternal age at delivery (< 25 years, 25-29 years, 30 – 34 years,  $\geq 35$  years), pre-pregnancy maternal body mass index (BMI, < 18.5, 18.5-24.9, 25.0-30.0, > 30 kg/m<sup>2</sup>), maternal educational level (< 2 years after high school, High school +2 years,  $\geq$  High school +3 years), household income, city of residence (Nancy / Poitiers), mode of delivery (vaginal, caesarean section), smoking during pregnancy (yes/no), maternal alcohol use during pregnancy (yes/no), maternal physician-diagnosis of pregnancy induced hypertension.

### ***Statistical analysis***

Urinary concentrations of phthalate metabolites were natural log (ln) transformed due to the non-normality of the distribution. For the purpose of present analysis, MECPP, MEHHP, MEOHP and MEHP were grouped together as sum  $\Sigma$ DEHP (DEHP being their parent compound). We calculated the molar sum of these DEHP metabolites (nanomoles per milliliter) by dividing each metabolite concentration by its molecular weight and then summing the individual concentrations.

The prevalence of pregnancy induced hypertension was computed. We applied multiple logistic regression analysis to examine the association between each phthalate metabolite and



ΣDEHP and pregnancy induced hypertension outcomes adjusted for potential confounders. The potential confounders were determined *a priori* from literature review [1, 3, 17, 18]. Further, the Directed Acyclic Graph (<http://www.dagitty.net/dags.html>) was used to see the hypothesis relations between biomarkers concentration, confounders and pregnancy induced hypertension outcomes. The confounders included in our final model were maternal smoking, maternal age, maternal BMI, maternal education level, gestational age, and number of siblings. Models were additionally adjusted for recruitment center. We used continuous metabolite levels in our first analysis and then we used categorical levels of the phthalates metabolites in our second analysis. All statistical analyses were conducted using Stata statistical software 14 (Stata Corp LP, 4905 Lakeway Drive, College Station, Texas 77845, USA) and considered a *p-value* < 0.05 as statistically significant.

### ***Ethical Approval***

The study was approved by the relevant ethical committees in France (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, Le Kremlin Bicêtre University Hospital, and Commission Nationale de l'Informatique et des Libertés), and all participating women gave informed written consent for their own participation and consent was obtained from both parents for each newborn child after delivery.

## **Results**

### ***Characteristics of study population***

Of the 2002 women recruited into the EDEN mother child cohort, 998 gave birth to boys and 604 women with available data on both pregnancy induced hypertension diagnosis and urine analysis for phthalates were selected for this study (Figure 1). The majority (98.5%) of these women were educated, 43.5% had less than two years of education after high school while 54.8% had more than that and between 25-34 years of age ( $29.86 \pm 4.8$ ) (Table 1). The

average BMI was  $23.1 \pm 4.5$ , while 26.4% of women were overweight or obese (BMI  $\geq 25$  kg/m<sup>2</sup>). The active smokers were 13.7% and 25% declared some alcohol intake during pregnancy. Four percent gave birth pre-maturely, 15.7% had caesarean section at delivery. The prevalence of pregnancy induced hypertension was found 4.80%, while the prevalence of preeclampsia was 2.32%. Whereas, the prevalence of pregnancy induced hypertension in overall EDEN Cohort was also the same 4.80%. The participants included in this study did not differ in major demographic characteristics except for maternal age, smoking and gestational age (Table S1). However, results did not change when adjusted for them in the final models.

### ***Prenatal exposure to phthalates***

Phthalate metabolites were detected in the urine of more than 97% of the mothers. MEP had the highest geometric mean (110.7  $\mu$ g/L), while MCNP had the lowest (1.5  $\mu$ g/L). The limit of detection (LOD) ranged from 0.2 to 0.6  $\mu$ g/L. A summary of detection frequency, as well as geometric means and select percentiles of urinary concentrations of phthalate metabolites are outlined in Table 2.

Spearman correlation coefficients between ln-transformed phthalate metabolites urinary concentrations are shown in Table S2. The majority of biomarkers were positively correlated, except for the correlation between MEP and MiBP, MECPP, MEHHP, MCOP, MCPP or MCNP. All other biomarkers were significantly correlated with each other (with correlation coefficients ranging from  $r = 0.08$ ,  $p < 0.05$  to  $r = 0.97$ ,  $p < 0.05$ ). We also observed that DEHP metabolites were highly correlated with each other ( $r \geq 0.77$ ,  $p < 0.05$ ).

### ***Associations between phthalate metabolites and pregnancy induced hypertension***

Low molecular weight phthalates metabolites; MEP and MBP were positively associated with pregnancy induced hypertension in crude (OR: 1.43 95% CI: 1.04-1.96, p-value = 0.02 and OR: 1.48 95% CI: 1.10-2.01, p-value =0.01) and in adjusted (OR: 1.47, 95% CI: 1.01-2.14, p-value = 0.04 and OR: 1.66, 95% CI: 1.11-2.47, p-value = 0.01) models respectively as shown in Table 3. We observed borderline association between one of the high molecular weight phthalate metabolite; Mono (3-carboxypropyl) phthalate in crude (OR: 1.46, 95% CI: 0.96-2.24, p-value = 0.08) as well as in adjusted model (OR: 1.56, 95% CI: 0.93-2.64, p-value = 0.09). We did not observe associations between other high molecular weight phthalate metabolites and pregnancy induced hypertension. The FigureS1 shows the scattered plot between levels of phthalates metabolites and occurrence of events during the gestational age of the mothers. Further, we did not find significant associations between the urinary concentrations of phthalates metabolites and preeclampsia in the mothers (data not shown).

While taking into account pregnancy induced hypertension quartiles, we did not observe any significant association. However, a significantly increased odds ratio for MBP metabolite was observed in the 4<sup>th</sup> quartile in crude (OR: 3.46, CI: 1.10-10.87, p-value = 0.03) as well as when adjusted for confounders (OR: 5.91 CI: 0.93-37.79, p-value = 0.06) as shown in Table 4. An association for  $\Sigma$ DEHP (OR: 5.45, CI: 0.85-34.84, p-value = 0.07) was also observed for the second quartile.

## **Discussion**

In this study, we report an association between maternal prenatal urinary concentration of low molecular weight phthalate metabolites including MEP and MBP and pregnancy induced hypertension. MEP is metabolite of Diethyl phthalate (DEP) used in plasticizers, automotive, cleaning and furnishing products, adhesives, sealants and in cosmetic products, while MBP is a metabolite of Di-n-butyl phthalate (DBP), used in diverse range of products such as PVC,

paints, printing inks, adhesives, aerosols and cosmetic products including hair sprays, perfume solvents and fixatives, skin emollients and nail polish. The ubiquitous use of these phthalates in so many different types of products signals its relevance as an environmental stressor, and indeed, more than 97% of the mothers included in our study tested positive for phthalate metabolites. We observed that the MEP and MBP which are a LMW phthalates and are frequently added to our daily used cosmetic products, shampoos, lotions, and other personal care products.

### ***Comparison of findings with other published work***

To our knowledge, this is the second study to assess the relationship of phthalate concentrations in relation to induced hypertension during pregnancy. An earlier research focused on a prospective birth cohort study from Cincinnati, USA investigated the relationship between for 9 phthalate monoester metabolites reflecting exposure to 6 phthalate diesters and gestational hypertension, preeclampsia, eclampsia and HELLP syndrome [12]. This study suggested that maternal urinary MBzP concentrations may be associated with increased diastolic blood pressure and risk of pregnancy induced hypertensive diseases. Our analyses, however, shows a significant association with MEP and MBP but not with MBzP phthalate metabolites, except for a partial significance in the 4<sup>th</sup> quartile (OR: 2.75, CI: 0.95-7.91, p-value = 0.06).

Another study from Boston, USA, investigating the relationship between Bisphenol A and phthalate metabolites and the risk of preeclampsia [1] found a significant association between preeclampsia and MEP and DEHP. In our present study, we found a significant association between pregnancy induced hypertension and MEP (OR: 1.47, CI: 1.01-2.14, p-value = 0.04) or MBP (OR: 1.66, CI: 1.11-2.47, p-value = 0.01) and a borderline significance in MCP (OR: 1.56, CI: 0.93-2.64, p-value = 0.09).

Other studies on phthalate exposure and blood pressure in children have also shown significant positive associations [2, 17, 18]. In studies done in the United States, [2, 18], cross-sectional analysis of a subsamples found increased urinary concentrations of MEP and DEHP were associated with increased blood pressure in children age 6-19 years. However, a study from Spain focused on a population based birth cohort observed that the sums of HMW phthalates as well as the sum of LMW phthalates were significantly related with lower systolic blood pressure in girls, but not in boys at the age of 4 and 7 years [17]. A prospective study on elderly adults from Uppsala, Sweden showed inverse associations between MEP and systolic and diastolic blood pressure [19]. Additionally, a cross-sectional study of older adults found increased serum concentrations of MBzP were related to several cardiovascular risk factors [11].

### ***Potential mechanisms***

The exact mechanisms describing phthalate interactions with pregnancy induced hypertension are still unclear; however they are likely to be multifactorial in nature and depend on diet, living style, genetic and environmental factors. Nutritional imbalances or environmental chemical exposures during pregnancy and development can increase the risk of disease and their effects may be share some common pathways [20]. Indeed, hormones, cytokines and nutritional components can both directly activate receptors that stimulate gene expression and also activate or inhibit the enzymes and pathways that are responsible for DNA methylation, chromatin re-modelling and non-coding RNAs which ultimately control gene expression. Thus, epigenetic regulatory pathways are likely sites for effects of both nutrient and environmental toxicant effects during development and potentially also across the lifespan [20]. There can be another possibility that, as phthalates particularly the LMW phthalate might be related to various cocktail of chemicals, including in cosmetics, it cannot be

excluded that the phthalate might be a proxy of another exposure or behavior that is the true cause of hypertension.

Studies have also suggested that exposure to phthalates during the early pregnancy may lead to early placental maladaptation, which increases the risk of higher blood pressure during the pregnancy and gestational hypertensive disorders [21]. Epidemiological evidence indicates that exposure to phthalates *in utero* is associated with increased blood pressure in childhood [2]. Studies have revealed that the risk of pregnancy induced hypertension may increase through oxidative stress, up-regulation of inflammatory markers (tumor necrosis factor alpha and interleukin 6), and inhibition of peroxisome proliferator-activated receptor gamma [9, 22, 23]. The possible mechanism here may involve phthalate-mediated deregulation of blood pressure and reduced endothelium-derived nitric oxide production, which is mainly produced by endothelial nitric oxide synthase, one of the key vessel relaxation factors in regulation of vascular tone [24]. In addition to the transcriptional regulation, endothelial nitric oxide synthase activity can be modulated by kinase-dependent phosphorylation at various sites.

### ***Strengths and limitations***

The nested cross-sectional design of our study is a sample of a population based prospective cohort that includes nutritional, environmental, biological and social factors starting *in utero*, which allowed us to control for potential confounders and to assess prenatal exposure before the expression of health outcomes. The proposed cohort design offers advantages over the traditional cross-sectional designs; the diagnosis of pregnancy induced hypertension was conducted by physicians, which ensures quality and we were able to further adjust for multiple potential confounders. The values of the exposure biomarkers were standardized for urine sampling conditions to reduce subject variability [15]. However, we were limited to one

urine sample per mother during the second trimester of pregnancy, thus we were unable to assess the concentration variability of each metabolite across the pregnancy. Furthermore, it is not clearly known at which point(s) in gestation the mothers have a higher risk of exposure, or even if exposure is relatively constant over the course of the pregnancy. Former studies have also used second trimester maternal urinary concentration for biomarkers [25, 26]. Consistency in urinary concentrations during pregnancy has been observed for some environmental exposure biomarkers and other studies have suggested that phthalate biomarkers are relatively stable for a period of weeks to months [27, 28]. Nonetheless, increasing the number of urine samples collected would have provided a more accurate estimate of average exposure during the gestation period. We also adjusted for many potential confounders; however residual confounding (if any) cannot be discarded.

In our study, we considered only male offspring because the initial purpose was to see the effects of phthalates on malformations of male genitalia [29]. Considering only males limits the generalization of our results, it is not a source of bias. From a statistical point of view, focusing on one sex is another way to increase the study accuracy when the sample size is limited. Another limitation of our study is small number of cases, however we had limited number of mothers tested for phthalates metabolites during the second trimester of the pregnancy. While we also did not tested for multiple hypothesis testing is another limitation of our study. Further, we also excluded all the mothers with previous history or family history of hypertension, and/or medication for hypertension, diabetes or kidney diseases before their pregnancy.

Creatinine correction is most often used for urinary biomarkers of phthalates, phenols, and pesticides. There are limitations to the usage of creatinine to normalize for urine dilution; different investigators have used specific gravity as an alternative of creatinine to adjust phthalate urinary biomarkers for urine dilution,[26, 30] but we did not have specific gravity

measurements. Nevertheless, specific gravity is extremely correlated with creatinine [31] and consequently it is not doubtless that we overcorrected for urine dilution. Regarding exposure assessment, it might be important to explore other techniques of assessment, particularly those that may offer a more exhaustive and coordinated picture of the individual environment, for instance by assessing particular items used in conjunction with indoor air levels and additional biomarkers of exposure.

The exposures we studied are relatively prevalent, and some biomarker urinary concentrations approach those with significant effects in experimental models. In a healthy cohort such as ours, effects of hormonally active environmental exposures may be small, yet a continuous exposure can have adverse impacts.

A further dimension to consider in future research is multiple exposures of hormonally active agents such as these. In terms of prevention, exposure to these chemicals can be better avoided if the contents of products are already known or listed on the products. Unfortunately, many phthalates are often not listed on the labels because they are considered non-active ingredients.

## **Conclusion**

We observed that prenatal exposure to certain phthalates, including MEP and MBP, were associated with pregnancy induced hypertension. Our data provide new suggestive evidence that prenatal exposure to certain phthalates may play a role in the development of pregnancy induced hypertension.

## **Abbreviations:**

BMI            Body Mass Index

BBzP           Benzylbutyl phthalate



CI	Confidence Interval
DEHP	di(2-ethylhexyl) phthalate
DBP	Di-n-butyl phthalate
DiBP	di-isobutyl phthalate
DiDP	di-isodecyl phthalate
DiNP	di-isononyl phthalate
HMW	high molecular weight
LOD	limit of detection
LMW	low molecular weight
MEP	Monoethyl phthalate
MBP	Mono-n-butyl phthalate
MiBP	Mono-isobutyl phthalate
MECPP	Mono(2-ethyl-5-carboxypentyl) phthalate
MEHHP	Mono (2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	Mono(2-ethyl-5-oxohexyl) phthalate
MEHP	Mono(2-ethylhexyl) phthalate
MBzP	Monobenzyl phthalate
MCOP	Monocarboxy-isooctyl phthalate
MCPP	Mono (3-carboxypropyl) phthalate

MCNP      Monocarboxy-isononyl phthalate

OR          Odds Ratio

SD          Standard Deviation

## **Declaration**

**Ethics approval and consent to participate**

The study was approved by the relevant ethical committees in France (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, Le Kremlin Bicêtre University Hospital, and Commission Nationale de l'Informatique et des Libertés), and all participating women gave informed written consent for their own participation and consent was obtained from both parents for each newborn child after delivery.

### **Consent for publication**

Consent for publication was taken from the relevant authority

### **Availability of data and material**

Data and Material was received from the PI (Professor Isabella Annesi-Maesano) of the EDEN Mother-Child Cohort

### **Competing interests**

none

### **Authors' contributions**

MHS has participated in study design, data analysis and interpretation, draft writing, editing and submission. CNM, BH, CGB, and IAM participated in study design, data interpretation and editing. All authors read and approved the final manuscript

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**Conflict of interest:** none

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**Table 1.** Characteristics of the study population and by centre.

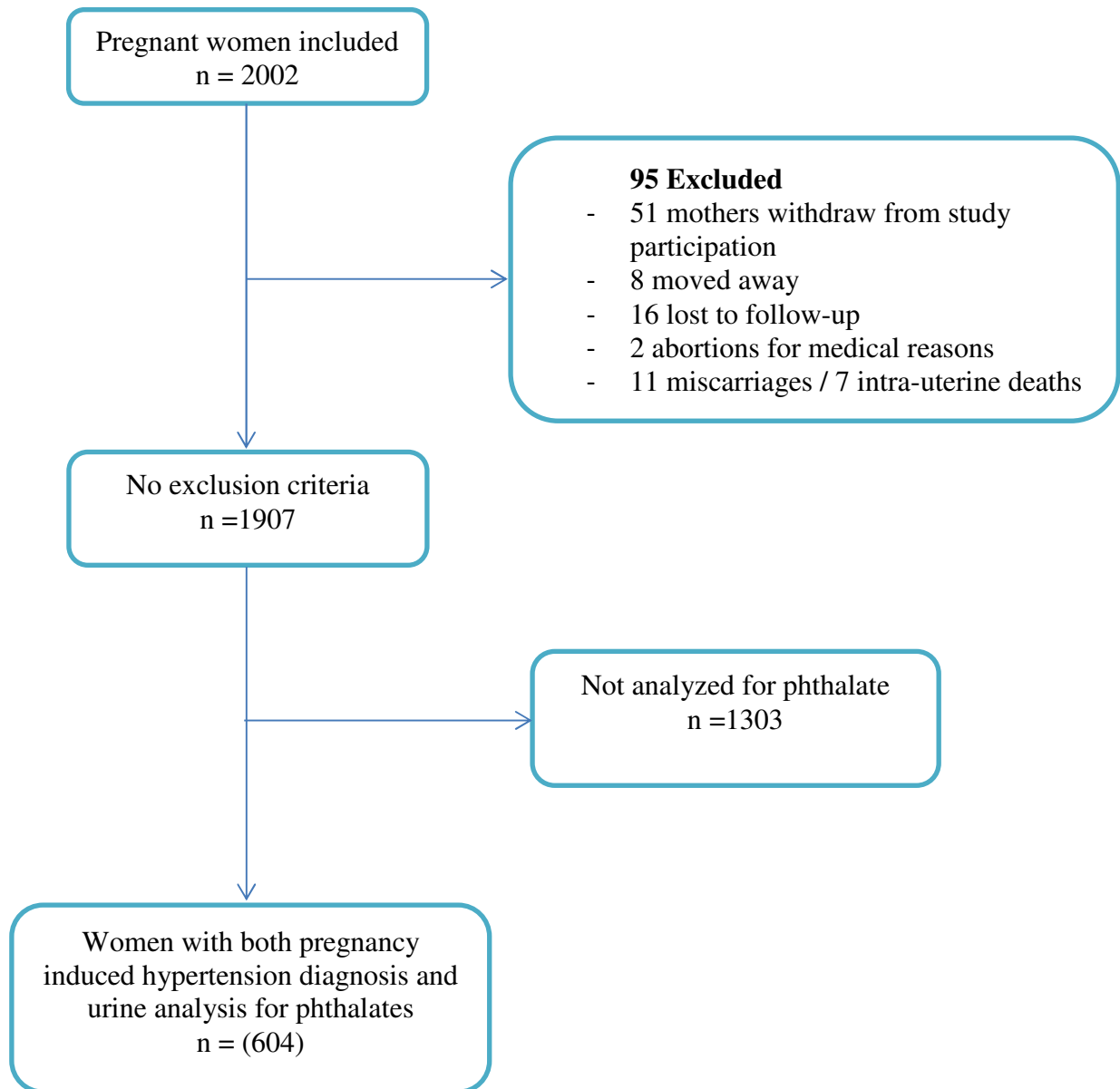
Characteristics	All n=604		Poitiers n= 347		Nancy n= 257		P value
	Mean ± SD	No. %	No. %	No. %	No. %		
<b>Maternal age (years)</b>	29.86±4.8						
<25	79	13.0	48	13.8	31	12.0	0.8
25 – 29	218	36.1	123	35.5	95	37.0	
30 – 34	205	34.0	120	34.6	85	33.1	
≥35	102	16.9	56	16.1	46	17.9	
<b>Parity</b>							
0	269	44.5	174	50.1	95	37.0	0.005
1	222	36.8	117	33.7	110	42.8	
≥2	113	18.7	56	16.2	52	20.2	
<b>BMI (kg/m<sup>2</sup>)</b>	23.1±4.5						
<18.5	57	9.4	27	7.9	30	11.7	0.4
18.5 – 24.9	379	62.9	217	62.5	162	63.0	
25 – 30	110	18.3	68	19.6	42	16.3	
>30	49	8.1	30	8.6	19	7.4	
Missing	9	1.5	5	1.4	4	1.6	
<b>Maternal education</b>							
<2 years after high school	263	43.5	172	49.6	91	35.4	0.004
High school +2 years	132	21.9	72	20.7	60	23.3	
≥ High school +3 years	199	32.9	98	28.3	101	39.4	
Missing	10	1.7	5	1.4	5	1.9	
<b>Active smoking (cig/day)</b>							
0	519	86.0	295	85.0	224	87.2	0.6

	<b>1 to 5</b>	60	9.9	39	11.2	21	8.1	
	<b>&gt;5</b>	23	3.8	12	3.5	11	4.3	
	<b>Missing</b>	2	0.3	1	0.3	1	0.4	
<b>Passive smoking</b>								
	<b>Yes</b>	192	31.8	127	36.6	65	25.3	
	<b>No</b>	405	67.1	216	62.3	189	73.5	0.01
	<b>Missing</b>	7	1.1	4	1.1	3	1.2	
<b>Alcohol during pregnancy</b>								
	<b>Yes</b>	151	25.0	72	20.8	79	30.7	
	<b>No</b>	450	74.5	274	78.9	176	68.5	0.01
	<b>Missing</b>	3	0.5	1	0.3	2	0.8	
<b>Gestational age</b>								
		39.4±1.4						
	<b>&lt;37 gestational week</b>	24	4.0	13	3.8	11	4.3	
	<b>≥37 gestational week</b>	580	96.0	334	96.2	246	95.7	0.7
<b>Employment</b>								
	<b>Yes</b>	458	75.9	256	73.8	202	78.6	
	<b>No</b>	142	23.5	89	25.6	53	20.6	0.3
	<b>Missing</b>	4	0.6	2	0.6	2	0.8	
<b>Caesarean section</b>								
	<b>Yes</b>	95	15.7	47	13.6	48	18.7	
	<b>No</b>	509	84.3	300	86.4	209	81.3	0.08
<b>Season of urine sample collection</b>								
	Winter	189	31.3	101	29.1	88	34.2	
	Spring	146	24.2	89	25.6	57	22.2	
	Summer	129	21.3	83	23.9	46	17.9	0.12
	Autumn	140	23.2	74	21.4	66	25.7	
<b>Time of sampling</b>								
	Midnight – 7:59	310	51.3	128	36.9	183	71.2	
	8:00 - 11:59	149	24.7	76	21.9	72	28.0	
	12:00 - 19:00	5	0.8	4	1.1	1	0.4	0.00001
	Missing	140	23.2	139	40.1	1	0.4	

*BMI; Body mass index*



**Figure 1:** Flow chart of the study.



**Table 2.** Distribution of phthalate metabolites concentration ( $\mu\text{g/L}$ ) in maternal prenatal urine ( $n = 604$ ).

Parent compound	Abbrev.	Phthalate metabolites	Abbrev.	LOD ( $\mu\text{g/L}$ )	%>LOD	Geometric mean (GM)	Minimum	Percentile					Maximum
								5th	25th	50th	75th	95th	
Diethyl phthalate	(DEP)	Monoethyl phthalate ( $\mu\text{g/L}$ )	MEP	0.6	100	110.7	7.9	21	51	96	195	714	4093.4
Di-n-butyl phthalate	(DBP)	Mono-n-butyl phthalate ( $\mu\text{g/L}$ )	MBP	0.2	100	51.6	2.8	12	28	43	73	438	2418.8
Di-isobutyl phthalate	(DiBP)	Mono-isobutyl phthalate ( $\mu\text{g/L}$ )	MiBP	0.2	100	42.7	1.5	12	25	39	69	166	689.9
Di(2-ethylhexyl) phthalate	(DEHP)	Mono(2-ethyl-5-carboxypentyl) phthalate ( $\mu\text{g/L}$ )	MECPP	0.2	100	40.5	2.6	12	25	38	62	160	2640.5
Di(2-ethylhexyl) phthalate	(DEHP)	Mono(2-ethyl-5-hydroxyhexyl) phthalate ( $\mu\text{g/L}$ )	MEHHP	0.2	100	26.9	1.7	6.8	16	27	44	103	2103.8
Di(2-ethylhexyl) phthalate	(DEHP)	Mono(2-ethyl-5-oxohexyl) phthalate ( $\mu\text{g/L}$ )	MEOHP	0.2	99.7	22.1	0.6	5.6	14	23	36	84	1441.4
Di(2-ethylhexyl) phthalate	(DEHP)	Mono(2-ethylhexyl) phthalate ( $\mu\text{g/L}$ )	MEHP	0.5	98	7.2	0.1	1.6	4.4	7.7	15	35	292.3
Benzylbutyl phthalate	(BBzP)	Monobenzyl phthalate ( $\mu\text{g/L}$ )	MBzP	0.3	100	19.7	1.6	4.5	11	18	33	104	970.4
Di-isononyl phthalate	(DiNP)	Monocarboxy-isononyl phthalate ( $\mu\text{g/L}$ )	MCOP	0.2	99	4.1	0.1	1.2	2.4	3.9	6.5	19	375.3
Di-n-octyl phthalate	(DOP)	Mono(3-carboxypropyl) phthalate ( $\mu\text{g/L}$ )	M CPP	0.2	100	2.1	0.1	0.7	1.3	1.9	3.4	9.1	78.7
Di-isodecyl phthalate	(DiDP)	Monocarboxy-isononyl phthalate ( $\mu\text{g/L}$ )	MCNP	0.2	97.5	1.5	0.1	0.5	0.8	1.2	2.2	9.5	686.8

**Table 3.** Association (Odd Ratio and 95% CI) between maternal urinary concentrations of phthalate metabolites and pregnancy induced hypertension.

Phthalate metabolite	Unadjusted			Adjusted <sup>a</sup>		
	OR	95% CI	P-Value	OR	95% CI	P-Value
<b>MEP</b>	1.43	1.04-1.96*	0.02	1.47	1.01-2.14*	0.04
<b>MBP</b>	1.48	1.10-2.01*	0.01	1.66	1.11-2.47*	0.01
<b>MiBP</b>	1.27	0.81-1.99	0.28	1.22	0.69-2.16	0.49
<b>MECPP</b>	1.26	0.82-1.95	0.29	1.22	0.68-2.21	0.49
<b>MEHHP</b>	1.21	0.79-1.83	0.37	1.16	0.67-1.99	0.59
<b>MEOHP</b>	1.19	0.78-1.83	0.41	1.12	0.64-1.95	0.69
<b>MEHP</b>	0.94	0.66-1.33	0.72	0.84	0.54-1.34	0.48
<b>MBzP</b>	1.31	0.91-1.89	0.15	1.08	0.66-1.78	0.75
<b>MCOP</b>	0.81	0.51-1.29	0.38	0.99	0.58-1.69	0.98
<b>M CPP</b>	1.46	0.96-2.24 <sup>†</sup>	0.08	1.56	0.93-2.64 <sup>†</sup>	0.09
<b>MCNP</b>	1.05	0.72-1.52	0.81	1.24	0.80-1.92	0.33
<b>ΣDEHP</b>	1.03	0.93-1.15	0.56	1.01	0.88-1.17	0.85

<sup>a</sup>OR adjusted for maternal smoking, maternal age, maternal BMI, maternal education level, gestational age, number of siblings, and recruitment centre

MEP = Monoethyl phthalate; MBP = Mono-n-butyl phthalate; MiBP = Mono-isobutyl phthalate; MECPP = Mono (2-ethyl-5-carboxypentyl) phthalate; MEHHP = Mono (2-ethyl-5-hydroxyhexyl) phthalate; MEOHP = Mono (2-ethyl-5-oxohexyl) phthalate; MEHP = Mono (2-ethylhexyl) phthalate; MBzP = Monobenzyl phthalate; MCOP = Monocarboxy-isoocetyl phthalate; M CPP = Mono (3-carboxypropyl) phthalate; MCNP = Monocarboxy-isononyl phthalate; DEHP = di(2-ethylhexyl) phthalate.

\*P<0.05

<sup>†</sup>P<0.10

**Table 4.** Association (Odd Ratio and 95% CI) between maternal urinary concentrations of phthalate metabolites and pregnancy induced hypertension by quartiles.

Phthalate metabolites		Quartiles			
		Q1(Reference)	Q2 OR (95% CI) P-value	Q3 OR (95% CI) P-value	Q4 OR (95% CI) P-value
MEP	Crude	1	1.63 (0.52-5.11) 0.39	0.98 (0.28-3.52) 0.99	2.29 (0.78-6.77) 0.13
	Adjusted	1	0.99 (0.19-5.12) 0.98	0.63 (0.09-4.24) 0.63	1.24 (0.26-5.92) 0.78
MBP	Crude	1	1.25 (0.33-4.78) 0.73	1.78 (0.51-6.23) 0.36	3.46 (1.10-10.87) 0.03*
	Adjusted	1	1.78 (0.25-12.77) 0.56	2.76 (0.37-20.40) 0.31	5.91 (0.93-37.79) 0.06 <sup>†</sup>
MiBP	Crude	1	2.75 (0.72-10.61) 0.14	3.49 (0.94-12.97) 0.06 <sup>†</sup>	2.75 (0.72-10.61) 0.14
	Adjusted	1	0.46 (0.07-3.08) 0.42	2.43 (0.49-11.98) 0.27	1.92 (0.35-10.46) 0.44
MECPP	Crude	1	1.41 (0.44-4.57) 0.55	2.07 (0.69-6.21) 0.19	1.41 (0.44-4.57) 0.55
	Adjusted	1	7.90 (0.83-75.43) 0.07 <sup>†</sup>	6.09 (0.62-59.70) 0.12	6.47 (0.66-63.11) 0.11
MEHHP	Crude	1	1.85 (0.60-5.65) 0.28	1.85 (0.60-5.65) 0.28	1.20 (0.36-4.04) 0.75
	Adjusted	1	2.95 (0.51-17.06) 0.22	2.46 (0.40-15.14) 0.33	2.29 (0.33-15.91) 0.39
MEOHP	Crude	1	4.25 (1.17-15.41) 0.02*	2.75 (0.71-10.61) 0.14	2.04 (0.50-8.31) 0.31
	Adjusted	1	16.08 (1.63-158.12) 0.01*	3.33 (0.26-42.47) 0.35	5.72 (0.52-62.95) 0.15
MEHP	Crude	1	0.58 (0.21-1.65) 0.30	0.79 (0.30-2.05) 0.62	0.48 (0.16-1.44) 0.19
	Adjusted	1	0.40 (0.07-2.22) 0.29	0.84 (0.19-3.62) 0.81	0.52 (0.09-3.08) 0.47
MBzP	Crude	1	1.42 (0.44-4.57) 0.55	0.79 (0.21-3.01) 0.73	2.75 (0.95-7.91) 0.06 <sup>†</sup>
	Adjusted	1	0.81 (0.15-4.21) 0.80	0.50 (0.08-3.11) 0.46	1.79 (0.39-8.25) 0.45
MCOP	Crude	1	0.99 (0.36-2.74) 0.99	0.86 (0.31-2.45) 0.79	0.74 (0.25-2.18) 0.58
	Adjusted	1	3.99 (0.70-22.68) 0.11	3.41 (0.49-23.49) 0.21	2.42 (0.36-16.17) 0.35
MCPP	Crude	1	1.41 (0.44-4.57) 0.55	1.41 (0.44-4.57) 0.55	2.07 (0.69-6.21) 0.19

	<b>Adjusted</b>	1	1.89 (0.32-10.71) 0.48	0.95 (0.13-6.53) 0.95	2.49 (0.54-11.52) 0.24
	<b>Crude</b>	1	0.99 (0.31-3.17) 0.98	1.17 (0.38-3.58) 0.77	1.71 (0.61-4.84) 0.31
<b>MCNP</b>	<b>Adjusted</b>	1	1.11 (0.19-6.51) 0.90	1.30 (0.24-6.92) 0.75	1.71 (0.32-9.11) 0.52
	<b>Crude</b>	1	1.63 (0.52-5.11) 0.39	2.07 (0.69-6.21) 0.19	1.21 (0.36-4.04) 0.75
<b>ΣDEHP</b>	<b>Adjusted</b>	1	5.45 (0.85-34.84) 0.07 <sup>†</sup>	3.39 (0.52-22.15) 0.20	3.18 (0.45-22.41) 0.24

OR adjusted for maternal smoking, maternal age, maternal BMI, maternal education level, gestational age, number of siblings, and recruitment centre

MEP = Monoethyl phthalate; MBP = Mono-n-butyl phthalate; MiBP = Mono-isobutyl phthalate; MECPP = Mono (2-ethyl-5-carboxypentyl) phthalate; MEHHP = Mono (2-ethyl-5-hydroxyhexyl) phthalate; MEOHP = Mono (2-ethyl-5-oxohexyl) phthalate; MEHP = Mono (2-ethylhexyl) phthalate; MBzP = Monobenzyl phthalate; MCOP = Monocarboxy-isoctyl phthalate; MCP = Mono (3-carboxypropyl) phthalate; MCNP = Monocarboxy-isononyl phthalate; DEHP = di(2-ethylhexyl) phthalate.

\*P<0.05

<sup>†</sup>P<0.10