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Master thesis

Exposure to environmental pollutants in association with blood pressure in pregnant women

Sventzouri Katerina
Nurse

Supervisors:

1. **Christos Lionis, Professor of General Practice and Primary Health Care, Clinic of Social and Family Medicine, , Division of Social Medicine, Faculty of Medicine, University of Crete**
2. **Marina Vafeiadi, Postdoctoral Researcher, Division of Social Medicine, Faculty of Medicine, University of Crete**
3. **Ploubidis George, Professor of Population Health and Statistics, Dep. of Social Science, Institute of Education, University College London**

Στην οικογένειά μου

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Υπό τη επίβλεψη των: 1.Λιονή Χρήστο
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Εισαγωγή: Η έκθεση της μητέρας σε περιβαλλοντικούς ρύπους κατά την διάρκεια της εγκυμοσύνης έχει συνδεθεί με την εμφάνιση αυξημένης αρτηριακής πίεσης και κατά συνέπεια με την προεκλαμψία. Αρκετές μελέτες έχουν διερευνήσει την πιθανή σχέση μεταξύ της έκθεση της μητέρας σε αιωρούμενα σωματίδια και σε μέταλλα με την αρτηριακή πίεση και τις επιπλοκές στην εγκυμοσύνη. Ωστόσο, μέχρι τώρα λίγες μελέτες έχουν αποδείξει το αντίκτυπο αυτής της έκθεσης στην εγκυμοσύνη.

Υπόθεση: Εάν κατά την διάρκεια της εγκυμοσύνης, η έκθεση της μητέρας σε πολλούς περιβαλλοντικούς ρύπους ταυτόχρονα επηρεάζει την αρτηριακή πίεση.

Στόχος: Ο στόχος της παρούσας έρευνας είναι να διερευνήσει την πιθανή συσχέτιση της έκθεσης σε POPs, Ocs, DAPs, PFAs phthalates, μέταλλα και αιωρούμενα σωματίδια κατά την διάρκεια της εγκυμοσύνης με την αρτηριακή πίεση.

Μέθοδος: Η παρούσα μελέτη αποτελεί μέρος της προοπτικής μελέτης μητέρας-παιδιού "Rhea". Σε αυτή την μελέτη συμπεριλήφθηκαν 1,332 έγκυες γυναίκες με καταγεγραμμένες μετρήσεις για την αρτηριακή τους πίεση στις αρχές και στα τέλη της εγκυμοσύνης. Από αυτές τις γυναίκες, 1,224 είχαν επίσης πληροφορίες για τουλάχιστον μία από τις επιλεγμένες εκθέσεις.

Αποτελέσματα: Δείχθηκε ότι, η έκθεση σε 1 mBzP (phalate metabolite), σχετίζεται με μείωση της συστολικής πίεσης κατά της διάρκεια της εγκυμοσύνης. Επίσης, η έκθεση

σε μία οργανοφωσφορική μεταβολίτη σχετίζεται με την μείωση της διαστολικής πίεσης στην διάρκεια της εγκυμοσύνης. Επιπλέον, η έκθεση σε συγκεκριμένες OCs σχετίστηκε με μείωση της αυτοαναφερόμενης αρτηριακής πίεσης στα τέλη της ολικής εγκυμοσύνης και η έκθεση σε DAPs σχετίστηκε με μείωση της αυτοαναφερόμενης συνολικής αρτηριακής πίεσης.

Συμπεράσματα:Τα ευρήματα που προκύπτουν δείχνουν θετική σχέση μεταξύ της έκθεσης σε συγκεκριμένους ρύπους και της υπέρτασης κατά την διάρκεια της εγκυμοσύνης. Ωστόσο χρειάζεται περαιτέρω διερεύνηση για να αποδειχτεί πόσο σημαντική είναι αυτή η σχέση.

Abstract

Title: Exposure to environmental pollutants in association with blood pressure in pregnant women.

By: Sventzouri Katerina

Supervisors: 1.Lionis Christos
2.Vafeiadi Marina
3.Ploubidis George

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Introduction: Maternal exposure to environmental pollutants during pregnancy has been associated with blood pressure and consequently, preeclampsia. Several studies have investigated the possible relationship between maternal exposure to particulate matter and minerals with blood pressure and pregnancy complications. However, so far, few studies have shown the impact of these exposures in pregnancy.

Hypothesis: If mother's exposure to several environmental pollutants affects blood pressure during pregnancy.

Aim: The aim of this study is to investigate the possible association of exposure to environmental pollutants during pregnancy, with blood pressure during pregnancy.

Methods: The present study is part of the prospective "Rhea" mother-child cohort. In this analysis 1332 pregnant women with information on blood pressure in early and/or late pregnancy were included. From this sample, 91,8% had also information for at least one of the selected exposures. Exposure to environmental chemical contaminants was assessed through determination of concentrations in serum and urine samples collected from the mother (1st trimester of pregnancy) and includes organochlorine compounds (polychlorinated biphenyls [PCBs] and organochlorine pesticides), per- and polyfluoroalkyl substances (PFAS), metals, phthalate metabolites, phenols, and organophosphate pesticide metabolites. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a standardized protocol. Hypertension was

defined, based on these measurements (SBP>130 OR DBP>85).Women reported doctor diagnosed hypertension during early (around 12 weeks of pregnancy) or late (around 30 weeks) pregnancy. Associations between biomarkers of exposure and blood pressure were investigated using linear or logistic regression analyses for continuous and categorical outcomes, respectively, and adjusted for potential confounders.

Results: This research showed that exposure to 1 phthalate metabolite (mBzP) was associated with a decrease in systolic BP and also, exposure to 1 organophosphate pesticide metabolite was associated with a decrease in diastolic BP. Moreover, exposure to specific OCs was associated with a decrease in self-reported blood pressure in late and total pregnancy and exposure to DAPs was associated with decrease in self reported total pregnancy blood pressure.

Conclusion: Our findings showed an association between exposure to pollutants and hypertension during pregnancy, but more research is needed to show how this interaction is.

Key words: pollutants, blood pressure, pregnancy, self-reported blood pressure, hypertension.

1) Introduction

1.1 Cardiovascular diseases and high blood pressure

Cardiovascular diseases are one of the leading causes of death and high blood pressure (BP) is a major contributing factor. In a research from 2002 to 2016 was found that, high blood pressure (HBP) was the leading risk factor contributing to global disease burden, accounting for more than 15% of all health loss in adults and responsible for 62% of all strokes and 49% of Acute Coronary Syndrome events (1).Hypertension is defined as either a systolic blood pressure (SBP) of 140 mm Hg or higher, a diastolic BP (DBP) of 90 mm Hg or higher, or both. Chronic hypertension, by definition, is diagnosed before pregnancy or before 20 weeks' gestation and persisting after delivery(2). Chronic hypertension is further classified as mild-to-moderate (SBP 140–159 mm Hg and/or DBP 90–109 mm Hg) or severe (SBP 160 mm Hg and/or DBP 110 mm Hg)(3).

1.2 Blood pressure in pregnant woman

Pregnant women are considered a sensitive population for hypertensive disorders as a result of increased stress on the cardiovascular system and endothelium. Hypertensive disorders during pregnancy are one of the leading causes of maternal and offspring mortality and morbidity(4). Hypertension can be chronic or start during pregnancy and can be associated with additional comorbidities that may lead to pre-eclampsia and preterm delivery(5).Hypertension in pregnancy contributes to maternal morbitity and mortality, while gestational preeclampsia and hypertension are the most common hypertensive disorders of pregnancy(HDP) respectively affecting around 2% and 10% of pregnancies 20 weeks f gestation(3). The criteria for diagnosis of HDP is as follows: two readings, showing a systolic blood pressure of ≥140mm Hg and/or a diastolic blood pressure of≥90mm Hg, taken over a period of 4 to 6 hours after 20 weeks gestation, in a woman who was normotensive prior to pregnancy(2). In addition to perinatal and maternal mortality, HDP is the leading cause of adverse pregnancy outcomes including placental abruption, preterm birth, and intrauterine growth retardation. 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(2). Several physiopathology mechanisms, including those associated with genetic, immune, and vasoactive factors have been invoked but despite their serious consequences, the biological mechanisms underlying HDP remain unclear. The first systematic analysis of all available published scientific literature and government reports on causes of maternal deaths was published in 2006 and provided an overall picture of the of the contribution of different causes to the burden of maternal deaths(6).

As many as 5% of pregnant women have chronic hypertension. Most of these patients will have essential hypertension but as many as 10% have secondary hypertension, with underlying endocrine or renal causes(7). Older age at child birth and prevalence of obesity contribute to a rising prevalence of chronic hypertension during pregnancy. Chronic hypertension is most easily diagnosed in a woman with documented pre-pregnancy hypertension, especially if she is already receiving antihypertensive therapy. Hypertension arising in the first trimester is most likely chronic hypertension(7). However, a diagnostic dilemma arises in women with late prenatal care who may be normotensive during the typical nadir in the second trimester and then become hypertensive in the late second or third trimester. It is challenging to distinguish chronic hypertension from gestational hypertension and, often, preeclampsia during the pregnancy(2).If hypertension persists after the postpartum period (6–12 weeks), then chronic hypertension is the retrospective diagnosis. Additionally, many women with well-documented preexisting hypertension may remain normotensive without therapy throughout pregnancy(8).

1.3 Hypertensive disorders and preeclampsia

However, the most significant complication of chronic hypertension is the development of superimposed preeclampsia, which develops in 20% to 40% of women with chronic hypertension(5). Preeclampsia is defined as new-onset hypertension after 20 weeks of gestation and proteinuria and/or evidence of end-organ compromise, including CNS symptoms (headache and/or visual changes), pulmonary edema, thrombocytopenia, renal insufficiency, or liver dysfunction(9).Similarly, chronic hypertension poses substantial risks to the fetus, including miscarriage, abruption, small-for-gestational age, preterm birth, and perinatal death. The perinatal mortality rate is higher in patients with superimposed preeclampsia compared with women with preeclampsia in women

without chronic hypertension(4). A variety of risk factors have been associated with increased probability of preeclampsia. Nonetheless, it is important to remember that most cases of preeclampsia occur in healthy nulliparous women with no obvious risk factors(8).

Although the precise role of genetic–environmental interactions on the risk and incidence of preeclampsia is unclear, emerging data suggest the tendency to develop preeclampsia may have some genetic component(7)**.** In Kinshasa, they demonstrated a very high exposure to pollutant metals in pregnant women and observed that women with hypertensive disorders and preeclampsia excreted higher quantities of metals than pregnant women without preeclampsia. Moreover, the differences in metal excretion between the two groups were less pronounced in the rainy season than in the dry season, when the incidence of preeclampsia is highest(10). In China, examined for first time the effect of air pollution on hypertensive disorders and also preeclampsia and modifying effects of meteorological conditions. They observed that preeclampsia risk increased gradually with quartiles of $PM_{10}$and SO_2 exposure, during the first trimester, second trimester and entire pregnancy. Also, significant interaction between $PM_{10}$and dew point temperature on preeclampsia were observed. Significant and stronger association between$PM_{10}$and preeclampsia were only apparent under relative high humidity condition (>95th percentile of dew point temperature). Ambient air pollutants, either individually or as proxies for the complex mixture of urban air pollution, including $PM_{2.5}$, PM_{10}, CO, O_3, NO_2, and NO_x, have been concerned to affect blood pressure (11).Another study which was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development showed that exposure to higher levels of criteria air pollutants in the second trimester was associated with an increased risk of gestational hypertension, and that exposure to higher levels of O3 , CO, and NOX/NO2 during 3-months preconception and in the first trimester were associated with a lower risk of preeclampsia. Conversely, exposure to higher ambient levels of VOCs throughout pregnancy was not associated with risk of gestational hypertension but was associated with an elevated risk of preeclampsia. Differences suggest that air pollutants have differential effects on the mechanisms underlying gestational hypertension. Findings are particularly notable given that most air pollution levels were below the Environmental Protection Agency's National Ambient Air Quality

Standards, even when Environmental Protection Agency's air quality standards are annual measures, longer time frames than pregnancy(12).

1.4 Hypertensive disorders and air pollution

To date, only a few epidemiologic studies have assessed associations between environmental exposures and blood pressure in pregnant women, with emerging evidence for ambient air pollution(12).However, some studies have almost exclusively considered the effects of single environmental exposures, lacking the ability to study the wide range of environmental factors to which an individual is simultaneously exposed to and could affect health(13).The exposome, described as 'the totality of human environmental exposures from conception onwards', recognizes that individuals are exposed simultaneously to a multitude of different factors and takes a holistic and agnostic approach to the discovery of etiological factors(14).Ambient concentrations of air pollutants such as particulate matter ≤10 and ≤ 2.5 μm in diameter (PM_{10} and $PM_{2.5}$, respectively), nitrogen dioxide (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), and ozone (O_3) were associated with hypertensive disorders of pregnancy and with preterm delivery(13). However, the association between air pollution and hypertensive disorder in pregnancy has been inconsistent, depending on the susceptible period, severity of hypertensive disorder, and air pollutants of concern in previous studies. The National Health Insurance Service–National Sample Cohort (NHIS-NSC) in Korea offers an opportunity for exploring the relationship between air pollution and hypertensive disorders of pregnancy among the general population. This cohort provides clinical risk factors and disease diagnoses in addition to general demographics(15). They restricted their analysis to Seoul, the capital of South Korea, which is densely populated (~ 10 million people) and highly polluted (annual average concentration of PM_{10} = 51.3 $\mu g/m^3$in 2010) compared to the World Health Organization guideline (PM_{10} = 20 $\mu g/m^3$). Previous epidemiological studies in Seoul reported associations between air pollution and adverse birth outcomes. Now, in their research the prevalences of hypertensive disorders of pregnancy were 5.7, 4.7, and 4.1 per 1000 pregnant women for gestational hypertension, preeclampsia, and Mg-preeclampsia, respectively. Although mostly null risk estimates were observed, there were generally increasing risk gradients for all pollutants, except for PM_{10}, to more severe forms of

hypertensive disorders of pregnancy. Risk estimates were higher with longer exposure periods than shorter periods, except for O_3. In particular, this study suggested an association between air pollution during pre-conceptional period and preeclampsia which has not been explored previously(15).

Another cohort study which was performed in Wuhan, China, explored the relation between gestational hypertension (GH) and exposure to particulate matters with an aerodynamic diameter ≤ 2.5 ($PM_{2.5}$) and ozone (O_3). In this study were involved 38.115 pregnant women and all information was collected from the Wuhan Maternal and Child Health Management Information System, using standardized quality control. After adjusting for major confounders and other air pollutants, a 10 μg/m^3 increase in $PM_{2.5}$ and O_3 concentrations was found to correlate to a 1.14-fold [95% confidence interval (95% CI):1.09,1.20]anda1.05-fold(95%CI:1.02,1.07)increaseinGHrisk,respectively.Additionally, stronger relationships between GH risk and $PM_{2.5}$ and O_3 exposure were observed in women who conceived in winter and summer, respectively. These findings suggest that air pollutants may contribute to the development ofGH(16).In Spain, another 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(17). A cohort study in Denmark showed that a 10-μg/m^3 increase in O_2 exposure during first trimester was associated with increased risk of preeclampsia (n = 1,880, adjusted odds ratio = 1.07 [95% confidence interval = 1.01, 1.14]) and pregnancy-induced hypertensive disorders (n = 2,430,adjustedodds ratio = 1.07 [1.01, 1.13]). A10 dB higher road traffic noise was also associated with increased risk of preeclampsia (1.10 [1.02, 1.18]) and pregnancy-induced hypertensive disorders (1.08 [1.02, 1.15]). For both exposures, the associations were strongest for mild preeclampsia (n = 1,393) and early-onset preeclampsia (n = 671), whereas higher risk for severe preeclampsia (n = 487) was not evident. In mutually adjusted models, estimates for both exposures decreased and only the association between O_2 and mildpreeclampsia remained. Although associations with the two exposures were generally not found to be independent of one another(18).

Another study showed that a modest but significant association between very small increases in umbilical cord blood lead and elevations in SBP and DBP during labor and delivery. This association was observed at blood lead concentrations well below the

current CDC recommended action level of 10 μg/dL for children and below the recommended level of 5 μg/dL for pregnant women(19). Their findings are consistent with previous studies on blood lead levels and blood pressure during pregnancy(20). Moreover, in a population of South African women was observed associations between maternal serum concentrations of DDT/E and elevated odds of HDP diagnosis based on self-report and data abstracted from medical record(21).

2. Aim

The aim of this study was to assess the association between exposure to a wide range of environmental exposures with blood pressure in pregnant women.

3. Population, material and methods

3.1 Study Population

The present study is part of the prospective "Rhea" mother-child cohort. Methods are described in detail elsewhere. Briefly, female residents (Greek and immigrants) who became pregnant during a period of one year starting in February 2007 were contacted and asked to participate in the study. The first contact was made at the time of the first comprehensive ultrasound examination (mean ± SD 11.96 ± 1.49 weeks) and several contacts followed after birth. To be eligible for inclusion in the study, women had to have a good understanding of the Greek language and be older than 16 years of age. Face-to-face structured questionnaires along with self-administered questionnaires and medical records were used to obtain information on several psychosocial, dietary, and environmental exposures during pregnancy and early childhood. In this analysis 1332 pregnant women with information on blood pressure in early and/or late pregnancy were included. From these sample, 91,8% had information for at least one of the selected exposures.

3.2 Environmental Exposures

Exposure to environmental chemical contaminants was assessed through determination of concentrations in serum and urine samples collected from the mother (1st trimester of pregnancy) and includes organochlorine compounds (polychlorinated biphenyls [PCBs] and organochlorine pesticides), per- and polyfluoroalkyl substances (PFAS),

metals, phthalate metabolites, phenols, and organophosphate pesticide metabolites.We calculated the molar sums of ΣDEHPm metabolites (MEHP, MEHHP, and MEOHP) and combined high and low molecular-weight phthalate metabolites as ΣHMWPm (ΣDEHPm and MBzP) and ΣLMWPm (MEP, MiBP, and MnBP) respectively. Molar sums were calculated by dividing metabolite concentrations by their molecular weight (MW) and summing across.Phthalate metabolites, phenols, and OP pesticide metabolites were adjusted for urinary creatinine.

3.3 Blood pressure outcomes

BP was measured during the clinical examination using a standardized protocol: after 5 min of rest in sitting position, 3 consecutive measurements were taken by oscillometric device with 1-min time intervals between them, in a pre-defined posture and in preference in the right arm. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) from each measurement were recorded, and the mean of the second and the third measurements was calculated and used in further analysis. Hypertension was defined, based on these measurements (SBP>130 OR DBP>85).Additional information was gathered through medical history questionnaires. Women reported doctor diagnosed hypertension during early (around 12 weeks of pregnancy) or late (around 30 weeks) pregnancy.

3.4 Potential confounders

Information on socio-demographic and lifestyle characteristics was obtained by questionnaires completed by women and during face-to-face interviews conducted by trained interviewers. We examined the effect of potential confounding variables that have an established or potential association with BP in pregnancy. Potential confounders included: maternal age (years), maternal education (low level: ≤6 years of school, medium level: 6 and ≤12 years of school and high level: university of technical college degree), parity (Primiparous / Multiparous), smoking during pregnancy (yes/no) and maternal pre-pregnancy BMI (Kg/m^2).

3.5 Statistical Analysis

We conducted descriptive analysis of the study population characteristics, exposure and outcome variables. Univariate associations were examined between exposure and outcomes and potential confounders via the chi-square-test for all categorical outcomes while in the case of continuous outcomes either the t-test (normal distribution data) or

the Mann-Whitney U-test (data which do not follow a normal distribution) was performed. Following the univariate associations, confounders were selected if they simultaneously associate with at least one exposure and one outcome with p-value <0.1.We estimated associations with each exposure variable independently using regression models. For every outcome variable, we first studied the association of interest in the crude model. Adjusted associations were obtained via linear or logistic multivariable regression analyses for continuous and categorical outcomes, respectively. All statistical analyses were performed using STATA version 13 (StataCorp LLC, TX).

4. Results

The characteristics of the study population are given in **Table 1**. Participating women were predominantly Greek, had a mean (±SD) age of 29.5 (±5.0) years at delivery, about half of them had medium educational level (49.6%) and were multiparous (57.4%). Before pregnancy, the mean (±SD) BMI was 24.4 (±4.9) kg/m^2. About a third of the study population smoked during pregnancy (35.8%).

Table 1. Study population

	N	Mean or %	SD
Maternal age (years)	1217	29.5	5.0
Pre-pregnancy BMI (kg/m2)	1204	24.4	4.9
Origin			
Greek	1103	90.6	
Other	115	9.4	
Education			
Low	255	21.0	
Medium	602	49.6	
High	356	29.4	
Parity			
Primiparous	516	42.6	
Multiparous	694	57.4	
Smoking			
No	775	64.2	
Yes	433	35.8	

The characteristics of the study population are given in **Table 2**. The SD of SBP was 10.2 and the SD of DBP was 9.7. From the participating women,1015 had no hypertension(92,61%) and 81 women had hypertension(7,39%). Self-reported hypertension in early pregnancy was the 3.01 of participating women(N=36) and self-reported hypertension in late pregnancy was the 4.58 of participating women(N=49). Finally, self-reported hypertension in total pregnancy was the 12.7 of participating women(N= 151).

Table2. Description of outcomes

	N	Mean or %	SD
Blood Pressure Measurements			
SBP	1096	106.7	10.2
DBP	1095	69.8	9.7
Hypertension			
No	1015	92.61	
Yes	81	7.39	

Self-reported hypertension		
Early pregnancy		
No	1160	96.99
Yes	36	3.01
Late pregnancy		
No	1022	95.42
Yes	49	4.58
Total pregnancy		
No	1038	87.3
Yes	151	12.7

Exposures studied individually in association with SBP, DBP and the odds of hypertension during pregnancy, are presented in **Table 3**. In overall, higher exposure to environmental chemicals was associated with a decrease or no change in blood pressure during pregnancy. Of the 34 environmental exposures examined, exposure to 1 phthalate metabolite (mBzP) was associated with a decrease in systolic BP (β = −4.22 mm□g (95%CI: −8.30, −0.15), while 1 perfluorinated compound (PFUNDA) was borderline significantly associated with a decrease in systolic BP (β = −3.57 mm□g (95%CI: −7.47, 0.32). Regarding diastolic BP, exposure to 1 organophosphate pesticide metabolite was associated with a decrease in diastolic BP (β = −1.91 mm□g (95%CI: −3.64, -0.19), while we found borderline significant associations with PM_{10}(β = −0.16 mm□g (95%CI: −0.33, 0.01) and 1 phthalate metabolite (mnBP) (β = −2.56 mm□g (95%CI: −5.52, 0.39). □xp□sure t□ 2 organophosphate pesticide metabolites(DEP, DETP) was associated with lower odds of hypertension during pregnancy [0.28 (95% CI: 0.11, 0.72; 0.58 (95& CI: 0.36, 0.92 respectively).

Table3. Associations between Air pollutants, Metals, OCs, PFAs, Phthalates and DAPs exposure and blood pressure during pregnancy.

		Blood Pressure Measurements					
		SBP		DBP		Hypertension	
Exposures		**Beta (95% CI)**	**p-value**	**Beta (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Air pollution							
PM_{10}	1	-0,02 (-0,19, 0,16)	0,843	**-0,16 (-0,33, 0.01)**	**0,072**	1,00 (0,93, 1,07)	0,940
$PM_{2.5}$	2	0,01 (-0,48, 0,49)	0,975	-0,09 (-0,56,0,39)	0,713	1,02 (0,85, 1,23)	0,795
PM $_{coarse}$	3	-0,04 (-0,20, 0,13)	0,672	-0,10 (-0,26, 0,06)	0,222	0,99 (0,92, 1,05)	0,704
PM $_{absorbance}$	4	-0,35 (-2,61, 1,90)	0,759	-0,33 (-2,54, 1,89)	0,772	0,69 (0,27, 1,73)	0,428
Metals							

Cadmium	5	-0,20 (-2,52, 2,11)	0,863	0,20 (-2,05, 2,46)	0,861	1,32 (0,51, 3,41)	0,565
Lead	6	-0,54 (-2,78, 1,70)	0,637	-0,84 (-3,01, 1,34)	0,450	1,01 (0,41, 2,50)	0,987
OCs							
HCB	7	0,33 (-2,82, 3,48)	0,837	-0,09 (-3,22, 3,03)	0,954	0,97 (0,26, 3,56)	0,963
DDE	8	-0,95 (-2,87, 0,98	0,335	-0,99 (-2,90, 0,92)	0,308	0,65 (0,29, 1,46)	0,296
PCB118	9	-0,74 (-3,80, 2,33)	0,636	0,82 (-2,22, 3,85)	0,599	0,53 (0,15, 1,86)	0,324
PCB153	10	-2,569(-6,07, 0,95)	0,153	-2,27 (-5,75, 1,21)	0,201	0,34 (0,08, 1,46)	0,146
PCB138	11	-1,77 (-5,03, 1,48)	0,286	-2,05 (-5,27, 1,18)	0,213	0,38 (0,10,1,41)	0,146
PCB180	12	-2,29 (-5,52, 0,94)	0,165	-2,48 (-5,68, 0,72)	0,129	0,42 (0,10, 1,67)	0,216
PCB170	13	-2,34 (-5,28, 0,61)	0,120	-2,14 (-5,06, 0,78)	0,150	0,50 (0,14, 1,74)	0,273
Total PCBs	14	-2.54 (-6,03, 0,95)	0,154	-2,42 (-5,88, 1,04)	0,171	0,35 (0,08, 1,52)	0,161
PFAs							
PFHxS	15	-2,97 (-8,17, 2,24)	0,262	-4,13 (-9,20, 0,93)	0,109	0,87 (0,16, 4,69)	0,874
PFNA	16	-0,30 (-4,02, 3,42)	0,873	-0,52 (-4,16, 3,12)	0,778	0,99 (0,30, 3,33)	0,992
PFOA	17	2,82 (-1,33, 6,97)	0,182	0,02 (-4,06, 4,11)	0,991	1,12 (0,30,4,16)	0,860
PFOS	18	-1,59 (-6,18, 3,00)	0,494	-1,66 (-6,15, 2,83)	0,467	0,76 (0,17, 3,45)	0,727
PFUNDA	19	**-3,57 (-7,47, 0,32)**	**0,072**	-3,35 (-7,16, ,46)	0,085	0,49 (0,14, 1,77)	0,279
Non Persistent							
BPA	20	1,84 (-1,56, 5,24)	0,287	1,43 (-2,04, 4,90)	0,417	1,23 (0,31, 4,96)	0,768
Phthalates							
mEP	21	0,21 (-2,20, 2,61)	0,865	-1,10 (-3,54, 1,34)	0,374	1,16 (0,45, 3,01)	0,758
mnBP	22	-2,16 (-5,06, 0,73)	0,143	**-2,56 (-5,52, 0,39)**	**0,089**	0,52 (0,12, 2,28)	0,382
miBP	23	1,14 (-2,84, 5,11)	0,573	2,93 (-1,09, 6,95)	0,152	3,55 (0,72, 17,54)	0,121
mBzP	24	**-4,22 (-8,30, 0,15)**	**0,042**	-1,18 (-5,30, 2,95)	0,574	0,60 (0,09, 4,18)	0,609
mEHP	25	-1,84 (-5,26, 1,59)	0,291	-1,13 (-4,37, 2,11)	0,493	0,28 (0,04, 2,25)	0,234
mEHHP	26	-0,41 (-3,64,2,82)	0,801	-0,15 (-3,43, 3,12)	0,926	0,55 (0,12,2,53)	0,441
mEOHP	27	-1,28 (-4,36,1,80)	0,412	0,74 (-2,40, 3,88)	0,641	0,38 (0,09, 1,69)	0,205
ΣDEHPm	28	-0,47 (-3,56,2,63)	0,788	0,31 (-2,84, 3,45)	0,847	0,32 (0,07, 1,41)	0,133
ΣHMWPm	29	-1,41 (-4,71, 1,89)	0,401	-0,04 (-3,40, 3,32)	0,983	0,27 (0,05, 1,35)	0,110
ΣLMWPm	30	-0,62 (-3,66, 2,41)	0,686	-1,33 (0,43, 4,41)	0,394	1,38 (0,43, 4,41)	0,583
DAPs							
DEP	31	-0,76 (-2,59, 1,06)	0,410	**-1,91 (-3,64, 0,19)**	**0,030**	**0,28 (0,11, 0,72)**	**0,008**
DETP	32	-0,15 (-0,90, 0,61)	0,699	-0,56 (-1,28, 0,16)	0,124	**0,58 (0,36, 0,92)**	**0,020**
DMP	33	-0,79 (-2,71, 1,13)	0,417	-0,99 (-2,82, 0,85)	0,289	0,59 (0,27, 1,29)	0,186

DMTP	34	0,00 (-1,32, 1,32)	0,998	-0,78 (-2,04, 0,48)	0,224	0,70 (0,42, 1,17)	0,178

Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter of less than 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of less than 10μm; PM_{coarse}, particulate matter with an aerodynamic diameter more than 2.5 μm but less than 10μm; PM_{abs}, absorbance of $PM_{2.5}$ filters;OCs, Organochlorine compounds;DDE, 4,4'dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; PCB, polychlorinatedbiphenyl; PFOA, perfluorooctanoate; PFNA, perfluorononanoate; PFUNDA, perfluoroundecanoate; PFHxS, perfluorohexanesulfonate; PFOS, perfluorooctanesulfonate; MEP, monoethylphthalate; MiBP, mono-iso-butylphthalate; MnBP, mono-n-butylphthalate; MBzP, monobenzylphthalate; MEHP, mono-2-ethylhexylphthalate; MEHHP, mono-2-ethyl-5-hydroxyhexylphthalate; MEOHP, mono-2-ethyl-5-oxohexylphthalate;ΣDEHPm, molar sums of DEHP metabolites (MEHP, MEHHP, MEOHP); ΣHMWPm, molar sums of high molecular-weight phthalate metabolites (ΣDEHPm and MBzP); ΣLMWPm, molar sums oflow molecular-weight phthalate metabolites (MEP, MiBP, and MnBP);BPA, bisphenolA; DMP, dimethylphosphate; DMTP, dimethylthiophosphate; DEP, diethylphosphate; DETP, diethylthiophosphate.

Exposures studied individually in association with self-reported early, late and total hypertension and the odds of hypertension are presented in **Table 4**. In overall, higher exposure to environmental chemicals was associated with a decrease or no change in blood pressure during pregnancy. Of the 35 environmental exposures examined, exposure to specific OCs was associated with a decrease in self-reported blood pressure in late and total pregnancy, DDE(late pregnancy: $\beta = 0.30$ mmH ,95%CI: 0.11, 0.30, total pregnancy: β=0.55 mmH 95%CI: 0.30,1.00) and PCB153(early pregnancy: β=9.52 mmH 95%CI: 0.87, 103.29) was borderline significantly associated with a decrease in blood pressure.In phthalates (ΣLMWPm) (total pregnancy : β=2,35 mmH 95%CI :0.88, -6,28) was borderline significantly associated with a decrease in blood pressure. Exposure to DAPs was associated with decrease in self-reported total pregnancy blood pressure, DEP(total pregnancy: β=0.49 mmH 95%CI: 0.26, -0.92), DETP (total pregnancy: β= 0.76 mmH 95%CI: 0.59, -0.98) and exposure to DMP in total pregnancy (β=0.56 mmH 95%CI: 0.30, -1.04)was borderline significantly associated with a decrease in systolic BP.

Table 4. Associations between Air pollutants, Metals, OCs, PFAs, Phthalates and DAPs exposure and self-reported Hypertension during early, late and total pregnancy.

	Self-reported Hypertension					
	Early pregnancy		Late pregnancy		Total pregnancy	
Exposures	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Air pollution						
PM_{10}	0,99 (0,89, 1,09)	0,778	1,01 (0,92, 1,10)	0,872	0,98 (0,93, 1,04)	0,472
$PM_{2.5}$	0,90	0,514	1,07	0,565	1,01	0,942

	(0,67, 1,22)		(0,85, 1,35)		(0,87, 1,16)	
PM_{coarse}	0,96	0,465	1,04	0,353	0,98	0,422
	(0,87, 1,07)		(0,96, 1,11)		(0,93, 1,03)	
$PM_{absorbance}$	0,39	0,247	1,08	0,883	0,65	0,223
	(0,08, 1,92)		(0,37, 3,17)		(0,32, 1,30)	
Metals						
Cadmium	0,70	0,616	0,90	0,858	1,00	0,999
	(0,17, 2,88)		(0,28, 2,86)		(0,50, 2,02)	
Lead	2,57	0,212	1,50	0,486	1,35	0,386
	(0,58, 11,27)		(0,48, 4,69)		(0,68, 2,68)	
OCs						
HCB	1,59	0,639	1,73	0,477	1,29	0,603
	(0,23, 11,12)		(0,38, 7,89)		(0,49, 3,39)	
DDE	0,60	0,407	**0,30**	**0,016**	**0,55**	**0,049**
	(0,18, 2,02)		**(0,11, 0,80)**		**(0,30, 1,00)**	
PCB118	3,52	0,233	0,60	0,519	0,83	0,708
	(0,45, 27,77)		(0,12, 2,86)		(0,32, 2,17)	
PCB153	9,51	0,064	0,96	0,969	0,91	0,867
	(0,87, 103,29		(0,15, 6,03)		(0,30, 2,78)	
PCB138	6,46	0,097	1,01	0,990	0,89	0,827
	(0,71, 58,37)		(0,19, 5,43)		(0,32, 2,49)	
PCB180	3,28	0,278	0,68	0,669	0,67	0,459
	(0,38, 28,20)		(0,12, 3,90)		(0,24, 1,91)	
PCB170	2,18	0,443	0,64	0,580	0,64	0,355
	(0,30, 16,06)		(0,13, 3,10)		(0,25, 1,65)	
Total PCBs	5,76	0,142	0,81	0,821	0,77	0,653
	(0,56, 59,68)		(0,13, 5,06)		(0,25, 2,36)	
PFAs						
PFHxS	NA		2,61	0,509	1,32	0,692
			(0,15, 45,12)		(0,33, 5,22)	
PFNA	10,54	0,114	5,86	0,146	1,36	0,549
	(0,57, 195,27		(0,54, 63,67)		(0,50, 3,70)	
PFOA	NA		3,14	0,374	1,40	0,549
			(0,25, 39,02)		(0,47, 4,16)	
PFOS	3,44	0,466	7,66	0,140	1,32	0,659
	(0,12, 94,99)		(0,51, 114,53		(0,39, 4,51)	
PFUNDA	3,40	0,417	3,90	0,324	0,98	0,968
	(0,18, 65.50)		(0,26, 58,53)		(0,33-, 2,89)	
Non Persistent						
BPA	4,59	0,251	1,32	0,778	1,75	0,313
	(0,34, 61,97)		(0,19, 8,90)		(0,59, 5,16)	
Phthalates						
mEP	NA		2,76	0,225	2,05	0,096
			(0,53, 14,27)		(0,88, 4.75)	
mnBP	1,65	0,719	0,63	0,673	0,85	0,775
	(0,11, 24,79)		(0,07,5,37)		(0,28, 2,55)	
miBP	2,17	0,676	0,95	0,973	2,43	0,204
	(0,06, 81,30)		(0,06, 15,22)		(0,62,9,58)	
mBzP	NA		2,86	0,418	1,62	0,517
			(0,22, 36,46)		(0,38, 6,97)	
mEHP	NA		2,889	0,335	1,19	0,816
			(0,33, 24.77)		(0,27, 5,21)	
mEHHP	NA		5,68	0,090	1,56	0,476
			(0,76,42,48)		(0,46, 5,29)	
mEOHP	NA		3,29	0,186	1,05	0,937
			(0,56, 19,29)		(0,32, 3,43)	
ΣDEHPm	NA		4,36	0,130	1,00	0,996
			(0,65, 29,27)		(0,30, 3,35)	
ΣHMWPm	NA		4,69	0,133	0,98	0,981
			(0,62, 36,22)		(0,27, 3,61)	
ΣLMWPm	NA		1,84	0,513	2,35	0,088

			(0,30, 11,41)		(0,88, 6,28)	
DAPs						
DEP	0.96 (0.35, 2,63)	0,931	1,27 (0,45, 3,58)	0,658	**0,49 (0,26, 0,91)**	**0,023**
DETP	1,01 (0,66, 1,54)	0,965	1,00 (0,66, 1,49)	0,982	**0,76 (0,59, 0,98)**	**0,037**
DMP	1,00 (0,36, 2,81)	0,996	0,39 (0,10, 1,63)	0,198	0,56 (0,30, 1,04)	0,065
DMTP	1,27 (0,62, 2,6-0)	0,513	0,76 (0,33, 1,76)	0.519	0,75 (0,51, 1,12)	0,162

Abbreviations: PM2.5, particulate matter with an aerodynamic diameter of less than 2.5 μm; PM10, particulate matter with an aerodynamic diameter of less than 10μm; PMcoarse, particulate matter with an aerodynamic diameter more than 2.5 μm but less than 10μm; PMabs, absorbance of PM2.5 filters; OCs, organochlorine compounds; DDE, 4,4'dichlorodiphenyl dichloroethylene; HCB, hexachlorobenzene; PCB, polychlorinated biphenyl; PFOA, perfluorooctanoate; PFNA, perfluorononanoate; PFUNDA, perfluoroundecanoate; PFHxS, perfluorohexane sulfonate; PFOS, perfluorooctane sulfonate; 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; ΣDEHPm, molar sums of DEHP metabolites (MEHP, MEHHP, MEOHP); ΣHMWPm, molar sums of high molecular-weight phthalate metabolites (ΣDEHPm and MBzP); ΣLMWPm, molar sums of low molecular-weight phthalate metabolites (MEP, MiBP, and MnBP); BPA, bisphenol A; DMP, dimethyl phosphate; DMTP, dimethyl thiophosphate; DEP, diethyl phosphate; DETP, diethyl thiophosphate.

5. Discussion

5.1 Main findings

In this prospective pregnancy cohort study we observed that higher exposure to environmental chemicals was associated with a decrease or no change in blood pressure during pregnancy. More specifically, this research showed that exposure to 1 phthalate metabolite (mBzP) was associated with a decrease in systolic BP and also, exposure to 1 organophosphate pesticide metabolite was associated with a decrease in diastolic BP. We also observed that exposure to 2 organophosphate pesticide metabolites (DEP, DETP) was associated with lower odds of hypertension during pregnancy.

Exposure to specific OCs was associated with a decrease in self-reported blood pressure in late and total pregnancy and exposure to DAPs was associated with decrease in self-reported total pregnancy blood pressure.

5.2 Discussion under the light of literature

Additionally, other studies suggest positive associations between exposure to some air pollutants during preconception and prenatal periods and hypertensive disorders of pregnancy among the general population.

To our knowledge up to date, a few studies have investigated the exposure of pregnant women to some phthalate metabolites, BPA, and parabens and they suggest that these associations were more frequently observed in the second trimester of pregnancy and remained statistically significant after correction for multiple testing for BPA only(22)(23)(21). Moreover, in China, they examined the effect of air pollution on preeclampsia and modifying effects of meteorological conditions. They observed that preeclampsia risk increased gradually with quartiles of PM10 and SO2 exposure, during the first trimester, second trimester and entire pregnancy. Also, significant interaction between PM10 and dew point temperature on preeclampsia were observed, such as our results(11).

Based on the Shanghai Maternal-Child Pairs Cohort (Shanghai MCPC), a significant association between PM2.5 exposure and altered BP parameters (SBP, DBP and MAP) was found in the early second trimester and exposure to the PM2.5 constituents was also found to be associated with BP alteration during the early second trimester(22).Scientists from Florida used the Florida birth registry data to investigate the associations between air pollutants and the risks of HDP in 22 041 pregnant women

in Jacksonville. They found that exposure to high levels of air pollution during early pregnancy and the full gestational period was associated with increased prevalence of HDP in Florida, USA(22).

5.3 Linitations and strengths of the study

It may be interest to examine this relationship in a study with larger sample and we hope that the present data could support another study in order to assess the relationship between prenatal exposure to air pollutants and environmental chemicals, and cardio metabolic risk factors in childhood.

5. 4 Impact of the study

We suggest that there is a need for more research about the effects of air pollutants to blood pressure of pregnant women and we hope that our study will be used by other scientists as data.

6.)Conclusion

The findings showed that higher exposure to environmental chemicals was associated with a decrease or no change in blood pressure during pregnancy.

Additionally, exposure to some environmental chemicals were borderline significantly associated with a decrease in systolic or diastolic BP.

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