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Full length article



Prenatal exposure to multiple persistent organic pollutants in association with adiposity markers and blood pressure in preadolescents

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ABSTRACT

Background: Several studies have reported that prenatal exposure to some persistent organic pollutants (POPs) is associated with higher adiposity in childhood. Few studies have assessed whether this finding persists into adolescence, and few have considered exposure to POPs as a mixture. This study aims to assess the association between prenatal exposure to multiple POPs and adiposity markers and blood pressure in preadolescents.

Methods: This study included 1667 mother-child pairs enrolled in the PELAGIE (France) and the INMA (Spain) mother-child cohorts. Three polychlorobiphenyls (PCB 138, 153 and 180, treated as a sum of PCBs) and three organochlorine pesticides (p,p'-Dichlorodiphenyldichloroethylene [p,p'-DDE], β-hexachlorocyclohexane [β-HCH], and hexachlorobenzene [HCB]) were assessed in maternal or cord serum. Body mass index z-score (zBMI), abdominal obesity (waist-to-height ratio > 0.5), percentage of fat mass, and blood pressure (mmHg) were measured at around 12 years of age. Single-exposure associations were studied using linear or logistic regressions, and the POP mixture effect was evaluated using quantile G-computation (qgComp) and Bayesian Kernel Machine Regression (BKMR). All models were adjusted for potential confounders and performed for boys and girls together and separately.

Results: Prenatal exposure to the POP mixture was associated with higher zBMI (beta [95 % CI] of the qgComp = 0.15 [0.07; 0.24]) and percentage of fat mass (0.83 [0.31; 1.35]), with no evidence of sex-specific association. These mixture effects were also statistically significant using BKMR. These associations were driven mainly by exposure to HCB and, to a lesser extent, to β-HCH. In addition, the single-exposure models showed an association between β-HCH and p,p'-DDE and higher systolic blood pressure, especially in girls (p,p'-DDE for girls = 1.00 [0.15; 1.86]). No significant associations were found for PCBs.

Conclusion: This study suggests that prenatal exposure to POPs, particularly organochlorine pesticides, remains associated with unfavorable cardiometabolic health up to the age of 12.

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1. Introduction

In several Member States of the European Region, one in three children aged 6–9 years is overweight or obese, and an increased prevalence of childhood obesity was reported between 2007 and 2017 (Hruby and Hu, 2015; Buoncristiano et al., 2021). Childhood obesity is associated with a higher risk of adult obesity as well as disability, premature death, cardiovascular disease, Type 2 diabetes, hypertension and chronic disease (Baker et al., 2007; Franks et al., 2010). Obesity is a multi-factorial disorder mainly linked to a high energy diet and lack of physical activity, though other factors may also explain the current epidemic of childhood obesity (Hruby and Hu, 2015); indeed the perinatal period is suspected of being a particularly sensitive window for the development of obesity and cardiovascular disease (Morton et al., 2016; Heindel et al., 2017). The Developmental Origins of Health and Diseases (DOHaD) concept assumes that events occurring in utero and during the first years of life can have long-term health impacts, with delayed adverse effects that appear later in life. This has been extensively reported for birthweight that is associated with a number of cardiovascular and metabolic disorders later in life (Bianchi and Restrepo, 2022). Since fetal organs and systems are still developing and the detoxification mechanisms are not yet fully mature, fetuses are especially vulnerable to exposure to environmental contaminants. Endocrine disruptors (chemicals that interfere with the functioning of the endocrine system) are of particular concern (Heindel et al., 2017; Grün and Blumberg, 2009).

Some persistent organic pollutants (POPs) are considered endocrine disruptors and suspected of altering hormone-regulated metabolic processes (Heindel et al., 2017; Grün and Blumberg, 2009). POPs, which include polychlorinated biphenyls (PCBs) and organochlorine pesticides (e.g., hexachlorobenzene (HCB), β -hexachlorocyclohexane (β -HCH), and p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE)), are ubiquitous synthetic compounds. Despite having been banned decades ago in most parts of the world and being under the control of the Stockholm Convention (Lallas, 2001), they persist in the environment and lead to a widespread exposure of the general population; current human exposure comes mainly from the fatty components of foods of animal origin (Weitekamp et al., 2021; Gasull et al., 2011). Due to their high lipophilicity and biomagnification properties, POPs are stored in adipose tissue. During pregnancy, they are released into the bloodstream, reaching fetuses and newborns via placental transfer and breastfeeding (Vizcaino et al., 2014; Garí et al., 2019).

In the 2010's, pooled analyses of several mother–child cohorts in Europe reported that prenatal exposure to PCB 153, but not p,p'-DDE, was associated with decreased birthweight (Casas et al., 2015; Govarts et al., 2012). More recently, a literature review on prenatal exposure to POPs, child growth and BMI reported associations between prenatal exposure to organochlorine pesticides and childhood obesity (Stratakis et al., 2021). Specifically, prenatal exposure to p,p'-DDE and HCB was associated, in a meta-analysis, with an increased BMI in children aged 2–11 years. However, no significant association was found between prenatal exposure to PCBs and child BMI. Of the 33 studies cited, just three were conducted in adolescence – a period prone to major endocrine and metabolic changes. We also note that very few studies have investigated exposure to β -HCH (Yang et al., 2021; Agay-Shay et al., 2015; Cupul-Uicab et al., 2013; Lauritzen et al., 2018).

Overweight is a well-known risk factor for cardiovascular diseases, but fewer studies have evaluated the effect of prenatal exposure to POPs on cardiovascular health directly. A review by Sanders et al. (2018) found only two studies which had assessed the effect of prenatal exposure to POPs on blood pressure in children (Sanders et al., 2018): one reported an increase in systolic or diastolic blood pressure in 4-year-olds with increased exposure to p,p'-DDE and PCBs (Vafeiadi et al., 2015) while the other reported higher diastolic blood pressure in 7–9 year-olds in association with PCBs (but not organochlorine pesticides) (Lee et al., 2016). Conversely, a third, more recent, study has reported that prenatal exposure to PCBs was associated with a decrease in diastolic blood

pressure in children aged 6 to 11 years (Warembourg et al., 2019).

These previous findings demonstrate the interest to pursue research studies about the role of prenatal exposures to POPs on cardiometabolic health of children. Indeed, it is necessary to study whether the association observed between prenatal exposure to some POPs and higher BMI during infancy and childhood persist at older ages, and if these exposures can be associated with higher blood pressure. In addition, there is a need to explore sex-specific effects and exposure to POPs as a mixture. Therefore, the aim of this study is to assess the association between prenatal exposure to multiple POPs and cardiometabolic parameters (adiposity markers and blood pressure) in 12-year-olds from two mother–child cohorts.

2. Materials and methods

2.1. Study population

The study population was drawn from two mother–child cohorts: the PELAGIE (*Perturbateurs endocriniens: Etude Longitudinale sur les anomalies de la grossesse, l'infertilité et l'enfance*) and the INMA (*Infancia y medio ambiente*) cohorts (Supplemental material, Figure A1). The PELAGIE cohort recruited 3421 women between 2002 and 2006, in Brittany (France) (Chevrier et al., 2013). Pregnant women were enrolled at the beginning of their pregnancy (<19 gestational weeks) by gynecologists, midwives, and ultrasonographers, and completed a self-administrated questionnaire. Data on newborn health and cord blood sample were collected at the maternity. Data on child development, health, and lifestyles were collected through self-administrated questionnaires at 2, 6 and 12 years of age. At 12 years old, a subgroup of children was invited to participate in a more in-depth follow-up performed in hospital settings (CHU of Rennes, France) that included a clinical examination to study their growth, pubertal development, and behaviors. Of the 933 participants invited to attend the clinical examination at 12 years, 559 (60 %) agreed to participate.

The INMA cohort is a multicenter cohort set up in Spain; INMA sub-cohorts from Gipuzkoa, Sabadell, and Valencia were considered in the present study. Between 2003 and 2008, these three sub-cohorts enrolled 2270 women at the beginning of their pregnancy (10th to 13th weeks of gestation) (Guxens et al., 2012). The women completed a questionnaire and provided a blood sample in the 1st trimester of pregnancy. Children were then followed up with questionnaires and clinical examination at 4–5, 7, 9, and 11 years of age, to collect data on their development, health, and lifestyles. Of the 1487 participants invited to the clinical examination at 11 years, 1262 (85 %) agreed to participate.

All participants from both cohorts provided informed consent.

In each sub-cohort, only those mother–child pairs for whom both exposure biomarker data and at least one anthropometric measurement during preadolescence (defined here as 11 to 13 years old) were available were included in the present study: a total of 1667 mother–child pairs.

2.2. Exposure assessment

POP concentrations were assessed by the *Centre de Toxicologie de Québec* (CTQ) at the *Institut national de santé publique du Québec* (INSPQ) in umbilical cord serum for the PELAGIE cohort and by the Institute of Environmental Assessment and Water Research (IDAEA-CSIC; Barcelona) or the Public Health Laboratory of Basque Country, in maternal serum (collected at 12 weeks of gestation) from the INMA sub-cohorts. The overall quality and accuracy for the analytical methods were monitored by the participation of each of the three laboratories to interlaboratory program including the Arctic Monitoring and Assessment Program (AMAP) for persistent organic pollutants in human serum (Chevrier et al., 2013; Tillaut et al., 2022; Llop et al., 2010; Goñi et al., 2009). In short, POP concentrations were determined by gas chromatography coupled with mass spectrometry in negative ion chemical

ionization mode (GC-NICI-MS) for the PELAGIE samples (Chevrier et al., 2013; Tillaut et al., 2022), by gas chromatography with electron capture detection (GC-ECD) confirmed by GC-NICI-MS for the INMA-Valencia samples (Llop et al., 2010), and by GC-ECD confirmed by GC-MS with electronic impact ionization (EI) for INMA-Sabadell and INMA-Gipuzkoa samples (Goñi et al., 2009). More details about the method used have been described elsewhere (Chevrier et al., 2013; Tillaut et al., 2022; Llop et al., 2010; Goñi et al., 2009). A total of 25 and 19 POPs were assessed in the PELAGIE and INMA cohorts, respectively. However, only those compounds detected in >50 % of samples in each sub-cohort were retained for the present study. These included three PCBs and three organochlorine pesticides: PCB 138, 153 and 180, p,p'-DDE, β -HCH, and HCB. Total lipid levels (g/L) were also calculated based on total cholesterol and triglyceride concentrations (as well as free cholesterol and phospholipid concentrations for the PELAGIE cohort) determined by means of enzymatic techniques (Chevrier et al., 2013; Llop et al., 2010).

Of the six compounds retained in the present study, the limit of detection (LOD) ranged from 0.01 $\mu\text{g/L}$ to 0.02 $\mu\text{g/L}$ in PELAGIE and from 0.008 $\mu\text{g/L}$ to 0.029 $\mu\text{g/L}$ in INMA-Valencia, and were equal to 0.071 $\mu\text{g/L}$ in INMA-Gipuzkoa and -Sabadell (Supplemental material, Table A1). To improve comparison of biomarker data measured in two different matrices, POP levels from the INMA cohort were converted into cord blood level equivalents by applying a conversion factor reported in the literature: Cord serum level = $0.2 \times$ maternal serum level (Govarts et al., 2012). All concentrations are expressed in micrograms per liter ($\mu\text{g/L}$). Because of the difference in the matrices used for the PELAGIE and INMA cohorts (cord vs. maternal blood), we decided not to consider lipids in the main analysis.

2.3. Outcome assessment

For both the PELAGIE and INMA cohorts, the clinical examination was carried out by trained health professionals.

Standing height (cm) was measured using a height gauge, and waist circumference (cm) using a tape measure. All measurements were performed at least twice; the average was calculated and used in the present study. Bioimpedance was used to determine the percentage of body fat mass (%), lean body mass (%), and total mass (kg). The body mass index (BMI, kg/m^2) was calculated as the ratio of total body mass to squared height. The BMI z-score (zBMI standardized on age and sex) was calculated in line with World Health Organization (WHO) references (de Onis, 2007). Children whose zBMI was greater than or equal to one were considered overweight or obese. Abdominal obesity was defined as a waist-to-height ratio (WtHR) greater than or equal to 0.5 (Browning et al., 2010).

Blood pressure was measured using an automatic oscillometric device. After 5 min at rest, systolic and diastolic blood pressure were measured at least twice in the sitting or lying position, depending on the sub-cohort. The average of 2 to 3 measures, expressed in mmHg, were calculated and used in the present analysis. Because blood pressure was not assessed in the INMA-Valencia sub-cohort, there was a study population of 1314 (79 %) for these outcomes.

The six main outcomes retained for the analysis were zBMI (continuous), percentage of fat mass (continuous, expressed in %), abdominal obesity (binary), overweight/obese (binary) and systolic and diastolic blood pressure (continuous). Analyses with blood pressure z-scores (standardized on age, sex and height) were also performed, and showed similar results (data not shown).

2.4. Covariates

Data on sociodemographic and lifestyle characteristics of the mothers was collected at inclusion – by self-administrated questionnaire for PELAGIE and by interview with a trained professional for INMA – and considered in the analysis as follow: age (continuous), education

(Primary or Secondary school; University), fish consumption (Less than twice a week; Between two and four times a week; More than four times a week), parity (Primiparous; Multiparous), smoking (Non-smoker; Smoker at conception; Smoker during the first trimester). Maternal height (self-reported for PELAGIE and measured for INMA) and self-reported weight of the mothers at the beginning of the pregnancy were used to calculate pre-pregnancy BMI (kilograms per square meter). Gestational weight gain was defined according to WHO recommendations (Less than recommended weight gain; Recommended weight gain; Higher than recommended weight gain) based on weight at inclusion (self-reported for PELAGIE and from medical record for INMA) and self-reported weight at the end of the pregnancy or gestational weight gain self-reported at birth or at the 2-year-old follow-up. Child sex (male/female) and birthweight (in grams) were collected from medical records. Lifestyle data of the children were collected by questionnaire administered to the mother close to the 11–12-year-old clinical visit: fish consumption (Less than twice a week; Between two and four times a week; More than four times a week) and sedentary behavior (time spent using screens in hour/week). Child age at the time of the clinical visit was collected (year) (Supplemental material Figure A2).

2.5. Statistical analysis

2.5.1. Data pre-processing

POP concentrations below the LOD were imputed within each sub-cohort using the maximum likelihood imputation technique, assuming a lognormal distribution (Helsel, 1990). A total of five imputations was run per sub-cohort. Concentrations were log transformed to approach a normal distribution and reduce the influence of high exposure levels. Pearson correlation coefficients were calculated to estimate correlations between POP exposures. Because PCB concentrations were highly correlated ($\rho > 0.80$), the sum of the three PCBs (PCB 138, 153, and 180) was calculated after conversion to their respective molecular basis; individual PCBs were not considered in the present study.

Missing data on covariates (up to 14 % for gestational weight gain) were imputed using the chained equations method (White et al., 2011). As recommended, a maximum of 25 variables were retained in the imputation model to predict incomplete variables, and some variables were forced as predictors (i.e., sub-cohort, child zBMI, maternal age, maternal education level, and maternal pre-pregnancy BMI).

A total of five imputed data sets was generated. Associations estimated within each imputed data set were then pooled according to the Rubin rule (Rubin, 1987). Missing data on exposures and outcomes were not imputed.

2.5.2. Exposure-health associations

Three complementary approaches were used to study the associations between prenatal exposure to POPs and the health outcomes of interest: a single-exposure approach and two multiple-exposure approaches which are described below.

First, each POP (β -HCH, HCB, p,p'-DDE, sum of PCBs) was studied independently in association with each outcome of interest using multivariable linear regressions for continuous outcomes and multivariable logistic regressions for binary outcomes. Linearity between exposures and outcomes was checked in Generalized Additive Models (GAM) using restricted cubic splines; associations with an effective degree of freedom > 1.5 was considered as a moderate departure from linearity and reported graphically.

Then, two methods were used to study the POPs as a mixture in order to take into account co-exposures. The first method is the quantile G-computation (qgcomp), a parametric statistical method which is a combination of weighted quantile sum regression and G-computation (Keil et al., 2020). This method involves converting all exposure variables into quartiles and then building a linear model estimating the joint effect of the mixture by simultaneously increasing all single exposures. The second method is the Bayesian Kernel Machine Regression (BKMR),

which is a non-parametric approach studying the effect of multi-exposures as a mixture. For this, the health outcome is regressed on a flexible function of the mixture components that is specified using a kernel function. The advantages of BKMR are that it takes into account non-linearity, non-additive effects and can handle correlations between exposures (Bobb et al., 2015). The overall effect of the mixture was estimated by setting the reference to the 25th percentile. The overall effect is interpreted as a change in health parameters when all POPs are set at a given percentile compared to the reference percentile (i.e., when all POPs are fixed to the 25th percentile). The BKMR models were run using the Markov chain Monte Carlo algorithm with 10,000 iterations. Two-by-two interactions between pollutants were visually inspected (“Interaction plots: 2-by-2 effect”).

All models were adjusted for potential confounding factors identified from a directed acyclic graph (DAG) using DAGitty (Shrier and Platt, 2008). The minimum sufficient adjustment set defined by the DAG included maternal age, maternal pre-pregnancy BMI, maternal education, maternal gestational weight gain, fish consumption during pregnancy, and parity. In addition, adjustment for sub-cohort (Pelagie; INMA-Gipuzkoa; INMA-Sabadell; INMA-Valencia), child sex, and child age was forced a priori in all models, as well as child height for the blood pressure outcomes. All models were performed for both sexes and separately for boys and girls since the literature suggested sex-specific associations between POP exposures and metabolic outcomes (Stratakis et al., 2021). For all analyses, all five imputed data sets were used, except for the BKMR method for which only the first imputed dataset was used.

The threshold for statistical significance was set to 5 %.

2.5.3. Sensitivity analyses

A number of sensitivity analyses were performed to evaluate the robustness of the findings:

- (1) we explored the impact of between-cohort heterogeneity on the results by conducting meta-analyses by sub-cohort and mixed regression models with the sub-cohort as a random effect.
- (2) we tested the effect of taking lipid levels into account by comparing the estimates obtained: i) without considering lipid levels, ii) adjusting the models for lipid levels, and iii) standardizing the POP levels for lipids. These analyses were performed separately according to the matrix used for the exposure assessment (cord vs maternal blood).
- (3) we adjusted the regression models for additional risk factors (not identified as confounder by the DAG): maternal smoking during pregnancy, child fish consumption, and child sedentary behaviors.
- (4) Prenatal exposure to POPs being associated with birthweight which in turn is known to predict cardiometabolic health later in life (Bianchi and Restrepo, 2022; Casas et al., 2015; Govarts et al., 2012), we explored if birthweight may mediate the association between exposures and health outcomes of interest (adiposity markers and blood pressure) by performing mediation analyses using model-based causal mediation analysis (Imai and Yamamoto, 2013).

The sensitivity analyses were performed for the single-exposure models only. To limit the reporting of isolated findings, the results of the sensitivity analyses will be commented in the text only for the statistically significant associations observed in the main analysis; all the associations are reported in Supplemental Material.

All analyses were performed with the R software version 4.0.2. The main packages used were “mice”, “bkmr”, “qgcomp”, “meta”, “mgcv” and “mediation”.

3. Results

3.1. Description of the study population

In total, 1667 mother–child pairs were included in the study (n = 518, 374, 422, and 353 from Pelagie, INMA-Gipuzkoa, -Sabadell, and -Valencia respectively). The main characteristics of the whole study population are presented in Table 1 and detailed by sub-cohort in Supplemental material Table A2. Overall, mothers had a high level of education, with 50 % having a university degree, and most (74 %) were non-smokers at the beginning of pregnancy. At the time of the clinical examination, the children had a mean age of 11.6 years old (SD = 0.9 year), with 31 % categorized as overweight or obese according to WHO reference charts. Differences across cohorts included INMA-Valencia as

Table 1
Characteristics of the study population (n = 1667).

	Mean ± SD or N (%)
Maternal characteristics	
Sub-cohort of inclusion	
PELAGIE	518 (31)
INMA-Gipuzkoa	374 (23)
INMA-Sabadell	422 (25)
INMA-Valencia	353 (21)
Maternal age	30.9 ± 3.9
Maternal pre-pregnancy BMI	23.0 ± 4.0
Weight gain during pregnancy	
Less than recommended weight gain	575 (40)
Recommended weight gain	343 (24)
Higher than recommended weight gain	518 (36)
Maternal educational level	
Primary or Secondary school	834 (50)
University	827 (50)
Parity	
Primiparous	856 (51)
Multiparous	808 (49)
Maternal smoking	
Non-smoker	1215 (74)
Smoker at conception	210 (13)
Smoker during the first trimester	227 (13)
Maternal fish consumption during pregnancy	
Less than twice a week	337 (20)
Between two and four times a week	159 (10)
More than four times a week	1164 (70)
Child characteristics at birth	
Gestational age (weeks)	39.6 ± 1.5
Child sex	
Girl	846 (51)
Boy	821 (49)
Birth weight (g)	3319 ± 467
Breastfeeding	
No	296 (19)
Yes	1271 (81)
Child characteristics at clinical examination	
Child age	11.6 ± 0.9
Child weight (kg)	42.7 ± 9.4
Child height (cm)	149.4 ± 8.9
Child BMI z-score (WHO references)	0.39 ± 1.2
Underweight	39 (2)
Normal	1114 (67)
Overweight/obese	497 (30)
Obese	17 (1)
Percentage of fat mass	22.7 ± 8.5
Abdominal obesity	
No	1401 (85)
Yes	249 (15)
Systolic blood pressure (mmHg)	109 ± 10.9
Diastolic blood pressure (mmHg)	62 ± 7.5
Time spent using screens (hour/week)	14.1 ± 9.3
Fish consumption (child)	
Less than twice a week	231 (14)
Between two and four times a week	612 (37)
More than four times a week	802 (49)

BMI: Body mass Index, SD: standard deviation.

the sub-cohort with the highest percentage of overweight/obese children (40 %) and PELAGIE the sub-cohort with the lowest percentage (10 %). Across all sub-cohorts, obesity affected no >2 % of the children.

3.2. Levels of exposure to POPs during pregnancy

The percentage of POP concentrations above the LOD ranged from 50 % (β -HCH in the INMA-Gipuzkoa sub-cohort) to 100 % (all of the PCBs in the PELAGIE sub-cohort) (Supplemental material, Table A1). Median POP concentrations ranged from 0.04 $\mu\text{g/L}$ for β -HCH to 0.15 $\mu\text{g/L}$ for p,p'-DDE in the whole study population (Table 2).

All correlations between compounds were positive, the highest being observed within PCBs (ρ ranging from 0.83 to 0.96) followed by the correlation between β -HCH and HCB ($\rho = 0.52$). The correlation matrices for each sub-cohort are available in [supplementary material](#) (Appendix Figure A3).

3.3. Association between prenatal exposure to POPs, adiposity markers and blood pressure

3.3.1. Single-exposure models

Single-exposure models showed that higher exposure to β -HCH and HCB was associated with higher zBMI (beta [95 % CI] = 0.12 [0.06; 0.18] and 0.15 [0.08; 0.22], respectively), higher percentage of fat mass (beta [95 % CI] = 0.82 [0.43; 1.21] and 1.02 [0.58; 1.46], respectively), and higher risk of being overweight/obese (OR [95 % CI] = 1.20 [1.05; 1.37] and 1.27 [1.08; 1.48], respectively) (Fig. 1 and Supplemental Table A3). These associations were statistically significant, both in the whole study population and after stratification by sex. Similar trends were observed for prenatal exposure to p,p'-DDE but only the association with higher percentage of fat mass in the whole study population was statistically significant (beta [95 % CI] = 0.46 [0.07; 0.86]). Higher systolic blood pressure was observed in association with higher exposure to β -HCH and p,p'-DDE in girls only (e.g., beta [95 % CI] for p,p'-DDE in girls = 1.00 mmHg [0.15; 1.86]); the increase in diastolic blood pressure was less marked and not statistically significant. Only the associations between p,p'-DDE and both systolic and diastolic blood pressure shown sign of heterogeneous effect according to child sex (p.value of the interaction term between p,p'-DDE and sex = 0.08 and 0.09, respectively). None of the POPs were associated with abdominal obesity and exposure to PCBs was not associated with any of the outcomes. Some non-linear dose-responses were suggested by GAM analyses, especially for β -HCH among boys, for which we observed U-shape associations with zBMI, percentage of fat mass and overweight/obese risk, and an inverse U-shape for systolic blood pressure (Supplemental Figure A4).

3.3.2. Multi-exposure models

Using quantile G-computation models, prenatal exposure to the POP mixture was associated with higher zBMI (qgComp beta [95 % CI] = 0.15 [0.07; 0.24]) and a higher percentage of fat mass (0.83 [0.31; 1.35]), both in the whole study population and by sex (Fig. 1). The mixture was also associated with a higher risk of being overweight/obese (OR [95 % CI] = 1.25 [1.04; 1.51]). Overall, HCB and β -HCH were the main contributors to the mixture (Supplemental Table A3). The

results obtained with BKMR were similar, though not statistically significant after stratification by sex. We observed increased zBMI and percentage of fat mass as exposure to each component of the mixture increased (Fig. 2), e.g., when all POPs were fixed to the median, the zBMI increased by 0.07 [0.03; 0.11], in comparison with when they were fixed to their 1st quartile. For both outcomes, HCB was the main contributor to the mixture effect with posterior inclusion probabilities > 0.90 (compared to < 0.35 for the other POPs). The BKMR models also suggested between-chemical interactions, especially on the percentage of fat mass: visually, we observed a negative exposure-response for PCBs and a positive and non-linear exposure-response for β -HCH, both of which became steeper at lower levels of HCB (Supplemental Figure A6).

Higher systolic blood pressure in association with the POP mixture was suggested, but did not reach statistical significance (Fig. 2).

3.4. Sensitivity analyses

Overall, similar results were observed across the different sets of sensitivity analyses. No strong heterogeneity between sub-cohorts was observed: all associations remain statistically significant and with little changes in effect estimate using linear mixed models considering sub-cohort as a random effect (Supplemental material Table A4), while a few associations (β -HCH and systolic blood pressure in girls; p,p'-DDE and percentage of fat mass) were no longer statistically significant in the meta-analyses of sub-cohort specific associations, even though they led to similar conclusions (Supplemental material Figure A7). Consideration of lipid levels had little impact on the results: adjustment for total lipid levels did not change associations, while lipid-standardization of POPs tended to increase effect estimates but also widen confidence intervals, especially when assessed in maternal blood (Supplemental material Figures A8). Additional adjustments for maternal smoking, child fish consumption and child sedentary time had no impact on the effect estimates (Supplemental Table A5), and no evidence of any mediation effect of birthweight was observed (Supplemental Tables A6).

4. Discussion

In this study, we evaluated the associations between prenatal exposure to multiple POPs and adiposity markers and blood pressure of 12-year-old preadolescents drawn from two mother-child cohorts. We observed that higher exposure to multiple POPs was associated with higher zBMI and body fat, and higher risk of being overweight/obese at age 12, with no evidence of sex difference. HCB was the main contributor to these effects, followed by β -HCH and p,p'-DDE. β -HCH and p,p'-DDE were also associated with higher systolic blood pressure, especially in girls.

Median levels of exposure to the POPs measured in our study population are generally lower than in previous existing studies: of the studies that did not standardize POP concentrations for lipids, levels varied from 0.05 $\mu\text{g/L}$ to 1.21 $\mu\text{g/L}$ for p,p'-DDE exposure (0.15 $\mu\text{g/L}$ in our study), from 0.04 $\mu\text{g/L}$ to 0.68 for HCB exposure (0.04 $\mu\text{g/L}$ in our study) and from 0.02 $\mu\text{g/L}$ to 0.42 $\mu\text{g/L}$ for PCB 153 (0.07 $\mu\text{g/L}$ in our study) (Govarts et al., 2012; Stratakis et al., 2021). Moreover, comparison of the median exposure levels of each sub-cohort led to the same

Table 2

Concentrations of POPs in cord blood¹ ($\mu\text{g/L}$) in the study population (N = 1667).

	LOD ²	% > LOD	Median [Q1; Q3]
beta-hexachlorocyclohexane (β -HCH)	0.0142	81.0	0.04 [0.02; 0.06]
Hexachlorobenzene (HCB)	0.0142	93.3	0.05 [0.03; 0.07]
p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE)	0.02	97.7	0.15 [0.09; 0.24]
Sum of Polychlorinated biphenyls 138, 153 and 180 (Sum of PCBs)	0.0142	97.9	0.09 [0.06; 0.14]

LOD: limit of detection; POP: Persistent organic pollutant; Q1-Q3: first quartile and third quartile.

¹ POP levels assessed in maternal blood samples for INMA cohort and converted into cord blood level equivalent (cord blood level = 0.2*maternal blood level).

² The highest LOD between PELAGIE and INMA data (after cord blood conversion of INMA levels) were retained.

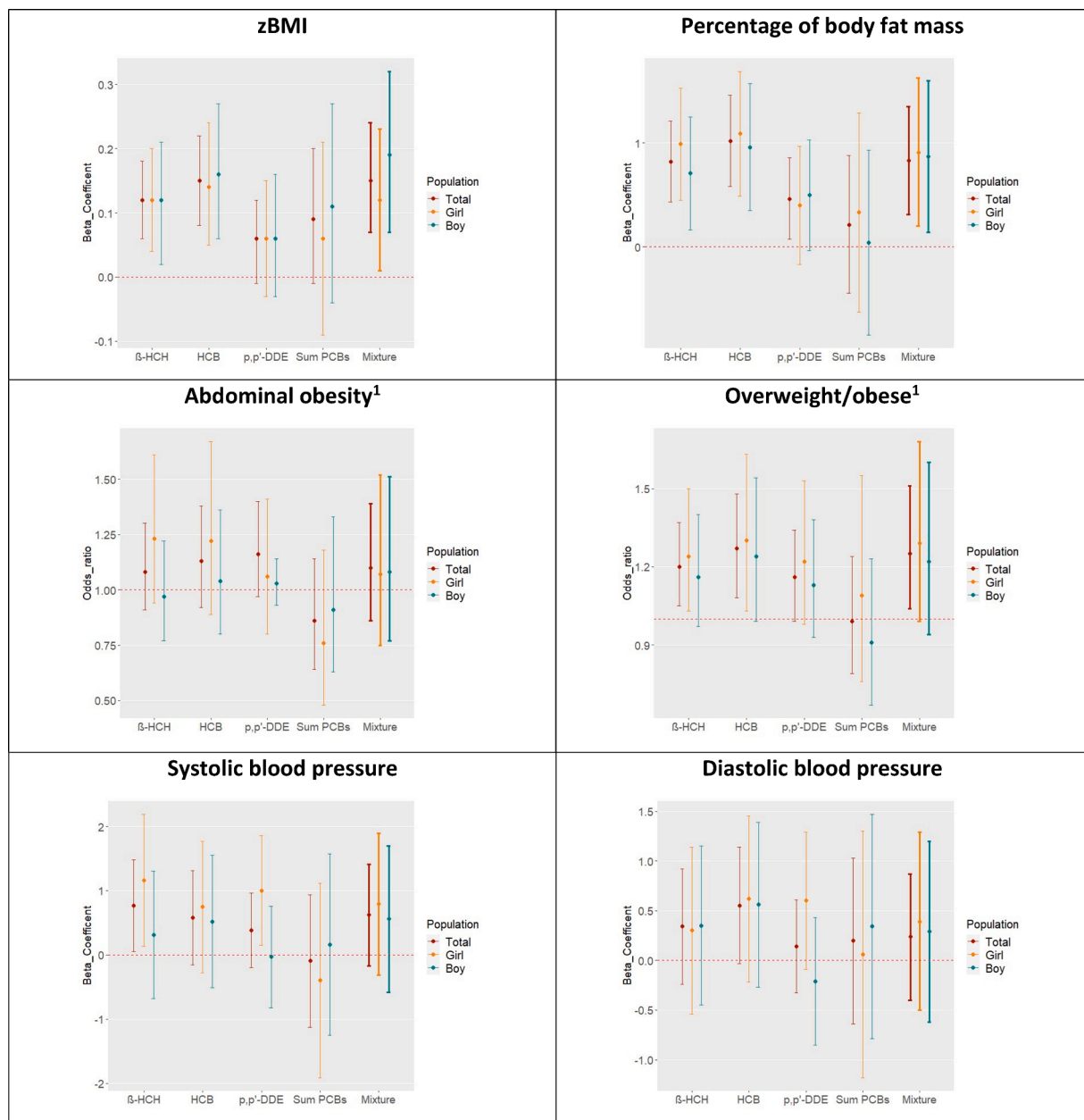


Fig. 1. Prenatal exposure to POPs in association with adiposity markers and blood pressure in preadolescents (n = 1667): results from single-exposure and Quantile G-computation modeling. Estimate (and 95 % CI) from the single-exposure models for β -HCH, HCB, p,p'-DDE and sum of PCBs and from Quantile G-computation for Mixture. Results are reported for girls and boys together (in red) and separately (yellow for girls and green for boys). β -HCH: beta-hexachlorocyclohexane; CI: Confidence interval; HCB: Hexachlorobenzene; POP: Persistent organic pollutant; p,p'-DDE: p,p'-dichlorodiphenyldichloroethylene; Sum PCBs: Sum of Polychlorinated biphenyls 138, 153 and 180; zBMI: Body mass index z-score. ¹Overweight/obese and Abdominal obesity are treated as a categorical variable with "No" as reference and expressed as an odds ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

conclusion, other than for the PELAGIE cohort (0.12 $\mu\text{g/L}$) which has a higher median PCB 153 concentration than the INMA cohort (0.04 $\mu\text{g/L}$ for Sabadell and 0.06 $\mu\text{g/L}$ for Gipuzkoa and Valencia).

Overall, our findings on adiposity markers are consistent with the results of a recent meta-analysis reporting higher zBMI during childhood (2–11 years old) in association with prenatal exposure to HCB (β [95 % CI] = 0.31 [0.09; 0.53]) and p,p'-DDE (β [95 % CI] = 0.12 [0.03; 0.21]), but not PCBs (β [95 % CI] = 0.10 [-0.07; 0.27]) (Stratakis et al., 2021). Studies at older ages are scarce (including four on organochlorine pesticides and four on PCBs), though they reported similar findings (Güil-Oumrait et al., 2021; Warner et al., 2017; Gladen et al., 2004; Berghuis et al., 2022; Dallaire et al., 2014; Tahir et al., 2020). A study performed on 379 Spanish children aged 4–18 years (INMA-Menorca cohort)

reported that prenatal exposure to p,p'-DDT (second vs. first tertile: β [95 %CI] = 0.23 [0.01; 0.45]), but not p,p'-DDE, was associated with increased zBMI, and prenatal exposure to HCB was associated with increased zBMI (third vs. first tertile: β [95 %CI] = 0.24 [0.01; 0.47]), percent of body fat mass (third vs. first tertile: β [95 %CI] = 2.93 [0.62; 5.24]), and waist-to-hip ratio (third vs. first tertile: β [95 %CI] = 0.27 [0.04; 0.51]) (Güil-Oumrait et al., 2021).

In another study that included 240 12-year-olds enrolled in the CHAMACOS cohort (in California), prenatal p,p'-DDE exposure was associated with several measures of adiposity in boys, but not in girls (e. g., p,p'-DDE and zBMI in boys: β [95 %CI] = 0.31 [0.02; 0.59]) (Warner et al., 2017). Conversely, two studies (one in 101 Dutch children aged 13 to 15 years and the other in 304 boys aged 11–20 years and born in the

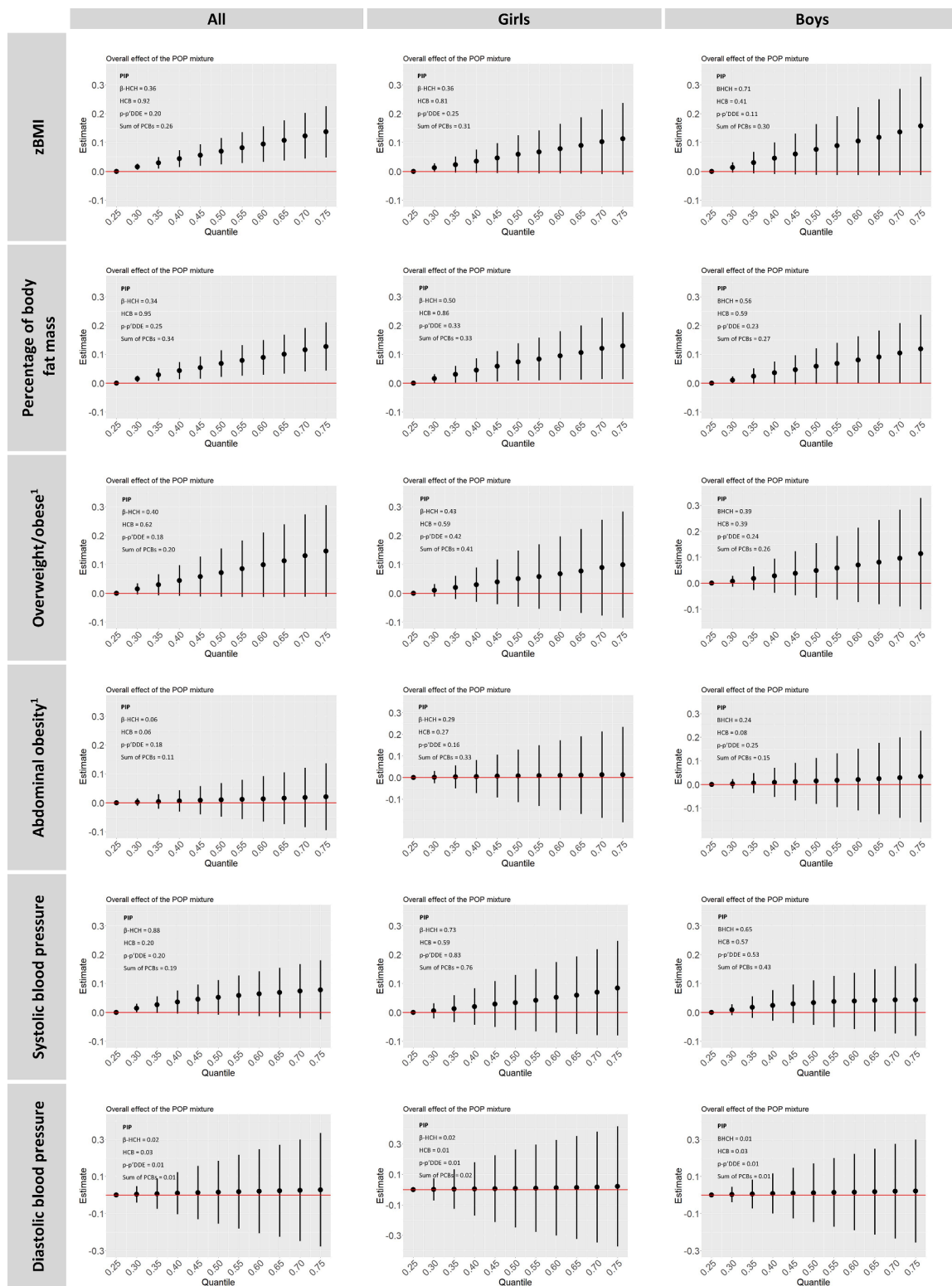


Fig. 2. Overall effect of the POP mixture on child adiposity markers and blood pressure: results from Bayesian Kernel Machine Regression (BKMR) modeling. Overall effect of the mixture (95 % CI), defined as the difference in the response (y-axis) when all of exposures are fixed at a specific percentile (x-axis), as compared to when all exposures are fixed at the 25th percentile. Posterior inclusion probabilities (PIP) provide a measure of exposure importance ranging from 0 to 1. Results are reported for girls and boys together and separately. All models are adjusted for maternal age, fish consumption during pregnancy, maternal BMI, maternal education, maternal gestational weight gain, parity, cohort, child sex and child age (as well as child height for the blood pressure outcomes). β -HCH: beta-hexachlorocyclohexane; CI: Credible interval; HCB: Hexachlorobenzene; PIP: Posterior inclusion probability; POP: Persistent organic pollutant; p,p'-DDE: p,p'-dichlorodiphenyldichloroethylene; Sum PCBs: Sum of Polychlorinated biphenyls 138, 153 and 180; zBMI: Body mass index z-score. ¹Overweight/obese and Abdominal obesity are treated as a categorical variable with “No” as reference and expressed as an odds ratio.

1960's in Philadelphia) did not observe any association between prenatal exposure to p,p'-DDE and anthropometric measures (Gladen et al., 2004; Berghuis et al., 2022). To our knowledge, only four studies have evaluated the association between prenatal exposure to β -HCH and BMI, and none of these were performed in adolescents: two reported a higher zBMI in infants and in 7-year-old children, (Yang et al., 2021; Agay-Shay et al., 2015) and the other two reported no association in 5–7 year-olds (Cupul-Uicab et al., 2013; Lauritzen et al., 2018). Of the four studies evaluating associations between prenatal exposure to PCBs and anthropometric measures in adolescents (Güil-Oumrait et al., 2021; Berghuis et al., 2022; Dallaire et al., 2014; Tahir et al., 2020), just one (performed on 212 Canadian adolescents) reported that higher prenatal exposure to PCB 153 was associated with a higher BMI and fat mass index (only in girls) (Tahir et al., 2020), while the other three observed no association (Güil-Oumrait et al., 2021; Berghuis et al., 2022; Dallaire et al., 2014).

The literature does include a few studies on prenatal exposure to POPs and blood pressure (Vafeiadi et al., 2015; Lee et al., 2016; Warembourg et al., 2019; Güil-Oumrait et al., 2021), among which only one was performed on adolescents (Güil-Oumrait et al., 2021). In overall, their findings are not consistent, thus limiting the comparison of our results obtained on β -HCH, p,p'-DDE and higher blood pressure in girls. Of the four studies looking at prenatal exposure to organochlorine pesticides, two reported higher blood pressure in association with HCB, p,p'-DDT or p,p'-DDE (Vafeiadi et al., 2015; Güil-Oumrait et al., 2021), while the other two reported no association with β -HCH, HCB, p,p'-DDT or p,p'-DDE (Lee et al., 2016; Warembourg et al., 2019). One study did report an association between prenatal exposure to PCBs and decreased blood pressure in children aged 6 to 11 years, (Warembourg et al., 2019) while the other three observed no association (Vafeiadi et al., 2015; Lee et al., 2016; Güil-Oumrait et al., 2021). In contrast with our findings, none of the two studies whose performed stratified analyses by sex have observed evidence of sex-specific association.

The long-term effect of developmental exposure on obesity could result from endocrine disruption, impaired adipocyte differentiation, and/or epigenetic changes (Heindel et al., 2017). DDE, HCB, and HCH are Androgen Receptor (AR) antagonists, DDE is also an Estrogen Receptor Alpha (ER α) agonist, and HCB and HCH are Estrogen Related Receptor Gamma (ERR γ) antagonists (Li et al., 2008). Estrogens and their receptors play a major role in the control of energy homeostasis, glucose metabolism and metabolic diseases (Mauvais-Jarvis et al., 2013). Several experimental studies have reported adverse effects of p,p'-DDT or p,p'-DDE on adipocyte differentiation and lipogenesis (e.g., changes in adipokines and master regulators of adipogenesis in mice preadipocytes and human MSCs, increased fatty acid uptake in NIH3T3-L1, increased proliferation of human preadipocytes) (Cano-Sancho et al., 2017). Because of the interplay between sex hormones, adipose tissues and energy homeostasis, a sex-specific effect of POPs on obesity could be expected; however, we did not observe evidence of any sex-specific effect. In the literature, inconsistent findings have been reported, with some associations observed in boys or in girls only, or a similar effect in both sexes (Stratakis et al., 2021). Conversely, we did observe a sex-specific effect for blood pressure: β -HCH and p,p'-DDE exposures were associated with higher systolic blood pressure in girls, but not in boys. This finding needs to be replicated in other studies, but this sex-specific effect could be explained by a disruption of sex steroid hormones. These hormones are involved in the regulation of some components of the renin-angiotensin system (RAS) and also play an important role in regulating cardiac physiology and cardiovascular health. In addition, both DDE and HCH are Progesterone Receptor (PGR) antagonists—according to a recent study, PGR plays a key role during cardiomyocyte maturation and activates sex-specific metabolic networks associated with oxidative metabolism (Sim et al., 2021). Other biological mechanisms capable of explaining the developmental programming of cardiovascular disease include disruption of the hypothalamus pituitary adrenal axis, alteration of renal structure and function, epigenetic

modifications, and oxidative stress (Morton et al., 2016).

The strengths of this study include its multicenter design, with 1667 mother–child pairs from two European countries and a long follow-up period running from pregnancy to preadolescence. In addition, we used advanced statistical methods to consider POP exposure as a mixture and to identify its main contributors. A number of potential confounding factors, mediator, and effect modifiers were considered, such as gestational weight gain (previously suspected of being a major confounder in the association between POPs and birthweight) (Verner et al., 2013), fish consumption as the main current source of exposure to some POPs, birthweight (which could lie in the causal path between POP exposure and child BMI), and child sex, for which we can expect heterogeneous POP effects. The consistency of results from the main analysis and the sensitivity analyses (including heterogeneous conclusions across sub-cohorts) reinforces the robustness of our findings.

The main limitation of this study lies in the heterogeneity between the PELAGIE and INMA cohorts. First, there is a difference in the assessment of exposure, with POP levels measured in umbilical cord blood samples for PELAGIE and in maternal blood samples for INMA. While POP cord blood levels were also available in part of our INMA study population (38 %), we have chosen to use POP maternal serum levels for all three INMA sub-cohorts, as a way of maintaining a homogeneous assessment of exposure within INMA (Lopez-Espinosa et al., 2016). Given that previous studies have reported a strong correlation between the two matrices, we have used a conversion factor to take this difference into account. We do not expect this decision to have any significant impact on our conclusion. In addition, the results of the meta-analyses by sub-cohort (i.e., regardless of the matrix used for POP measurement) are consistent with the main results. Other sources of heterogeneity between both cohorts exist, including age of the children, prevalence of overweight/obesity, socio-economic characteristics, and potential country-specific behaviors. Again, the consistency in the results after stratification by sub-cohort and using mixed effect models (with a random effect on the sub-cohort) reinforces our confidence in the findings.

5. Conclusion

This study suggests that prenatal exposure to a background-level of POPs, particularly organochlorine pesticides, remains associated with adiposity markers up to age 12 in both boys and girls. HCB was the major contributor to these effects, followed by beta-HCH and p,p'-DDE. β -HCH and p,p'-DDE were also associated with higher systolic blood pressure in girls. No significant associations were found for PCBs.

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CRediT authorship contribution statement

Elke Rouxel: Data curation, Formal analysis, Writing – original draft, Visualization. **Nathalie Costet:** Data curation, Formal analysis, Writing – original draft. **Christine Monfort:** Data curation, Investigation, Writing – review & editing. **Karine Audouze:** Funding acquisition, Investigation, Writing – review & editing. **Lourdes Cirugeda:** Data curation, Writing – review & editing. **Eric Gaudreau:** Investigation, Writing – review & editing. **Joan O. Grimalt:** Investigation, Writing – review & editing. **Jesus Ibarluzea:** Investigation, Writing – review & editing. **Fabrice Lainé:** Investigation, Writing – review & editing. **Sabrina Llop:** Investigation, Writing – review & editing. **Maria-Jose Lopez-Espinosa:** Investigation, Writing – review & editing. **Florence Rouget:** Investigation, Writing – review & editing. **Loreto Santa-Marina:** Investigation, Writing – review & editing. **Martine Vrijheid:** Funding acquisition, Investigation, Writing – review & editing. **Cécile Chevrier:** Funding acquisition, Investigation, Writing – review & editing, Supervision. **Maribel Casas:** Funding acquisition, Conceptualization, Investigation, Writing – original draft. **Charline Warembourg:** Conceptualization, Funding acquisition, Investigation, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2023.108056>.

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